

# Antimicrobial stewardship strategies in wound care: evidence to support the use of dialkylcarbamoyl chloride (DACC)-coated wound dressings

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## Abstract

**Background:** Traditionally, infections are treated with antimicrobials (for example, antibiotics, antiseptics, etc), but antimicrobial resistance (AMR) has become one of the most serious health threats of the 21<sup>st</sup> century (before the emergence of COVID-19). Wounds can be a source of infection by allowing unconstrained entry of microorganisms into the body, including antimicrobial-resistant bacteria. The development of new antimicrobials (particularly antibiotics) is not keeping pace with the evolution of resistant microorganisms and novel ways of addressing this problem are urgently required. One such initiative has been the development of antimicrobial stewardship (AMS) programmes, which educate healthcare workers, and control the prescribing and targeting of antimicrobials to reduce the likelihood of AMR. Of great importance has been the European Wound Management Association (EWMA) in supporting AMS by providing practical recommendations for optimising antimicrobial therapy for the treatment of wound infection. The use of wound dressings that use a physical sequestration and retention approach rather than antimicrobial agents to reduce bacterial burden offers a novel approach that supports AMS. Bacterial-binding by dressings and their physical removal, rather than active killing, minimises their damage and hence prevents the release of damaging endotoxins.

**Aim:** Our objective is to highlight AMS for the promotion of the judicious use of antimicrobials and to investigate how dialkylcarbamoyl chloride (DACC)-coated dressings can support AMS goals.

**Method:** MEDLINE, Cochrane Database of Systematic Reviews, and Google Scholar were searched to identify published articles describing data relating to AMS, and the use of a variety of wound dressings in the prevention and/or treatment of wound infections. The evidence supporting alternative wound dressings that can reduce bioburden and prevent and/or treat wound infection in a manner that does not kill or damage the microorganisms (for example, by actively binding and removing intact microorganisms from wounds) were then narratively reviewed.

**Results:** The evidence reviewed here demonstrates that using bacterial-binding wound dressings that act in a physical manner (for example, DACC-coated dressings) as an alternative approach to preventing and/or treating infection in both acute and hard-to-heal wounds does not exacerbate AMR and supports AMS.

**Conclusion:** Some wound dressings work via a mechanism that promotes the binding and physical uptake, sequestration and removal of intact microorganisms from the wound bed (for example, a wound dressing that uses DACC technology to successfully prevent/reduce infection). They provide a valuable tool that aligns with the requirements of AMS (for example, reducing the use of

antimicrobials in wound treatment regimens) by effectively reducing wound bioburden without inducing/selecting for resistant bacteria.

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An increasing number of microorganisms are acquiring antimicrobial resistance (AMR) to agents (for example, antibiotics) that are used to fight them. This is an important challenge to clinical practice and a significant drain on budgetary resources worldwide.<sup>1,2</sup> The problem is exacerbated by the fact that development of new antibiotics is slow and in decline, and is being outpaced by the increasing resistance of these microorganisms; therefore, new strategies to tackle this problem are needed.<sup>3–5</sup> Progress has been made using strong infection control and targeted use of antibiotics, leading to a reduction in infections of antibiotic-resistant microorganisms.<sup>6</sup> Antimicrobial stewardship (AMS) programmes have provided a systematic effort to inform, educate and persuade prescribers of antimicrobials to follow evidence-based prescribing to stem antibiotic overuse and help reduce AMR.<sup>2</sup> Nevertheless, because of AMR, and in addition to AMS programmes, new methods of treating resistant bacteria are urgently required, particularly in wound care. This has been highlighted by the European Wound Management Association (EWMA) as being a key challenge for clinicians working in the wound care field.<sup>7,8</sup> It has also been underlined by initiatives with which EWMA are currently involved, such as AMS podcasts,<sup>9</sup> and establishing partnerships with organisations and groups that have mutual and synergistic objectives on the AMR agenda (such as the British Society for Antimicrobial Chemotherapy).<sup>7</sup>

This article presents the case (by providing laboratory and clinical evidence) for using wound dressings that provide a physical mechanism of antimicrobial action to effectively prevent and/or treat wound infections, while supporting the AMS premise of reducing antibiotic usage.

## **Methods**

Medline, Cochrane Database of Systematic Reviews, and Google Scholar were searched for relevant articles regarding the use of wound dressings and AMS in wound care, published between January 1970 and November 2020. The following keyword search strategy was used: ‘antimicrobial stewardship’, ‘wound AND dressing’, ‘ulcer’ and ‘antibiotic resistance’. In addition, the authors also conducted a manual search of relevant wound care journals not cited in Medline/PubMed (for example, Wounds UK and Wounds International).

Data from both randomised and non-randomised clinical trials, clinical cohort studies and case series reports written in English were included. In vitro studies, case reports, case series and articles not written in English were excluded. This article was not intended to be a systematic review or meta-analysis but as a ‘narrative overview’.<sup>10</sup>

## **Wound infection treatments**

Antimicrobial agents

An important aspect of wound management is the use of antimicrobial agents to treat wound infection, which is one of the most frequent complications of wounds, particularly hard-to-heal wounds.<sup>11</sup> In the worst cases, wound infection can lead to life-threatening conditions.<sup>12</sup> Fig 1 illustrates a hard-to-heal wound infected by *Pseudomonas aeruginosa*.

There is a myriad of strategies for the treatment of wound infection in wound care. Traditional antimicrobials (for example, antibiotics and antiseptics) directly reduce bioburden by inhibiting the growth/bacterial cell division of wound microorganisms<sup>13</sup> and/or killing them to provide bioburden control. Novel approaches aid the physical removal of intact microorganisms from wounds (for example, the binding to and removal of microorganisms by DACC-coated wound dressings) rather than actively killing bacteria, providing a physical mechanism for the control of bioburden.<sup>14,15</sup>

Antimicrobials used in wound care can be divided into several broad categories including antibiotics, biocides and anti-infective biologics (Fig 2). The risk of developing AMR has led to the recommendation that topical antibiotics should not be used for the treatment of hard-to-heal wounds.<sup>11</sup> Non-antibiotic antimicrobials widely used in wound care include antiseptics, such as chlorhexidine,<sup>16</sup> povidone or cadexomer iodine,<sup>17,18</sup> polyhexamethylene biguanide (PHMB),<sup>19</sup> metals (for example, silver)<sup>20</sup> and natural products (for example, honey).<sup>21,22</sup> As with the use of antibiotics, the widespread use of low-concentration antiseptics has raised concerns about the possibility of the emergence of antiseptic resistance,<sup>23</sup> although there has been little discussion of antiseptic resistance in treatment guidelines.<sup>24</sup>

In topical form, antimicrobials may be helpful where there is localised (surface) infection of hard-to-heal wounds,<sup>11</sup> although some topical antimicrobials (for example, antiseptics) may delay wound healing,<sup>11,25,26</sup> cause periwound skin irritation,<sup>11</sup> and have potential cytotoxic effects in the wound bed, especially with long-term treatment.<sup>25,27</sup> This negative aspect of antimicrobial treatment has led to debate surrounding the use of topical antimicrobials in wound treatment, with reports of in vitro cytotoxicity with chlorhexidine<sup>28</sup> and povidone-iodine,<sup>29,30</sup> and adverse clinical reactions.<sup>31</sup>

#### Antimicrobial dressings

The development of new drugs and target opportunities (i.e., bacterial binding and removal rather than active killing) is a fundamental requirement in the battle against AMR. Antimicrobial dressings are an example of limiting exposure of antimicrobials to local sites of infection and are an important tool in current antimicrobial therapy: the use of combinations of antibiofilm/antimicrobial agents has been shown to manage infection and biofilm, and to facilitate healing progression.<sup>32</sup>

In terms of selective targeting of bacteria, several antimicrobial agents have been incorporated into different dressing types.<sup>33</sup> Common antiseptics, such as silver, iodine and PHMB can provide effective antibacterial action across a broad range of wound pathogens and there is an increasing body of in vitro evidence in support of their use.<sup>2,8,34</sup>

In contrast, there are wound dressings that do not contain active agents, but that act by binding bacteria to prevent/reduce wound infection. They do this by reducing the local bioburden of a wound via the physical uptake, sequestration and removal of microorganisms from the wound bed. There is a significant body of clinical evidence in support of dialkylcarbamoyl chloride (DACC)-coated dressings preventing and reducing infection in wounds via bacterial binding,<sup>35</sup> and it illustrates how these dressings, acting by physical means, can be used successfully to prevent/treat wound infections, and be aligned to support an AMS strategy.

DACC is a fatty acid derivative that is highly hydrophobic, and hydrophobicity plays a crucial role in the adherence of microorganisms to surfaces.<sup>36</sup> The microorganisms commonly responsible for causing surgical site infections (SSIs) or for colonising hard-to-heal wounds generally have hydrophobic extracellular surfaces and will irreversibly adhere to the DACC coating on dressings.<sup>37</sup> Several microorganisms important in wound infection have been shown to bind to DACC-coated material (Fig 3), including multidrug resistant microorganisms (MDROs) (for example, methicillin-resistant *Staphylococcus aureus* (MRSA)) and microorganisms present as part of biofilms.<sup>38</sup> A range of studies exploring numerous wound types (for example, SSIs, hard-to-heal wounds, burns) have shown the effective use of DACC-coated dressings in the prevention and management of wound infection and in reducing wound bioburden (Table 1 and Table 2).

Once microorganisms are bound to the DACC-coated dressing (Fig 3) they can be removed from the wound.<sup>39</sup> This reduces the bioburden of a wound and enhances wound healing: for example, clinical studies have shown elimination of the signs of infection in many patients with colonised or infected wounds when treated with DACC dressings (Table 2). In addition, Stanirowski et al.<sup>40</sup> demonstrated that the use of bacterial-binding dressings following caesarean section has the potential to reduce the incidence of SSI and costs of treatment. The reduced microorganism load then helps to create optimal wound conditions for healing.<sup>39</sup> As the mechanism of antimicrobial action with DACC is physical binding and removal, the lack of microorganism cell killing and disruption—as would happen with the action of antibiotics, other antimicrobial agents or antiseptics—prevents the release of endotoxin into the wound bed, minimising additional inflammatory stimulus.<sup>41</sup>

In a recent systematic review, Totty et al.<sup>35</sup> commented that, due to the physical nature of DACC's proposed mechanism of action, there is no risk of bacteria developing resistance. In addition, these

dressings bind antibiotic-resistant microorganisms such as MRSA.<sup>38,42</sup> Relying on a physical, bacterial-binding mode of antimicrobial action means that these dressings do not release any chemical or pharmacological antimicrobial agents, which may account for the lack of adverse effects to date for the use of DACC-coated dressings and suggests that these dressings may be used in all wound patient groups.<sup>43</sup>

### **Antimicrobial resistance**

Discussion on antimicrobial resistance tends to focus on antibiotic resistance. But, as with the use of antibiotics, the widespread use of biocides, such as antiseptics, particularly at low levels, has raised concerns about the possible emergence of antiseptic resistance in microbes,<sup>23</sup> a concern that must be acknowledged. However, the data regarding the mechanism of resistance and the involvement of antiseptic resistance in wounds are limited compared with antibiotic resistance.<sup>24</sup>

Bacteria exposed to sub-lethal doses of antibiotics can mutate and resist antibiotic treatments via the natural selection of resistance-conferring genetic changes.<sup>44</sup> The widespread use of antibiotics in hospitals and the community setting, together with them being regarded as safe and effective, as well as inexpensive, has led to their misuse, through use without a prescription and overuse for self-limiting infections.<sup>45–47</sup> There are few studies that have attempted to quantify the level of inappropriate antibiotic prescribing.<sup>48</sup> Data on the prevalence of the inappropriate use of antimicrobials vary. A US study in 2007 stated that in hospitals, up to 50% of antimicrobial use was inappropriate.<sup>49</sup> A more recent survey in 2016 suggested that an estimated 30% of outpatient, oral antibiotic prescriptions may have been inappropriate.<sup>50</sup> Another study suggests that approximately 20% of antibiotics are inappropriately prescribed in UK primary care settings.<sup>48</sup>

The world is facing a rapidly worsening crisis related to the rise in the rates of resistance of bacterial pathogens to available therapeutic antimicrobial agents—even to many ‘last resort’ agents.<sup>7,51</sup> AMR is a growing public health challenge worldwide that was identified as one of the top 10 threats to global health by the World Health Organization (WHO) in 2019.<sup>52</sup> According to a recent analysis, between 2000 and 2015, global consumption of antibiotics increased by 65%, from 21.1–34.8 billion defined daily doses (DDDs), while the antibiotic consumption rate increased by 39%, from 11.3–15.7 DDDs per 1000 individuals per day over the same period. If this trend continues unabated, global antibiotic consumption in 2030 is poised to be up to 200% greater than the 42 billion DDDs estimated for 2015.<sup>53</sup>

Over the last 30 years or so, AMR has been increasing, especially in healthcare environments,<sup>51</sup> while no new classes of antibiotics have been developed and there have been no new classes of antibiotics

given regulatory approval since the late 1980s.<sup>7,54</sup> Current antibiotics may become ineffective within 20 years.<sup>51</sup> Largely due to inappropriate clinical use and misuse of antimicrobials, microorganisms have acquired—in a variety of ways—a resistance to drugs resulting in what has been termed an ‘epidemic’ of bacterial resistance.<sup>55,56</sup> The inappropriate use of antibiotics represents the most important factor in the spread of drug-resistant microorganisms.<sup>57</sup> At the current rate, it is estimated that AMR could kill an estimated 10 million people per year and cost in the region of \$100–200 trillion USD globally by 2050.<sup>58</sup> Recent research has shown that 1-in-3 people will be given antibiotics in any one year and at least 20% of these prescriptions are inappropriate.<sup>59</sup> In 2015, AMR was estimated to cause over 50,000 deaths annually in Europe and the US and was projected to reach 10 million by 2050.<sup>60</sup> The cost to the US healthcare system alone for antibiotic-resistant infections is between \$21 billion and \$34 billion each year.<sup>61</sup> According to the WHO, AMR could well be a global catastrophe within our lifetime, with many people becoming incapacitated or dying from simple infections that have become complicated.<sup>62</sup>

Resistant microorganisms identified to date span a spectrum of bacteria that are responsible for and exacerbate many diseases. The WHO has identified the priority pathogens that require new antibiotics (Table 3).

#### Antimicrobial resistance in wounds

Generally, the causes of the spread of MDROs are various but inappropriate use of antibiotics represents the most important factor.<sup>57</sup> Direct consequences of infections with MDROs include longer duration of illness, increased mortality, prolonged length of hospital stay and increased costs.<sup>63,64</sup> Antibiotics are frequently prescribed for patients with non-bacterial infections<sup>65</sup> increasing antibiotic selection pressure and increasing MDROs.<sup>66</sup> Treatments for wound infection that do not involve the use of antibiotics, antimicrobials or antiseptics are essential to promote AMS practices.<sup>67</sup> Products that offer an alternative approach to the management of increasing bacterial load in hard-to-heal wounds, such as dressings with a physical mode of action, are effective in wound bioburden management as there is no risk of bacteria developing resistance.<sup>68,69</sup> A recent Best Practice Statement on the wound management strategies for AMS indicates that, for infection management, dressings that do not contain an active/pharmaceutical component, and instead have a physical mode of action to reduce bacterial load, offer an ideal option in the drive to promote AMS practices.<sup>70</sup>

A wound is an injury involving any break in skin integrity. A rapid wound healing response is necessary to prevent blood loss and seal the wound from external contaminants, after which the healing process continues to re-establish normal tissue function.<sup>71</sup> Acute wounds (for example, from surgery or



trauma) heal via a series of sequential and overlapping steps; the inflammatory, proliferative and the remodelling phases.<sup>72,73</sup> Hard-to-heal wounds neither heal properly nor progress through these sequential, healing response phases.<sup>74</sup>

All open skin wounds are colonised by bacteria acquired from either the host (commensal microorganisms) or the external environment.<sup>75</sup> Wounds generally provide a warm, moist and nutritive environment that promotes bacterial proliferation, and the level of bioburden varies according to the magnitude of bacterial presence in the wound.<sup>76</sup> Wound microorganisms can also persist in hard-to-heal wounds as a biofilm—a complex, sessile community of microbes attached to the surface of a wound that is tolerant to treatment (including antibiotics) and the host defence.<sup>77–79</sup> Particularly in hard-to-heal wounds, such as ulcers, with their compounding influences (for example, the patient’s underlying disease processes), the persistent presence of high levels of bacteria can contribute significantly to the chronic nature of these wounds.<sup>80–82</sup>

The bioburden, as well as the virulence of the organisms, the synergistic action of different bacterial species and the ability of the host to mount an immune response, determine the transition from contamination to colonisation to infection.<sup>83,84</sup> Infection cannot be predicted by the presence of a specific type of microorganism or by a quantity of bacteria<sup>85</sup> and the host immune response plays a critical role in determining whether wound infection occurs.<sup>86</sup>

Wound infection is a significant problem in both acute (surgical) wounds leading to SSIs and hard-to-heal wounds:<sup>68</sup>

- SSIs occur in wounds created because of a surgical procedure and are one of the most important causes of healthcare-associated infections (HCAs). In a national SSI surveillance report for NHS hospitals in England (for the period April 2012 to March 2017), the cumulative 30-day SSI incidence rate was 1.26%, ranging between 9.97% for large bowel surgery and 0.54% for knee prosthesis.<sup>87</sup> Due to the large number of surgical procedures conducted annually, the financial and social costs associated with SSIs can be considerable.<sup>88</sup> A UK prevalence survey undertaken in 2006 suggested that approximately 8% of patients in hospital had an HCAI, with SSIs accounting for 14% of these.<sup>89</sup> Approximately 5% of patients who had undergone a surgical procedure were found to have developed an SSI, which can double their length of hospital stay<sup>90</sup> and thus increase the costs of healthcare.<sup>91</sup> These infections are associated with considerable morbidity and over one-third of postoperative deaths may be related, at least in part, to SSIs.<sup>92</sup> More widely, a systematic review confirms that a significant number of SSIs occur following various surgical specialties in European countries and it was noteworthy that the incidence of SSI was as high as 36% in one of the studies reviewed,<sup>93</sup> suggesting that infections are a persistent complication of surgery

- Hard-to-heal wounds are defined as wounds that have ‘...failed to proceed through an orderly and timely process to produce anatomic and functional integrity’,<sup>94</sup> and are susceptible to microbial invasion and infection which can lead to serious complications, including associated skin problems, delayed healing, wound enlargement and systemic infection.<sup>95</sup> Hard-to-heal wounds prone to infection include venous leg ulcers, diabetic foot ulcers and pressure ulcers.<sup>95–97</sup> Hard-to-heal wound infections are responsible for considerable morbidity and significantly contribute to escalation in the cost of healthcare.<sup>98,99</sup> Infections usually lead to the use of increased clinician resources, more expensive products and drugs, and increased morbidity and rehabilitation time.<sup>100</sup> The potential for infection to add significant costs to wound treatment has been highlighted in a study which showed that wound infection was one of the factors associated with the greatest duration of health professionals’ time and was associated with the highest drug costs.<sup>101</sup>

Hard-to-heal wounds pose particular problems: taking weeks (or months) to heal,<sup>102</sup> often polymicrobial and requiring broad-spectrum antimicrobial treatments.<sup>25,103</sup> Some clinicians believe that antibiotic therapy should be continued until healing occurs, but there is no evidence to support this belief.<sup>104</sup> Also, as wounds are at risk of recurring infections, patients are often exposed to repeated courses of antibiotic therapy.<sup>7</sup> Since hard-to-heal wounds are highly inflamed tissues and may therefore appear infected when they are not, this may lead to inappropriate/over-prescribing of antibiotics with both infected and uninfected wounds that cause antibiotic-resistant infections.<sup>105</sup>

The threat of AMR in wounds has been recognised for over 20 years<sup>106,107</sup> and many bacterial species (for example, *Staphylococcus*, *Pseudomonas*, *Peptoniphilus*, *Enterobacter*, *Stenotrophomonas*, *Fingoldia* and *Serratia*) have been identified in hard-to-heal wounds.<sup>108</sup> *Pseudomonas aeruginosa* and *Staphylococcus aureus* are both methicillin-resistant and particularly prevalent in hard-to-heal wounds,<sup>109</sup> burns<sup>110</sup> and SSIs.<sup>111</sup>

The inappropriate use of antimicrobials is common to all specialties, but there are some problems that are specific to wound care: infection can be difficult to diagnose in hard-to-heal wounds; there is a lack of guidelines for the treatment of infected hard-to-heal wounds; clinicians may be unsure when to use antibiotics or be concerned that failing to use them could result in a bad outcome; and patients may demand unnecessary antibiotic therapy.<sup>112</sup> Infection maintains inflammation and is a major contributor to delayed healing in hard-to-heal wounds.<sup>83</sup> The identification of microbes in a hard-to-heal wound does not necessarily prove the presence of infection.<sup>112</sup> The diagnosis of infection is based on clinical features rather than on any reliable diagnostic test,<sup>112</sup> and these signs of infection can vary depending upon the underlying pathology.<sup>113</sup>

Antimicrobial tolerance

Tolerance has been defined as the ability of bacteria to survive antibiotic exposure without developing resistance.<sup>114</sup> Tolerance has also been reported to invariably precede antibiotic resistance, which indicates that preventing tolerance may offer new insight into controlling antibiotic resistance.<sup>114</sup> This tolerance mechanism has been associated with persistent, chronic infections.<sup>115,116</sup> Whereas antibiotic resistance is genetically induced via either mutations or horizontal gene transfer, antibiotic tolerance involves bacterial survival via dormant persister cell<sup>117</sup> and biofilm phenotypic states.<sup>118</sup> Although biofilm falls outside of the current definition of AMS, greater awareness of the existence, ubiquity and consequences of environmental biofilm among healthcare practitioners is crucial to improving hygiene practices, and controlling the emergence and spread of antibiotic resistance in healthcare facilities.<sup>119</sup>

### **Antimicrobial stewardship**

There have been several global initiatives with the aim of addressing the problem of AMR.<sup>120</sup> AMS is one global initiative for overcoming AMR to reduce the use of prescribed antibiotics.<sup>121</sup> At its most general, ‘stewardship’ can be defined as the responsible planning and management of a resource<sup>7</sup> where a successful AMS programme (ASP) optimises the use of antimicrobials to improve patient outcomes via careful programme planning and implementation based upon current knowledge and practices.<sup>122</sup> Successful AMS and, more generally, ASPs must be a collaborative multidisciplinary team effort across the whole of a patient’s care that results in the timely and optimal selection and use of antimicrobial agents (see Box 1 for key AMS actions). Nurses in particular have been identified as playing a central role in the application of stewardship to patients.<sup>123–125</sup> The primary aim is to achieve the best clinical outcome for the patient<sup>7</sup> and the Centers for Disease Control and Prevention (CDC) simplifies AMS as ‘...patients get the right antibiotics at the right time for the right duration’.<sup>126</sup> While antibiotic stewardship programmes (ASPs) have demonstrated success in reducing costs, there is limited quality evidence of their effectiveness to reduce antibiotic resistance.<sup>127,128</sup> The effectiveness of ASPs in reducing antibiotic-resistant infections has been variable,<sup>129–132</sup> and significant push is required for the benefits of ASPs in reducing the incidence of antibiotic-resistant microorganisms. A recently updated Cochrane review, based on more than 200 studies from diverse settings, found that AMS interventions in hospitals result in greater compliance with treatment guidelines, reduced total duration of antimicrobial treatment, and lead to shorter lengths of hospital stays without adversely impacting patient mortality.<sup>133</sup> Another systematic review and meta-analysis by Schuts et al.<sup>134</sup> supported application of several AMS interventions, including guideline-directed use of empiric antimicrobials, de-escalation, switching from intravenous to oral therapy, antibiotic restrictions, therapeutic monitoring and bedside consultations in terms of improved patient outcomes, reduced costs and occurrence of adverse events. Despite the evident advantages and gains,

managing successful AMS programmes in healthcare institutions is challenging in general and even more so in resource-constrained environments.<sup>135</sup>

#### Antimicrobial stewardship in wound care

The clinical, economic and patient-related consequences of wound infection place major burdens on healthcare systems.<sup>136,137</sup> Wound infection is one of the most frequent complication of hard-to-heal wounds and can contribute to further extending the time taken for these wounds to heal.<sup>138</sup> Therefore, effective solutions for wound infection are important. There have been several consensus documents and guidelines published to help clinical professionals make appropriate decisions about antibiotic use.<sup>7,8,11,139</sup> Due to the recognition of AMR as a significant problem, AMS is rapidly becoming embedded within the specialist area of wound management. The British Society for Antimicrobial Chemotherapy and EWMA position paper highlights AMS as being central to appropriate use of antimicrobials (including antibiotics), improving patient outcomes, reducing microbial resistance and decreasing the spread of infections caused by MDROs.<sup>7,140</sup> It concludes that available evidence is limited, but suggests that applying AMS principles to the care of patients with wounds should help to reduce the unnecessary use of systemic or topical antibiotic therapy, and ensure the safest and most clinically effective therapy for infected wounds.<sup>7</sup> Antimicrobial stewardship must include consideration of both antibiotic and antiseptic use, but most of the information and guidelines that discuss the principles of antimicrobial stewardship fail to distinguish between these two groups of antimicrobials.<sup>24</sup>

With the increasing appreciation of the importance of AMS in wound care to counter the growing threat of AMR, several initiatives have been put in place to reduce the threat of AMR. These include:

- Expedited identification and diagnosis of bacteria: early and accurate diagnosis of infection ensures the targeted and appropriate treatment of the identified microorganism to reduce the potential for using ineffective antibiotics on resistant strains and thereby avoid exacerbation of the AMR threat<sup>141</sup>
- Auditing/education (including demonstration of successful treatment outcomes): suitable monitoring and analysis of prescribing habits is important to ensure that antibiotic prescribing is appropriately within local and national guidelines. The benefits of undertaking audits to understand antimicrobial usage, and to help identify areas to target to improve AMS, have been highlighted in several studies<sup>142–145</sup>

While an AMS approach can be applied generally to all types of infection, it has been tailored to specific conditions, such as cutaneous wounds that are particularly problematic. Part of the

development of pathways of care to prevent, minimise and treat wound infections includes reducing excessive use of dressings coated with active ingredients.

#### Limitations

This review is narrative, and while reviewers can summarise and make comments about a collection of studies, such reviews do not include the calculation of effect sizes that examine the strength (or lack thereof) of the effectiveness of an intervention. The quality of a narrative review may be improved by borrowing from the systematic review methodologies that are aimed at reducing bias in the selection of articles for review and employing an effective bibliographic research strategy. This may be a method that can be employed in future.

#### Key points

- Antimicrobial resistance to antibiotics is a burgeoning problem in healthcare, not least in the treatment of patients with infected wounds
- Antimicrobial stewardship in wound care is designed to reduce the impact of antimicrobial resistance
- Future treatment of infection in wounds will need to look at reducing the use of antibiotics and integrate alternative methods of its prevention and treatment
- Wound dressings that use physical methods (bacterial-binding) of infection management are an ideal solution to antimicrobial resistance and should be aligned with antimicrobial stewardship
- This article presents evidence that supports the integration of dressings that act by a physical means in helping to manage wound infection.

#### **Conclusions and recommendations**

Antibiotics are essential for treating wounds where there is evidence of infection, and where treatment is required to prevent further spread into deep tissues and the development of sepsis.<sup>33</sup> However, the development of AMR has not only affected the treatment of infections in general, but also impacted upon the prevention/treatment of wound infection. The development of AMS programmes has gone some way to alleviating the challenge of AMR, but alternatives to antibiotics are urgently required. Wound dressings that act via bacterial-binding—which does not involve the use of any antimicrobial agents—use the properties of the dressing material to reduce bioburden by physically removing bacteria, thereby promoting wound bed progression. These wound dressings show clinically proven efficacy in reducing wound bioburden (including antibiotic resistant microorganisms), preventing wound infection, and decreasing the use of antibiotics within the

premise of AMS via a purely physical mechanism of action, making them an important tool to fight AMR.

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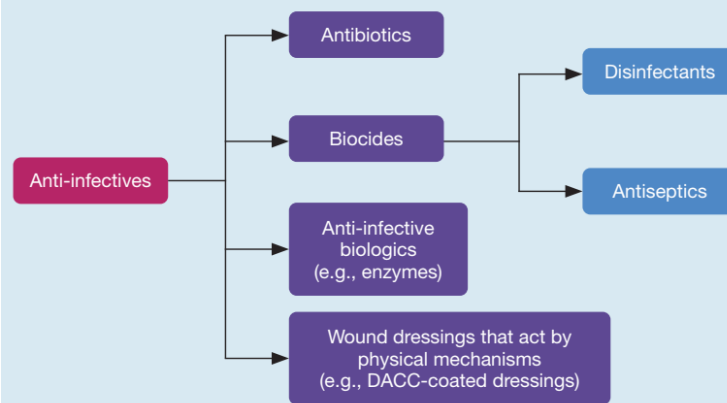
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**Fig 1.** A leg ulcer infected with *Pseudomonas aeruginosa* that produces green pigmentation (image supplied by Medetec Ltd, copyright Medetec <http://www.medetec.co.uk>)



**Fig 2.** Schematic classification of antimicrobials (modified from Edwards-Jones and Spruce, 2019<sup>51</sup>). DACC—dialkylcarbamoyl chloride



**Fig 3.** Dialkylcarbamoyl chloride (DACC)-coated dressing incubated with a mixture of microorganisms: *Staphylococcus aureus* (yellow), *Pseudomonas aeruginosa* (or *Enterococcus faecalis* (blue)), *Klebsiella* spp (green) and *Candida albicans* (orange). Note that microorganisms bind both to each other and to the dressing material. (Colourised scanning electron microscopy image to aid in distinguishing microorganisms)<sup>39,146</sup>



**Table 1. Studies assessing microorganism binding with DACC-coated dressings**

Study	Microorganisms	Main Results
Wadström et al., 1985 <sup>148</sup>	<i>Staphylococcus aureus</i>	In a porcine infected wound model, hydrophobic dressing eliminated infection and enabled wound healing; infection remained with non-hydrophobic dressings
Bowler et al., 1999 <sup>149</sup>	<i>Staphylococcus aureus</i> <i>Pseudomonas aeruginosa</i>	DACC-coated dressing absorbed and retained test microorganisms in a laboratory test system and performed better than calcium alginate dressing
Ljungh et al., 2006 <sup>39</sup>	<i>Staphylococcus aureus</i> <i>Pseudomonas aeruginosa</i> <i>Enterococcus faecalis</i> <i>Bacteroides fragilis</i> <i>Fusobacterium nucleatum</i> <i>Candida albicans</i>	Significant levels of binding to DACC-coated dressing for all microorganisms tested; binding was observed after 10 minutes and peaked at two hours; reducing hydrophobicity of microorganisms led to hydrophobic dressings being less effective
Brackman et al., 2013 <sup>150</sup>	<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	DACC-coated dressing bound <i>Staphylococcus aureus</i> suspension culture before biofilm formation in a laboratory test; DACC-coated dressing was able to significantly prevent biofilm formation in biofilms grown in an in vitro hard-to-heal wound model
Geroult et al., 2014 <sup>151</sup>	<i>Mycobacterium ulcerans</i>	Microorganism showed significantly higher binding to DACC-coated dressings compared with the control dressing
Ronner et al., 2014 <sup>42</sup>	<i>Staphylococcus aureus</i> (including MRSA)	All <i>Staphylococcus aureus</i> strains bound equally well to DACC-coated dressings in laboratory studies, regardless of microorganism antibiotic sensitivity
Cooper and Jenkins, 2016 <sup>38</sup>	MRSA <i>Pseudomonas aeruginosa</i>	DACC-coated dressing effectively binds both MRSA and <i>Pseudomonas aeruginosa</i> biofilms in a laboratory test; <i>Pseudomonas aeruginosa</i> had a higher affinity for the dressing than MRSA

DACC—dialkylcarbamoyl chloride; MRSA—meticillin-resistant *Staphylococcus aureus*

**Table 2. Summary of key clinical studies in the use of DACC-coated dressings in acute and hard-to-heal wounds and skin infections**

Wound type	Main results
Acute	<ul style="list-style-type: none"> <li>• Infection rates in DACC and daily cleansing with 0.5% chlorhexidine groups showed no difference in overall rates of infection in newborn infants (n=2441) requiring umbilical cord stump dressing<sup>152</sup></li> <li>• Surgical site infection (SSI) rates in DACC and SSD groups were 1.8% and 5.2%, respectively (p=0.04), in patients (n=543) undergoing elective or emergency caesarean section<sup>40</sup></li> <li>• 75.7% (78/103) of patients who underwent pilonidal sinus surgery healed after 75 days' treatment with DACC compared with 60.0% (58/97) in the control alginate group (p=0.023)<sup>153</sup></li> <li>• DACC associated with a significant reduction in SSI rates compared with standard dressings (1% versus 10%, p&lt;0.05) in the early postoperative period of patients (n=200) undergoing nonimplant vascular surgery<sup>43</sup></li> <li>• 36.9% relative risk reduction at 30 days in DACC versus standard care for SSI after vascular surgery (n=144)<sup>154</sup></li> <li>• SSI rates in DACC and standard surgical dressing groups were 2.8% and 9.8%, respectively (p=0.08), in patients (n=142) undergoing elective or emergency caesarean section. In five (7.0%) cases of wound infection in the control group systemic antibiotics were started, whereas they were not required in the DACC group (p=0.03)<sup>155</sup></li> <li>• 81% of wounds (n=116, including acute wounds such as post-traumatic and post-surgical wounds) were treated successfully for infection when treated with DACC. 21% of the wounds healed and 72% improved<sup>156</sup></li> <li>• A majority of burn wounds (n=27) treated with DACC appeared clean (59%), dry (51%) and pink (51%), with 27% appearing to have healed<sup>157</sup></li> <li>• DACC is as effective as normal saline dressings + 2% mupirocin in eliminating bacterial infection from infected epidermolysis bullosa wounds (n=14) and promotes faster healing compared with the use of NSD<sup>158</sup></li> <li>• Burn wounds were assessed as cleaner and had less bacterial growth in patients (n=13) with wounds dressed with DACC dressing compared with burn wounds treated with control dressings<sup>159</sup></li> <li>• 50% of &lt;15% superficial-partial thickness burns in children (n=10) healed within seven days of treatment with DACC, 70% within 14 days and 100% within 21 days<sup>160</sup></li> </ul>
Hard-to-heal	<ul style="list-style-type: none"> <li>• 81% of wounds (n=116, including wounds such as VLU, DFUs and PUs) were treated successfully for infection when treated with DACC. 21% of the wounds healed and 72% improved<sup>156</sup></li> <li>• DACC, when used as a contact layer as part of NPWT, reduced level of infection in PUs (n=50) with moderate or high levels of infection<sup>161</sup></li> <li>• Infection reductions in DACC and a silver-containing hydrofibre group were 73.1% and 41.6%, respectively (p&lt;0.00001), in patients (n=40) with critically colonised or locally infected ulcers<sup>162</sup></li> <li>• Patients with infected PUs treated with DACC (19/33) as an addition to specified guidelines for PU treatment (which included systemic antibiotics) showed improved wound bed (p=0.034), increased level of debridement (p=0.048), lower periwound inflammation (p=0.028) and reduced number of days of treatment (p=0.041) compared with the control group (14/33) treated according to specified guidelines alone<sup>163</sup></li> <li>• All SFUs (n=29) showed reduced signs of infection after four weeks' treatment with DACC with 27.6% of wounds having healed<sup>164</sup></li> <li>• DACC treatment in patients (n=21) with non-healing wounds promoted wound healing (60%), reduced exudate levels (100%) and reduced wound odour (58%)<sup>165</sup></li> <li>• Reduction in bacterial load in all wounds (n=19) when treated with DACC and 66% of wounds reduced in size in patients with leg ulcers<sup>166</sup></li> <li>• Leg ulcers (n=14) treated with DACC reduced in average surface area from 1.74cm<sup>2</sup> to 1.15cm<sup>2</sup> over four weeks' treatment<sup>167</sup></li> <li>• DACC reduced infection in 86% of hard-to-heal wounds of varying aetiology (n=13) with signs of infection. Reduction in wound size observed in 79% of wounds<sup>168</sup></li> </ul>
Skin infections	<ul style="list-style-type: none"> <li>• 75% (15/20) of patients with interdigital fungal infections improved or healed by day 10 of treatment with DACC ribbon. Four patients (20%) remained unchanged<sup>169</sup></li> </ul>
<p>DACC—dialkylcarbonyl chloride; DFU—diabetic foot ulcer; NPWT—negative pressure wound therapy; NSD—normal saline dressing; PU—pressure ulcer; SSD—silver sulfadiazine; VLU—venous leg ulcer</p>	

**Table 3. World Health Organization priority antibiotic-resistant pathogens<sup>170</sup>**

Priority	Pathogen
Critical	<i>Acinetobacter baumannii</i> , carbapenem-resistant <i>Pseudomonas aeruginosa</i> , carbapenem-resistant <i>Enterobacteriaceae</i> , carbapenem-resistant, ESBL-producing
High	<i>Enterococcus faecium</i> , vancomycin-resistant <i>Staphylococcus aureus</i> , methicillin-resistant, vancomycin-intermediate, and resistant <i>Helicobacter pylori</i> , clarithromycin-resistant <i>Campylobacter</i> , fluoroquinolone-resistant <i>Salmonellae</i> , fluoroquinolone-resistant <i>Neisseria gonorrhoeae</i> , cephalosporin-resistant, fluoroquinolone-resistant
Medium	<i>Streptococcus pneumoniae</i> , penicillin-non-susceptible <i>Haemophilus influenzae</i> , ampicillin-resistant <i>Shigella</i> , fluoroquinolone-resistant
ESBL—extended spectrum beta-lactamases	

**Box 1: Actions for antimicrobial stewardship**

Avoid prescribing antimicrobials when they are not indicated

Prescribe an appropriate regimen when antimicrobial therapy is indicated

Prescribe antimicrobial therapy for the correct duration, at an optimal dose and via the most appropriate route

Use an agent that has the least risk of adverse events for the patient

Adapted from Dryden et al., 2011<sup>147</sup>