The Role of Topical Antiseptic Agents Within Antimicrobial Stewardship Strategies for Prevention and Treatment of Surgical Site and Chronic Open Wound Infection

Christopher D. Roberts,^{1,*} David J. Leaper,² and Ojan Assadian³

¹Clinical Resolutions, Hessle, United Kingdom.

²Institute for Skin Integrity and Infection Prevention, University of Huddersfield, Huddersfield, United Kingdom.

³Department for Skin Integrity and Infection Prevention, University of Huddersfield, Huddersfield, United Kingdom.

Scope and Significance: The topical use of antiseptics for wound care has a role in an antimicrobial stewardship strategy. However, the details of this role need clarification. Further clinical research into the use of topical antiseptics in wound care would lower the risk of furthering antibiotic resistance and contribute to more effective antibiotic use. As part of this research, experimental and surveillance data are needed on the resistance and tolerance patterns associated with topical antiseptic use in wound infections.

Objective: The development of antibiotic resistance presents global challenges in terms of patient harm and increased healthcare costs. The treatment of “at risk” and infected wounds contributes to this conundrum. Synergies between antibiotics and antiseptics and their appropriate combined use need exploration.

Approach: A review of available evidence on the appropriateness of antiseptics as a fundamental component of antimicrobial stewardship strategies has been undertaken.

Innovation: Opening up new ways of thinking and identifying gaps of knowledge will lead to optimizing justification of antimicrobial choices and combinations. This may lead to changes in practice in terms of solutions for the prevention and treatment of wound infection.

Conclusion: Antiseptics are an integral part of antimicrobial stewardship strategies for the prevention and treatment of surgical site and chronic open wound infections.

Keywords: antimicrobial stewardship, antiseptics, antibiotic resistance, wound infection

Christopher D. Roberts, PhD, MBA

Submitted for publication July 18, 2016.
Accepted in revised form September 5, 2016.

*Correspondence: Clinical Resolutions, 378
Boothferry Road, Hessle HU130JS, United Kingdom
(e-mail: chris@clinicalresolutions.co.uk).

INTRODUCTION

IN AN INTERVIEW, shortly after winning the Nobel Prize in 1945 for his discovery of penicillin, Sir Alexander Fleming suggested how useful antibacterial drugs were likely to be and also how dangerous the world could become without them. He also predicted the risk and dangers of antibiotic resistance related to inappropriate antibiotic use: “The thoughtless per-

son playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism”; and that “... the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant.” This was the first call for antibiotic stewardship. In truth, this observation was based on partial truth

based on limited knowledge. In fairness to Fleming, at this time there was little or no consideration of mechanisms for causing resistance that occupy research efforts today. These include horizontal gene transfer, inducible resistance, heteroresistance, colonization resistance, genetic piggybacking, and clonal interference—these topics all modify his predictions in various ways. Interestingly, Fleming had also had a long research interest in the use of topical antimicrobials (the antiseptics), which are alternatives to antibiotics for some indications where topical administration is feasible. In a Hunterian address, he suggested that antiseptics can exercise a beneficial effect in infected wounds, which they can do with little host toxicity when used appropriately. Antiseptics are being overlooked in these days of antibiotic resistance and their use perhaps ought to be revisited and recognized as being part of an antimicrobial stewardship program.¹

Infection is one of the most frequent complications of nonhealing wounds. The clinical, economic, and patient-related consequences place major burdens on healthcare systems. During the 19th century, antiseptics became available for treating wounds, but following the discovery of antibiotics clinicians began to rely on antibiotics instead of antiseptics for preventing and treating systemic and localized infections. In addition, reports of cytotoxicity discouraged the use of antiseptics in wound care.² However, from the 1980s, research by both academic institutions and industry led to a plethora of antimicrobials (mainly antiseptic wound products being developed for topical application to wounds). The main rationale for such products was that multiple sites were targeted within the bacterial cell; they exhibited a broader antimicrobial spectrum and resulted in a lower skin sensitization rate.³ Although the lack of evidence in the form of randomized trials for demonstrating efficacy of antiseptics in treating wound infection is acknowledged, a substantial amount of evidence exists from the laboratory to the bedside

that supporting the use of such products can result in promising clinical outcomes, no detrimental effect on wound healing, and to date, an encouraging lack of resistance development.^{4–6} There is a compelling argument to revisit the wider use of antiseptics in the light of increasing antimicrobial resistance (such as Methicillin-resistant *Staphylococcus aureus* [MRSA], enterobacteriaceae, and enterococci) and microbial emergence (specifically *Clostridium difficile*) related to antibiotic overuse and misuse. This is of particular relevance to the fields of surgical incisions and chronic open wound management. The aim of this strategy is not to replace antibiotics with antiseptics, but to use antiseptics topically wherever possible to maintain effectiveness of antibiotics, and reserving them for appropriate systemic treatment, thereby helping to prevent the development of microbial resistance.

There are many different classes of antiseptics; none of which have yet to present a risk of developing clinically relevant antimicrobial resistance,^{7–10} which is caused by underdosing and inappropriate or prolonged administration of antibiotics. Antiseptics may be divided into six large classes (Table 1).^{11–14} Selection of these various compounds depends on their chemical and physical properties and the clinical indications for which they can be used. In general, there are no “good” or “bad” antiseptics, but only those which are appropriately or inappropriately used in the right indications, at the right concentrations with an informed decision on when to administer and when to stop them. Their efficacy against the relevant microbial spectrum, particularly in the presence of blood or exudate, varies depending on their distinct chemical features.

CLINICAL PROBLEM ADDRESSED

Antiseptics are not being given due consideration by infection control and microbiology experts in terms of their potential importance in providing

Table 1. Overview of antimicrobial compounds used as disinfectants or antiseptics in healthcare (Assadian, 2016)

Alcohols	Aldehydes	Oxidatives	Phenols	QACs	Guanidines
Ethanol	Formaldehyde	Ozone	Phenol	Benzalkonium chloride	Polyhexanide
Isopropanol	Glutaraldehyde	Peroxides	Pentachlorophenol	Benzethonium chloride	Chlorhexidine
n-propanol	Glyoxal	Peroxicarbon acid	Cresol	Mecetronium ethylsulfate	Alexidine
Methanol	Methenamine	Hydrogen peroxide	Chlorocresol	Cetrimide	Pyridines
Butanol	Propenal	Sodium perborate	Thymol	Cetylpyridinium chloride	Octenidine
Chlorbutanol	Piperonal	Hypochlorous acid	Eugenol	Benzoxonium chloride	Dipyrrithione
Glycerol	Dimethylol dimethyl hydantoin	Benzoyl peroxide	Biphenyl	Tetrazolium chloride	Na-PYRION
Benzylalkohol	Hexamethylenetetramine	Halogens	Bisphenols		Zinc pyrithione
2-phenoxyethanol	Chloroallyl chloride	Chlorine	Chloroprene		Pyrimidines
Bronopol		Hypochlorites	Hexachlorophene		Hexetidine

QACs, quaternary ammonium compounds.

synergies with antibiotics in attempts to reduce the formation of antimicrobial resistance. This is especially relevant in the field of wound care and surgical site management.

MATERIALS AND METHODS

A systematic review of peer-reviewed articles was undertaken in the following manner. The National Library of Medicine PubMed database was searched using the terms antimicrobial stewardship, antiseptics and stewardship, antimicrobial stewardship guidelines, resistance to antiseptics, antiseptics on wounds, and antiseptic mechanisms of action.

RESULTS

Antibiotic resistance and supply

Following widespread media coverage, and missives from the Chief Medical Officer for the Department of Health for England,¹⁵ the general public are becoming well acquainted with the concept of antibiotic resistance.^{16,17} Nevertheless, parents of a child with a viral illness or junior attending staff looking after an in-patient with an unexplained postoperative temperature find it hard to resist a demanding parent or the need to prescribe an antibiotic, often of inappropriate wide spectrum and dose. Until relatively recently, new antibiotics have always been found to fill the therapeutic gaps caused by resistance, but although there is a wide range of antibiotics still available, previously effective oral antibiotics, such as ciprofloxacin (a quinolone), now have little effective use for treating a wide range of infections in primary and secondary healthcare.¹⁸ Broad-spectrum antibiotics, such as linezolid (an oxazolidinone), doripenem (a carbapenem), daptomycin (a cyclic peptide), and tigecycline (a glycylcycline), have all had early resistance reported since their introduction over the last 15 years. This failure of research to produce new antibiotic formulations has been associated, to some extent, with poor commercial reward compared with the development of drugs to treat more lucrative medical conditions, but this is no longer the case. Government incentives have been introduced to encourage the large pharmaceutical companies to refocus research resources back into new antibiotic identification and development.

It is hard to conceive of a world without antibiotics. First, vulnerable young and old patients, and immune-compromised and cancer chemotherapy patients, would succumb to infections for which there were no effective antibiotics; then, treatable infections, such as meningitis, bacteremia, and

pneumonia, would become fatal again, as would postpartum and neonatal infections; and invasive procedures such as transplantation, major prosthetic contaminated procedures, and cancer surgery might become much riskier.

However, to maintain the effectiveness of systemic antibiotics for future generations, it seems prudent to use other antimicrobial compounds for the treatment or prevention of infection, wherever possible. For instance, it has been shown that topically applied antiseptics may be as effective as antibiotics in treatment of certain, early localized infections, particularly in open and chronic wounds. An example where antiseptics have been used to treat infection, and be as equally effective as antibiotics, involved a study of 450 women with confirmed bacterial vaginosis (BV).¹⁹ One hundred fifty patients in each arm were randomized to 7 days of topical vaginal metronidazole, 7 days of topical administration of octenidine hydrochloride/phenoxylethanol (OCT), or 14 days OCT treatment alone. Control smears were taken after each treatment period and, overall, 63% of patients were cured from BV with no significant differences between the three study arms (metronidazole: 61%, 7 days OCT: 58%, and 14 days OCT: 71%). The topical antiseptic was as effective as the antibiotic therapy with metronidazole. Interestingly, patients stated that OCT treatment was more comfortable, easier to apply, and with fewer side effects, with no development of vaginal candidiasis.

Antibiotic usage associated with breaks in the skin

Breaks in the skin created through surgical incisions or by tissue breakdown or loss associated with chronic conditions, contribute significantly to the burden of antibiotic use. This will continue to increase as trends in the demographics of the U.K. population mean that the numbers and costs of incisional and chronic wounds are likely to increase significantly in the next 25 years. The Office for National Statistics estimates that the population of the United Kingdom will increase by 9.7 to 74.2 m in 2039. The number of people more than 60 years is projected to cross 20 million by 2030.²⁰ The prevalence of noninsulin-dependent diabetes (type 2) is also strongly correlated with age, and expected rise in patients with diabetes could increase the number of new cases of diabetic foot ulceration (DFU) by 25,000 a year. This example demonstrates that chronic wounds alone represent a significant financial burden to the U.K. National Health Service and it has been estimated that there are 200,000 individuals suffering from a chronic wound at any one

time.^{1,21} The costs of skin breakdown have been likened to a “silent epidemic.” A high proportion of costs associated with the care of both acute and surgical wounds in terms of resource and treatment are driven by postoperative or general wound complications, the most common being infection. There is little recognition, under the overall banner of antimicrobial stewardship, that wound management contributes significantly to the use of antibiotics overall and no recognition whatsoever to the use of topical antiseptics, which are so commonly used in this clinical domain, but not formally recognized as an integral component of the stewardship concept.

Healthcare-associated infections

Antibiotic resistance has become a global health economic burden related to the overuse and misuse of antibiotics (as Fleming predicted) with a significant attendant morbidity and mortality.^{22–24}

This has been well exemplified by the rise of MRSA in bacteremias and acute and chronic wounds. As a direct consequence, effective antibiotics may not be available to treat specific infections because of multiple resistance. A clear distinction needs to be made about the difference between antibiotic resistance and the protection against any antimicrobial furnished by biofilm. Antibiotic resistance is mediated through genetic adaptation, although plasmid transfer and transposons cannot be unconjugated, whereas the antimicrobial protection afforded by biofilms can be disrupted mechanically and delayed in reforming by antiseptics and disinfectants. Biofilm management is pertinent to open chronic wound care, but biofilms may also be included in acute wounds and be a factor in surgical site infection (SSI) and delayed healing and treated inappropriately with antibiotics alone.²⁵ The wider use of antiseptics in antimicrobial sutures, surgical gloves, preadmission antiseptic showering, skin preparation, and surgical drapes has all been shown to reduce SSI.^{1,26}

Antibiotic stewardship

Antibiotic stewardship is being widely recommended,^{1,27} but this has not included a recommendation for a wider use or reintroduction of antiseptics. The four major goals for antimicrobial stewardship have been summarized as follows:

- (1) optimization of therapy for individual patients;
- (2) prevention of antibiotic overuse, misuse, and abuse;
- (3) minimization of development of resistance in all care environments;

- (4) thereby improving patient safety and outcomes.^{1,28}

Competency frameworks have been published by societies and national bodies, which involve responsibility of the whole multidisciplinary prescribing team with support from an antimicrobial stewardship committee.²⁹ The designated competency antibiotic prescribing framework involves: (1) understanding of the principles of infection prevention and control and demonstration of competence in preventing and controlling infections and (2) understanding of antimicrobial resistance and antimicrobials, their modes of action, and the spectrum of action of antimicrobials and the mechanisms of resistance. Within the field of antibiotics, the assignment of MIC values and categorical break points (traditionally susceptible, intermediate, and resistant)³⁰ is now defined by various professional organizations. This information helps provide an understanding of the key elements of prescribing appropriate concentrations of antimicrobial agents for prophylaxis and treatment. (3) Demonstrating an understanding of antimicrobial stewardship in day-to-day practice. (4) Demonstrating continuing professional development in antimicrobial prescribing and stewardship.

Put simply, stewardship should ensure the correct antibiotic at the correct dose and the correct time, for the correct duration; every time. This applies equally to the use of prophylactic antibiotics in prosthetic and contaminated surgery. They are part of the care bundle, which has been proposed,³¹ to minimize the risk of SSIs. Despite these national guidelines, the incidence of SSI is not falling and can partly be attributed to poor definitions, surveillance, and compliance.^{32,33} As part of a care bundle with outstanding monitoring and compliance, the reliance on antibiotics could feasibly be reduced. This could include the use of perioperative antiseptic-related products mentioned earlier.

Recognition of infection in surgical and chronic open wound healing by secondary intention relies mainly on clinical diagnosis (Tables 2 and 3), and the indications for antibiotic therapy are clear (Table 4). In open wounds, healing by secondary intention, the use of antibiotics needs special consideration. The

Table 2. *Clinical (celsian) localized signs of acute infection*

Pain (dolor)
Swelling (tumor)
Warmth (calor)
Redness (rubor)
Loss of function (functio laesa recognized much later)

Table 3. *Clinical signs of infection in chronic wounds*

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- Abnormal or excessive granulation tissue
 - Bleeding from fragile surface at dressing change
 - Increasing pain
 - Persistent odor
 - Bridging and pocketing of purulent material
 - Delayed healing
-

use of antibiotics in this situation needs specific indications; the concept of critical colonization and localized infection, in particular, requires careful consideration.³⁴ Topical antibiotics, such as mupirocin, have been used for MRSA suppression; aminoglycosides have been used in beads in treatment of prosthetic infections, but do risk development of resistance; certainly overuse of mupirocin has led to increasing resistance.³⁵ Several consensus groups, who have addressed how to treat wound infections, have recommended not using topical antibiotics. Although the hard scientific evidence for this is lacking, in the current environment it makes both clinical and microbiological sense to consider this approach carefully.

Antiseptics and chronic wound care

A wider use of topically applied antiseptics in antimicrobial therapy, particularly in the case of open wounds, needs greater emphasis and the case for this is the basis of the remainder of this article. Commonly used antiseptics for this purpose include iodine in various forms (povidone-iodine and cadexomer iodine), chlorhexidine, silver and polyhexamethylene biguanide³⁶ in solutions for lavage, gels, and surgical and chronic wound dressings. Table 1 highlights a more generic summary of antiseptic agents for both general and wound use. It is recognized in the EWMA consensus document on antimicrobials in nonhealing wounds (2013)³⁶ that evidence bases for antiseptics need to be strengthened, but published evidence in peer reviewed journals has extensively supported their use with many sources originating from laboratory experiments.⁴ There have been fewer corroborating clinical publications, particularly those which involve adequately powered, randomized clinical trials,^{37,38} although this latter area continues to

expand. Guidance is in place to direct appropriate use of antiseptic dressings to meet the clinical challenges of an increasing bacterial continuum of infection and contamination/colonization.⁵ The focus being a strategy of starting antiseptics, coupled with maintenance debridement, at the first signs of localized infection, also known as covert or pre-infection, but now widely recognized as “critical colonization.” Equally important, there is a need to stop, or escalate, treatment based on wound assessment and reevaluation at 2 week intervals. It is generally recognized that successful use of a topical antiseptic should be conducted within a 2–6 week window.

However, there may be sound clinical and microbiological reasons to continue therapy for longer periods of time for higher risk wounds such as DFUs as part of an infection prevention strategy. One essential piece of information, which is still elusive, is that there has been no definition of categorical “break points” agreed for the introduction of antiseptics. Authors of many publications have designated their own undefined definitions to delineate susceptible and resistant microbial strains and try to compare therapeutic antiseptic options.³⁹ Despite this, the emergence of resistant organisms to topically applied antiseptics has not yet presented the theoretical, but potentially catastrophic consequences, which are associated with the continued use of antibiotics. However, national and international guidelines and publications, which have addressed antimicrobial stewardship, have failed to recognize the important contribution that topically applied antiseptics can make in conjunction with or as an alternative to systemic antibiotics in wound care.

Many challenges exist related to the lack of standardization for various antiseptic testing methods and, to complicate the issue further, many wound dressings or skin disinfectant systems make use of different delivery systems, which release and replenish identical antiseptics in a variety of concentrations. This questions whether one antiseptic agent is necessarily representative of others during the standardization of break-point, laboratory-based experiments. For example, a case has been made for the use of topical silver dressings, which have a high degree of Ag⁺ release, and demonstrably faster killing times against Gram positive, Gram negative, and other species.⁸ A question which has been raised is whether alternative dressings, which release lower levels of silver cations, are more likely to cause selection for resistance, particularly if the silver concentration is sublethal. Dressings with a faster acting and more effective antimicrobial effect

Table 4. *When should antibiotics be used for wound infection?*

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- Increasing bioburden (critical colonization out of control)
 - Cellulitis
 - Lymphangitis and lymphadenopathy
 - Osteomyelitis
 - Bacteremia
 - Life-threatening sepsis, multiple organ dysfunction, and septic shock
 - Large numbers of potential pathogens (critical colonization/localized infection)
 - Compromised host defences (immunosuppression, diabetes)
-

should present less risk for the development of microbial resistance selection. It must be recognized that translation of laboratory data to the clinical situation can pose challenges and does not rule out the possibility of new strains being able to penetrate and survive in poor quality tissue. In addition to the use of topical application of antiseptics to reduce bacterial load, several other approaches have been developed that can complement antiseptic application, including debridement, cleansing, and water-jet-based systems for removal of devitalized tissue.³ Certainly, in the case of nanocrystalline silver dressings, the higher levels of silver cations released and replenished, and the associated rapid speed of kill, have overcome the mechanisms of survival which even the most antibiotic-resistant organisms, such as NDM-1 strains present.⁴⁰ Data have shown that the use of such dressings can reduce bioburden in a wound and help reduce both signs and symptoms of infection and infection rates.^{41–43}

DISCUSSION

In most published reports and guidelines, which relate to the principles of antimicrobial stewardship, there is little information on distinguishing antibiotics from other antimicrobial agents. A key goal is to develop strategies to preserve which effective antimicrobials we have and that includes topical antiseptics. This should improve patient outcomes and reduce the risk and burden of resistance developing, and the collateral damage that inevitably follows. In the field of wound care, the contributions of both separate and combined use of antibiotics and topical antiseptics have resulted in many successful and improved clinical outcomes associated with reducing infections, which significantly delay wound healing. What is concerning is the ever increasing burden in terms of costs and numbers of wounds driven by demographic changes, which have major impacts on resource utilization within global healthcare systems. One of the controversies actively debated within the wound care field is when to start using an antimicrobial agent and whether an antibiotic should be the first choice in treatment. There has been universal agreement that topical antibiotics should not be part of any therapeutic strategy.^{5,44,45} However, topical antibiotics commonly used to treat superficial skin infections have included mupirocin,⁴⁶ clindamycin, polymyxin, neomycin, and fusidic acid, and they have led to increased patterns of resistance development.⁴⁷

The continuum of bacterial burden associated with, and leading to, the development of overt

wound infection has included many terms to act as a trigger point to regain microbiological control, but definitions of such a stage remain vague. In clinical terms, the transition of a wound from the stage of colonization to local infection has been referred to as “critical colonization”.⁴⁸ As this is a particularly critical phase in the treatment of wounds, the transition should by all means be prevented. Critical colonization has been equated with delayed healing and as such has been termed local infection by many.⁵ The development of localized infection should lead healthcare professionals to make decisions based on early or worsening clinical signs and symptoms. In terms of embracing the concept of antimicrobial stewardship, it would seem prudent not to use an antibiotic when signs and symptoms of infection are absent, but vigilance of wound progress would be essential with avoidance of the use of antibiotics or antiseptics as a “just in case” preventative strategy. When early signs of deterioration occur, it would seem prudent to consider the use of an appropriate antiseptic agent first. Many such compounds have been used over centuries with few, if any, problems associated with the development of microbial resistance.^{3,46}

Break points are discriminatory antimicrobial concentrations used in the interpretation of results of susceptibility testing to define isolates as susceptible, intermediate, or resistant.⁴⁹ The purpose of susceptibility testing is an attempt to integrate potency of the test antimicrobial and, whenever possible, to review this relationship in the light of clinical experience following therapy in day to day practice or in clinical trials. Within Europe, there are a number of active national break-point committees and their activities are coordinated through the European Committee on Antimicrobial Susceptibility testing (EUCAST). In terms of topically applied antiseptics used in wound care, our search did not find any similar testing programs or coordinating bodies. Within the wound care literature, major focus is directed to identifying wound infection with emphasis on signs, symptoms, and organism collection and subsequent identification.⁵⁰ Little to no information was found in terms of utilizing break-point values to aid initial choice of topical antiseptic and subsequent monitoring of clinical outcomes.

There appears to be a strong case for including the topical use of antiseptics in any antimicrobial stewardship strategy and to develop testing programs through independent research to determine break/trigger points, which generally exist with the use of antibiotic treatment. There is a critical gap in our knowledge base, which needs to be filled to achieve completeness in terms of achieving these end goals of

antimicrobial stewardship in wound care. This could enhance the broadest range of antimicrobial exposure and contribute collectively to a better solution and with a wider use of antiseptics, a lowered risk of development of resistance. It is recognized that further challenges exist because of the lack of standardization of antimicrobial testing methods, especially within the wound care sector. To complicate matters, dressings containing the same antimicrobial may make use of different delivery systems that release the active agent in a variety of concentrations. The question of whether one antimicrobial agent is necessarily representative of others is a recognized challenge for the standardization of antibiotic break points, but modern antiseptic delivery systems are even more complex.

Microbiologists, pharmacists, and infectious disease consultants are the gatekeepers who oversee antimicrobial stewardship strategies, with their clinical colleagues, but it is essential that their knowledge base should include the use of topical antiseptics. Within the burn care and intensive care settings, the medical microbiologist is an integral part of the clinical team. This is not always the case in both acute and primary care settings when treating problem wounds. Decisions regarding the choice of topical antiseptics are taken by individuals who have had limited training in interpreting microbiological data; and in the absence of break-point data, choosing the most appropriate treatment poses difficulties. Reliance is made on observing wound progress at around 1–2 week intervals⁵ as recommended by consensus groups and then making decisions about stopping, changing, or continuing therapy. The implementation of antimicrobial stewardship training programs for General Practitioner, other medical and nursing professions, microbiologists, and pharmacists can be seen across all healthcare settings. What is woefully lacking is a component of such educational initiatives that include support for how topical antiseptic use in wound care fits into the “bigger picture.” Even when higher evidence levels for such compounds are lacking in terms of quantity, their use in wound care is undoubtedly universal and will continue to be so.

The resistance and tolerance patterns associated with use of topical antiseptic use need to be part of wound follow-up procedures and should be a key area for future research. Data from such surveillance programs will provide essential data to help justify therapeutic choices within combined stewardship programs. As to the future, there is a need to establish conclusively whether there is a clear

KEY FINDINGS

- Topical antiseptics do offer alternative solutions to infection prevention on appropriate wounds, at appropriate concentrations, used for appropriate periods of time.
- The potency of topical antiseptics can be equivalent or better than antibiotics.
- One key knowledge gap to be filled is the determination of categorical break points associated with MIC or MBCs of topical antiseptics.

cut differentiation between antibiotic and antiseptic resistance in wound pathogens and whether antiseptics in clinical use can truly select for resistance. At the same time, continued research is needed to understand the responses of antiseptics to new and emerging pathogens and within the broad concept of antimicrobial stewardship provide synergies to provide a more sufficient means of bacterial inactivation and subsequent kill.

INNOVATION

This review will help to create innovative thinking in terms of optimizing therapeutic choices for infected wounds, “at risk” wounds, and incision sites. This thinking may not lead to first line use of antibiotics, but a more detailed consideration of alternative options such as topical antiseptics.

ACKNOWLEDGMENTS AND FUNDING SOURCES

No funding was given or requested during the completion of this article.

AUTHOR DISCLOSURE AND GHOSTWRITING

The content of this article was expressly written by the authors listed. No Ghostwriters were used to write this article.

ABOUT THE AUTHORS

Christopher D. Roberts, PhD, MBA, has a background in medical microbiology. He has extensive experience in conducting clinical research within the wound care field and also research associated with the role of microbes on wound healing processes in both acute and chronic wounds. He is now principal consultant at Clinical Resolutions Wound care. **David J. Leaper, DSc, FRCS, FACS**, was a general surgeon and is now Emeritus professor of Surgery at the University of Newcastle upon Tyne in the United Kingdom. He is still active in research and teaching in the fields of wound

healing and surgical site infection. **Ojan Assadian, MD, DTMH**, received a medical degree from the University of Vienna, Austria, in 1997 and a Diploma in Tropical Medicine and Hygiene, from the London School of Hygiene and Tropical Medicine, in 2000. In 2015, he was appointed as Professor of Skin Integrity and Infection Prevention at the University of Huddersfield, England, where his research and teaching work focuses on diagnostic,

treatment, and prevention of infection, including wound infections. His other research interests focus on epidemiology of healthcare-associated infections, chronic wounds and wound infection, prevention of surgical site infection, characteristics and clinical application of antiseptics, medical use of low-temperature plasma, and infection control aspects of hospital construction. He is President of the Austrian Society for Infection Control.

REFERENCES

1. Leaper D. Topical antiseptics in wound care: time for reflection. *Int Wound J* 2011;8:547–549.
2. Brennan SS, Leaper DL. The effect of antiseptics on the healing wound: a study using the rabbit ear chamber. *Brit J Surg* 1985;72:780–782.
3. Drosou A, Falabella A, Kirsner RS. Antiseptics on wounds an area of controversy. *Wounds* 2003;15:149–166.
4. Cooper R. A review of the evidence for the use of topical antimicrobial agents in wound care. *World Wide Wounds* 2004.
5. Wound Infection in Clinical Practice: An International consensus. World Union of Wound Healing Societies Principals of Best Practice. London: MEP, Ltd., 2008.
6. Lachapelle JM, Castel O, Casado AF, et al. Antiseptics in the era of bacterial resistance—a focus on povidone iodine. *Clin Pract* 2013;10:579–592.
7. Directorate General for Health and Consumers. Opinion on triclosan. Antimicrobial resistance. www.ERLec.europa.eu/health/scientific_committees/consumer_safety/index_en.htm 2010 (last accessed August 12, 2010).
8. Chopra I. The increasing use of silver-based products as antimicrobial agents—a useful development or cause for concern. *J Antimicrob Chemother* 2007;59:587–590.
9. Cooper R. Honey as an effective antimicrobial treatment for chronic wounds: is there a place for it in modern medicine? *Chronic Wound Care Manag Res* 2014;1:15–22.
10. Moore K, Gray D. Using PHMB antimicrobial to prevent Wound Infection. *Wounds UK* 2007;3:96–107.
11. Assadian O. Octenidine dihydrochloride: chemical characteristics and antimicrobial properties. *J Wound Care* 2016;25:3–6.
12. Salami S, Innocent I, Owoeye. A comparison of the effect of chlorhexidine, tap water and normal saline on healing wounds. *Int J Morphol* 2006;24:673–676.
13. Greener M. Octenidine: antimicrobial activity and clinical efficacy *Wounds UK* 2011;7:74–78.
14. Kim JH, Sung GJ, Sae KK, et al. Wound healing evaluation of benzalkonium chloride-loaded hydrocolloid in the wound infection model. *J Pharm Investig* 2012;42:327–333.
15. Davies S. Annual Report of the Chief Medical Officer. Volume Two, 2011. Infections and the rise of antimicrobial resistance CMO Report. www.dh.gov.uk/health/2013/03/cmo-vol2 (last accessed August 2016).
16. Leaper D. European Union antibiotic awareness day. Relevance for wound care practitioners. *Int Wound J* 2010;7:314–315.
17. Department of Health. UK Five Year Antimicrobial Resistance Strategy 2013 to 2018. www.gov.uk/government/publications/uk-5-year-antimicrobial-resistance-strategy-2013-to-2018 (last accessed August 2016).
18. Livermore DM, Hope R, Reynolds R, et al. Declining cephalosporin and fluoroquinolone non-susceptibility among bloodstream Enterobacteriaceae from the UK: links to prescribing change? *J Antimicrob Chemother* 2013;68:2667–2674.
19. Novakov Mikic A, Budakov D. Comparison of local metronidazole and a local antiseptic in the treatment of bacterial vaginosis. *Arch Gynecol Obstet* 2010;282:43–47.
20. National population projections for UK 2014 based. Office for National Statistics, 2015.
21. Posnett J, Franks PJ. The burden of chronic wounds in the UK. *Nursing Times* 2008;104:44–45.
22. Department of Health, Expert Committee on Antimicrobial Resistance and Healthcare Associated Infection and PHE. Antimicrobial Prescribing and Stewardship Competencies, 2013. www.gov.uk/government/uploads/system/uploads/attachment_data/file/253094/ARHA/prescrcompetencies_2_.pdf (last accessed August 2016).
23. WHO. Antimicrobial Resistance: Global Report on Surveillance, 2014. www.who.int/drugresistance/documents/surveillance-report/en/ (last accessed August 2016).
24. ECDC and EMEA. ECDC/EMEA Joint Technical Report. The Bacterial Challenge: Time to React, 2009. www.ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf (last accessed August 2016).
25. Edmiston CE, McBain AJ, Roberts C, Leaper DJ. Clinical and microbiological aspects of biofilm-associated surgical site infections. In: Donelli G, ed. *Biofilm-Based Healthcare-Associated Infections Volume 1, Chapter 3. Advances in Experimental Medicine and Biology*. Switzerland: Springer International Publishing, 2015:47–67.
26. Leaper DJ, Ousey K. Evidence update on prevention of surgical site infection. *Curr Opin Infect Dis* 2015;28:158–163.
27. Department of Health and Department for Environment, Food and Rural Affairs. UK Five Year Antimicrobial Resistance Strategy 2013 to 2018. www.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf (last accessed August 2016).
28. Doron S, Davidson LE. Antimicrobial stewardship. *Mayo Clinic Proc* 2011;86:1113–1123.
29. Ashiru-Oredope D, Cookson B, Fry C. On behalf of the Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection Professional Education Subgroup. Developing the first national antimicrobial prescribing and stewardship competences. *J Antimicrob Chemother* 2014;69:2886–2888.
30. MacGowan AP, Wise R. Establishing MIC breakpoints and the interpretation of in vitro susceptibility tests. *J Antimicrob Chemother* 2001;48 Suppl: 17–28.
31. NICE. Surgical site infection: prevention and treatment of surgical site infections. Clinical Guideline 74 2008.
32. Leaper DJ, Tanner J, Kiernan M, Assadian O, Edmiston CE. Surgical site infection: compliance with guidelines and care bundles. *Int Wound J* 2015;12: 357–362.
33. Tanner J, Kiernan M, Leaper D, Baggott R. Reliable surgical site infection surveillance with robust validation is required. *J Hosp Infect* 2013; 154:270.

34. Leaper DJ, Assadian O, Edmiston CE. Approach to chronic wound infections. *Br J Dermatol* 2015;173: 351–358.
35. Poovelikunnel T, Gethin G, Humphreys H. Mupirocin resistance: clinical implications and potential alternatives for the eradication of MRSA. *J Antimicrob Chemother* 2015;70:2681–2692.
36. EWMA document. Antimicrobials and non-healing wounds. Evidence, controversies and suggestions. *J Wound Care* 2013;22:S1–S89.
37. Tredget EE, Shankowsky HA, Groenveld MN, Burrell RE. A matched pair randomised study evaluating the efficacy and safety of Acticoat silver coated dressing for the treatment of burn wounds. *J Burn Care Rehabil* 1998;19:531–537.
38. Jull A, Walker N, Parg V, Molan P, Rodgers A. Randomised clinical trial of a honey-impregnated dressing for venous ulcers. *Br J Surg* 2008;95:175–182.
39. Cooper R, Gray D. Is Manuka Honey a credible alternative to silver in wound care. *Wounds UK* 2012;8:54–56.
40. Hope R, Mustaq S, Vaughan K, Woodmansey E, Roberts C, Livermore D. The in-vitro antibacterial activity of nanocrystalline silver dressings against bacteria with NDM-1 carbapenemase. Poster at 22nd European Wound Management Association Conference Vienna 2012. [www.smith-nephew.com/pagefiles/46427/acce-10-0612nae%20ndm%201%20ewma%20hope%20112%20acticoat%20invitro%20activity_woodmansey%20final%20\(2%205\).pdf](http://www.smith-nephew.com/pagefiles/46427/acce-10-0612nae%20ndm%201%20ewma%20hope%20112%20acticoat%20invitro%20activity_woodmansey%20final%20(2%205).pdf) (last accessed August 2016).
41. Sibbald RG, Contreras-Ruiz J, Coutts P, et al. Bacteriology, inflammation and healing: a study of nanocrystalline silver dressing in chronic venous leg ulcers. *Adv Skin Wound Care* 2007;20:549–558.
42. Fong J, Wood F, Fowler B. A silver coated dressing reduces the incidence of early burn wound cellulitis and associated costs of in-patient treatment. Comparative patient cost audits. *Burns* 2005;31:562–567.
43. Gago M, Garcia F, Gatzelu V, et al. A comparison of 3 silver containing dressings in the treatment of infected chronic ulcers. *Wounds* 2008;20:273–278.
44. Gould IM, MacKenzie FM, Struelens MJ, van der Meer JMW. Towards a European strategy for controlling antibiotic resistance Nijmegen, Holland August 29–31, 1999. *Clin Microbiol Infect* 2000;6:670–674.
45. Lipsky BA, Hoey C. Topical antimicrobial therapy for treating chronic wounds. *Clin Infect Dis* 2009; 49:1541–1549.
46. Upton A, Lang S, Heffernan H. Mupirocin and *Staph aureus*: a recent paradigm of emerging antibiotic resistance. *J Antimicrob Chemother* 2003;51:613–617.
47. Sathish A, Kok SY, Lim TC, et al. Topical antibacterials and global challenges on resistance development. *Trop J Pharm Res* 2015;14:919–924.
48. White R, Cutting K. Critical colonisation—a concept under scrutiny. *Ostomy Wound Manage* 2006; 52:50–56.
49. Turnridge J, Patterson DL. Setting and revising antibacterial susceptibility break points. *Clin Microbiol Rev* 2007;20:391–408.
50. Vowden P, Vowden K, Karville K. Antimicrobial dressings made easy. *Wounds Int* 2011;2:1–6.

Abbreviations and Acronyms

BV	= bacterial vaginosis
DFU	= diabetic foot ulceration
GP	= general practitioner
MRSA	= Methicillin-resistant <i>Staphylococcus aureus</i>
SSI	= surgical site infection