Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

TITLE: Topical Antimicrobials and Antimicrobial Dressings for the Management of Venous Leg Ulcers: Clinical Effectiveness and Guidelines

DATE: 15 September 2014

RESEARCH QUESTION

1. What is the clinical effectiveness of topical antimicrobial use without wound dressing application on both infected and non-infected venous leg ulcers (VLU)?

2. What is the clinical effectiveness of topical antimicrobial use with regular, non-antimicrobial wound dressing application on both infected and non-infected VLUs?

3. What is the clinical effectiveness of antimicrobial dressing application on both infected and non-infected VLUs?

4. What are the evidence-based guidelines regarding the use of antimicrobial products on VLUs in the absence of signs and symptoms of infection?

5. What are the evidence-based guidelines regarding the use of topical antimicrobials and antimicrobial dressings for the management of VLUs?

KEY FINDINGS

Three systematic reviews, one meta-analysis, eight randomized controlled trials, five non-randomized studies, and two evidence-based guidelines were identified regarding topical antimicrobials and antimicrobial dressings for the management of venous leg ulcers.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 9), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was limited to English language documents published between January 1, 2009 and September 8, 2014. Internet links were provided, where available.

The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.

SELECTION CRITERIA

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Patients with venous leg ulcers (VLU)
Intervention	Q1 and 2: Topical antimicrobials (included, but not limited to, silver, iodine, acticoat) Q3: Antimicrobial dressings Q4 and 5: Both topical antimicrobials and antimicrobial dressings
Comparator	Q1: No comparator, regular non-antimicrobial dressings, antimicrobial dressings Q2: No comparator, antimicrobial dressings Q3: No comparator, topical antimicrobials without regular dressings, topical antimicrobials with regular dressings
Outcomes	Clinical effectiveness (clinical benefit including impact on healing and harms) Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, guidelines

RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, and evidence-based guidelines.

Three systematic reviews, one meta-analysis, eight randomized controlled trials, five non-randomized studies, and two evidence-based guidelines were identified regarding topical antimicrobials and antimicrobial dressings for the management of VLU. No health technology assessments were identified.

Additional references of potential interest are provided in the appendix.

OVERALL SUMMARY OF FINDINGS

Three systematic reviews, one meta-analysis, eight randomized controlled trials, five non-randomized studies, and two evidence-based guidelines were identified regarding topical antimicrobials and antimicrobial dressings for the management of venous leg ulcers.

The meta-analysis[4], based on four randomized controlled trials, found evidence to suggest that silver releasing foam dressing was the preferred treatment in patients with hard to heal VLUs, compared to dressings without an active ingredient. Findings from the systematic reviews, [1-3] randomized controlled trials,[5-12] and non-randomized studies[13-17] varied by antimicrobial therapy

used and by comparator group; thus, the use of certain antimicrobials in the treatment of VLU remains unclear. Details of these studies are presented in Table 2.

The identified evidence-based guidelines[19,20] provide conflicting information regarding the use of silver dressings. One evidence-based guideline[19] recommends that silver dressings not be used in the routine care of VLUs. In addition, there was insufficient evidence available to produce recommendations regarding the use of cadexomer iodine, povidone iodine, mupicrocin, peroxide, or phenytoin.[19] Another guideline[20] states that the use of silver dressings or cadexomer iodine may be considered as alternatives to other topical antimicrobials. This guideline[20] recommends that topical antimicrobial therapy may be appropriate for superficial infections, provided that therapy is culture guided.

Table 2: Summary of Findings of Systematic Reviews, Randomized Controlled Trials, and Non-Randomized Studies

First Author, Year	Population	Intervention	Comparator	Author Findings and Conclusions
Systematic Reviews				
O'Meara, 2014[1]	• 45 RCTs (N = 4,486)	• Cadexomer iodine (11 RCTs) • Povidone-iodine (six RCTs) • Peroxide-based (four RCTs) • Silver-based (12 RCTs) • Other antibiotics (three RCTs) • Other antiseptics (two RCTs)	• Standard care • Hydrocolloid dressing • Paraffin gauze • Dextranomer • Tripeptide copper complex • Moist or foam dressings • Growth factor • Placebo • Other antimicrobial dressings	• The use of silver dressings was not recommended. • The use of cadexomer iodine was supported by some evidence. • Antimicrobials should only be used in cases with clinical infection.
Valle, 2014[2]	• 37 studies	• Antimicrobial dressings	• Not specified	• Healing of chronic VLU may be improved with some antimicrobial dressings when compared to compression alone. • Based on limited, poor-quality literature.

Table 2: Summary of Findings of Systematic Reviews, Randomized Controlled Trials, and Non-Randomized Studies				
First Author, Year	**Population**	**Intervention**	**Comparator**	**Author Findings and Conclusions**
Zenilman, 2013[3]	• 60 studies	• Advanced wound dressings	• Simple dressings	• Advanced dressings, including those with antimicrobials, did not provide more effective wound healing when compared to simple dressings.
Randomized Controlled Trials				
O'Halloran, 2014[5]	• N = 61	• BioxyQuell aqueous oxygen peroxide	• Placebo (sterile water)	• Compared to placebo, patients treated with an aqueous oxygen peroxide experienced greater healing and wound size reduction at six and 12 months, but not at eight or 12 weeks.
Senet, 2013[6]	• N = 181	• Biatain-Ag wound dressing	• Biatain wound dressing	• Biatain-Ag was found to be more effective than Biatain without silver, especially in patients with a poor healing prognosis.
Harding, 2012[7]	• N = 281 • AQUACEL® Ag (N-145) • Urgotul® Silver (N=136)	• AQUACEL® Ag wound dressing	• Urgotul® Silver wound dressing	• Non-inferiority study • AQUACEL® Ag and Urgotul® Silver were both found to be effective at reducing wound size and promoting VLU healing.

Table 2: Summary of Findings of Systematic Reviews, Randomized Controlled Trials, and Non-Randomized Studies				
First Author, Year	**Population**	**Intervention**	**Comparator**	**Author Findings and Conclusions**
Vanscheidt, 2012[8]	• N = 126 • OHP (N = 60); • Ringer solution (N = 66)	• OHP	• Ringer solution	• Treatment of venous ulcers with OHP was found to be safe and effective. • Time to complete ulcer healing was comparable with Ringer solution.
Belcaro, 2010[9]	• N = 148; categorized by VLU or diabetic ulcer	• Multivalent silver oxide ointment	• Standard care	• Complete ulcer healing and reduction in wound surface area after four weeks greater in patients who received multivalent silver ointment.
Kerihuel, 2010[10]	• N = 60	• Actisorb Silver 220	• Hydrocolloid	• Compared with controls, activated charcoal dressings with silver improved wound healing and were better tolerated.
Romanelli, 2010[11]	• Not available	• Polihexanide and betaine wound solution	• Not specified	• Compared to controls, bacterial burden was found to be reduced in patients who received a cleaning solution containing propyl betaine and polihexanide.
Michaels, 2009[12]	• N = 304 • Antimicrobial dressing (N = 107); • Control dressing (N = 106); • Observational arm (N = 91)	• Silver-donating dressings	• Non-silver low-adherent dressing	• Time to healing and proportion of patients experiencing ulcer healing was not different between controls and those with a silver-donating dressing.

Table 2: Summary of Findings of Systematic Reviews, Randomized Controlled Trials, and Non-Randomized Studies				
First Author, Year	**Population**	**Intervention**	**Comparator**	**Author Findings and Conclusions**
Non-Randomized Studies				
Forlee, 2014[13]	• N = 14	• DURAFIBER Ag dressing	• No comparator	• In ulcers with signs of clinical infection, a new gelling fibre dressing with silver was effective at reducing signs of infection and improving quality of life.
Scotton, 2014[14]	• N = 94	• Topical antibiotic use	• No comparator	• The longer use of topical antibiotics was independently correlated with worse healing rates after one year.
Belcaro, 2011[15]	• Not available	• Silver oxide ointment	• Best management	• Use of silver oxide ointment as one component of the wound dressing was found to improve healing in patients after four weeks and compared to controls.
Lantis, 2011[16]	• N = 24	• Silver sulphadiazine powder foam dressing	• No comparator	• Foam dressing with sustained-release silver sulphadiazine powder improved ulcer healing.
Cesarone, 2010[17]	• N = 73	• Crystacide hydrogen peroxide cream	• Standard care	• Use of Crystacide improved the healing of venous ulcerations when compared to controls.

RCTs = randomized controlled trials; OHP = octenidine dihydrochloride/phenoxyethanol; VLU = venous leg ulcer.

REFERENCES SUMMARIZED

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

1. O'Meara S, Al-Kurdi D, Ologun Y, Ovington LG, Martyn-St JM, Richardson R. Antibiotics and antiseptics for venous leg ulcers. Cochrane Database Syst Rev. 2014;1:CD003557. PubMed: PM24408354

2. Valle MF, Maruthur NM, Wilson LM, Malas M, Qazi U, Haberl E, et al. Comparative effectiveness of advanced wound dressings for patients with chronic venous leg ulcers: a systematic review. Wound Repair Regen. 2014 Mar;22(2):193-204. PubMed: PM24635169

3. Zenilman J, Valle MF, Malas MB, Maruthur N, Qazi U, Suh Y, et al. Chronic venous ulcers: a comparative effectiveness review of treatment modalities [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2014 Jan [cited 2014 Sep 15]. (AHRQ Comparative Effectiveness Review; no. 127). Available from: http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1737

4. Leaper D, Munter C, Meaume S, Scalise A, Mompo NB, Jakobsen BP, et al. The use of biatain Ag in hard-to-heal venous leg ulcers: meta-analysis of randomised controlled trials. PLoS ONE [Internet]. 2013 [cited 2014 Sep 15];8(7):e67083. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3699549 PubMed: PM23843984.

Randomized Controlled Trials

5. O'Halloran PD, Winter PK, Otter JA, Adams NM, Chewins J. Aqueous oxygen peroxide treatment of VLUs in a primary care-based randomised, double-blind, placebo-controlled trial. J Wound Care. 2014 Apr;23(4):176, 178, 180-76, 178, 181. PubMed: PM24762381

6. Senet P, Bause R, Jorgensen B, Fogh K. Clinical efficacy of a silver-releasing foam dressing in venous leg ulcer healing: a randomised controlled trial. Int Wound J. 2013 Feb 4. PubMed: PM23374589

7. Harding K, Gottrup F, Jawien A, Mikosinski J, Twardowska-Saucha K, Kaczmarek S, et al. A prospective, multi-centre, randomised, open label, parallel, comparative study to evaluate effects of AQUACEL(R) Ag and Urgotul(R) Silver dressing on healing of chronic venous leg ulcers. Int Wound J. 2012 Jun;9(3):285-94. PubMed: PM22066961

8. Vanscheidt W, Harding K, Teot L, Siebert J. Effectiveness and tissue compatibility of a 12-week treatment of chronic venous leg ulcers with an octenidine based antiseptic--a randomized, double-blind controlled study. Int Wound J. 2012 Jun;9(3):316-23.

PubMed: PM22074592

9. Belcaro G, Cesarone MR, Errichi BM, Ricci A, Dugall M, Pellegrini L, et al. Venous and diabetic ulcerations: management with topical multivalent silver oxide ointment. Panminerva Med. 2010 Jun;52(2 Suppl 1):37-42.
PubMed: PM20657533

10. Kerihuel JC. Effect of activated charcoal dressings on healing outcomes of chronic wounds. J Wound Care. 2010 May;19(5):208, 210-08, 215.
PubMed: PM20505594

11. Romanelli M, Dini V, Barbanera S, Bertone MS. Evaluation of the efficacy and tolerability of a solution containing propyl betaine and polihexanide for wound irrigation. Skin Pharmacol Physiol. 2010;23 Suppl:41-4.
PubMed: PM20829661

12. Michaels JA, Campbell WB, King BM, Macintyre J, Palfreyman SJ, Shackley P, et al. A prospective randomised controlled trial and economic modelling of antimicrobial silver dressings versus non-adherent control dressings for venous leg ulcers: the VULCAN trial. Health Technol Assess. 2009 Nov;13(56):1-114, iii.
PubMed: PM19939335

Non-Randomized Studies

13. Forlee M, Rossington A, Searle R. A prospective, open, multicentre study to evaluate a new gelling fibre dressing containing silver in the management of venous leg ulcers. Int Wound J. 2014 Aug;11(4):438-45.
PubMed: PM24602074

14. Scotton MF, Miot HA, Abbade LP. Factors that influence healing of chronic venous leg ulcers: a retrospective cohort. An Bras Dermatol [Internet]. 2014 May [cited 2014 Sep 15];89(3):414-22. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4056698
PubMed: PM24937814.

15. Belcaro G, Cesarone MR, Errichi BM, Ricci A, Antelman P, Dugall M, et al. Silver oxide ointment wound dressing in venous ulcerations: home, self-management. Panminerva Med. 2011 Sep;53(3 Suppl 1):29-33.
PubMed: PM22108474

16. Lantis JC, Gendics C. In vivo effect of sustained-release silver sulphadiazine foam on bioburden and wound closure in infected venous leg ulcers. J Wound Care. 2011 Feb;20(2):90-6.
PubMed: PM21378685

17. Cesarone MR, Belcaro G, Errichi BM, Ricci A, Bavera P, Ippolito E, et al. Faster healing of venous ulcers with crystacide: a clinical and microcirculatory 8-week registry study. Panminerva Med. 2010 Jun;52(2 Suppl 1):11-4.
PubMed: PM20657528

Guidelines and Recommendations

18. Scottish Intercollegiate Guidelines Network. Management of chronic venous leg ulcers [Internet]. Edinburgh: Healthcare Improvement Scotland; 2013 [cited 2014 Sep 15]. (SIGN Guideline; 120). Available from: http://www.sign.ac.uk/guidelines/fulltext/120/recommendations.html
See 4.3.1 Topical Antimicrobials and Antiseptics

19. Wound, Ostomy, and Continence Nurses Society (WOCN). Guideline for management of wounds in patients with lower-extremity venous disease. Mount Laurel (NJ): WOCN; 2011 Jun 1. 58 p. (WOCN clinical practice guideline series; no. 4).
Summary available from: http://www.guideline.gov/content.aspx?id=38249 [cited 2014 Sep 15].
See: Section on Antibiotics

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APPENDIX – FURTHER INFORMATION:

Non-Randomized Studies

Clinical Motivations

20. Truchetet F, Guibon O, Meaume S. Clinicians' rationale for using a silver dressing: the French OMAg+E observational study. J Wound Care. 2012 Dec;21(12):620, 622-0, 625. PubMed: PM23299274

Guidelines – Uncertain Methodology

21. Maessen-Visch MB, de Roos KP. Dutch Venous ulcer guideline update. Phlebology. 2014 May 19;29(1 suppl):153-6. PubMed: PM24843102

22. Kelechi TJ, Johnson JJ, WOCN Society. Guideline for the management of wounds in patients with lower-extremity venous disease: an executive summary. J Wound Ostomy Continence Nurs. 2012 Nov;39(6):598-606. PubMed: PM23138493

Review Articles

Research Gaps

23. Lazarus G, Valle F, Malas M, Qazi U, Maruthur N, Zenilman J, et al. Chronic venous leg ulcer treatment: future research needs. Identification of future research needs from comparative effectiveness review no. 127 [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2014 Jan [cited 2014 Sep 15]. (Future research needs paper; no. 34). Available from: http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=1839&pageaction=displayproduct

General Wound Care for Venous Ulcers

24. Mosti G. Wound care in venous ulcers. Phlebology. 2013 Mar;28 Suppl 1:79-85. PubMed: PM23482540