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Review

Executive summary

Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration

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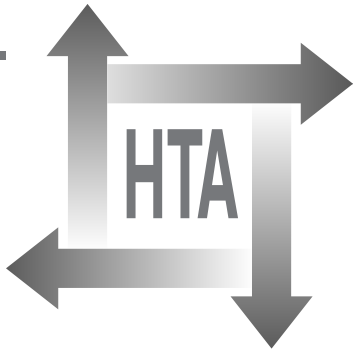

Executive summary

Background

Chronic wounds, including pressure sores, leg ulcers, diabetic foot ulcers and other kinds of wounds, healing by secondary intention are common in both acute and community settings. The prevention and treatment of chronic wounds includes many strategies, including the use of various wound dressings, bandages, antimicrobial agents, footwear, physical therapies and educational strategies. This review is one of a series of reviews, and focuses on the prevention and treatment of diabetic foot ulcers and the role of antimicrobial agents in chronic wounds in general.

Objectives

To assess the clinical- and cost-effectiveness of

- prevention and treatment strategies for diabetic foot ulcers and
- systemic and topical antimicrobial agents in the prevention and healing of chronic wounds.

Methods

Data sources

Nineteen electronic databases were searched, including MEDLINE, CINAHL, Embase and the Cochrane Library. Relevant journals, conference proceedings and bibliographies of retrieved papers were hand-searched. An expert panel was consulted.

Study selection

Randomised and non-randomised trials with a concurrent control group, which evaluated any intervention for the prevention or treatment of diabetic foot ulcers, or systemic or topical antimicrobials for chronic wounds (diabetic foot ulcers, pressure ulcers, leg ulcers of various aetiologies, pilonidal sinuses, non-healing surgical wounds, and cavity wounds) and used objective measures of outcome such as:

- development or resolution of callus
- incidence of ulceration (for diabetic foot ulcer prevention studies)
- incidence of pressure sores (pressure sore prevention studies)
- any objective measure of wound healing (frequency of complete healing, change in wound size, time to healing, rate of healing)
- ulcer recurrence rates
- side-effects
- amputation rates (diabetic foot ulcer treatment studies)
- healing rates and recurrence of disease, among others, for pilonidal sinuses.

Studies reporting solely microbiological outcomes were excluded.

Decisions on the inclusion of primary studies were made independently by two reviewers. Disagreements were resolved through discussion. Data were extracted by one reviewer into structured summary tables. Data extraction was checked independently by a second reviewer and discrepancies resolved by discussion.

All included studies were assessed against a comprehensive checklist for methodological quality.

Included studies

Diabetic foot ulcers

Thirty-nine trials which evaluated various prevention and treatment modalities for diabetic foot ulcers: footwear (2), hosiery (1), education (5), screening and foot protection programme (1); podiatry (1) for the prevention of diabetic foot ulcers; and footwear (1), skin replacement (2), hyperbaric oxygen (2), ketanserin (3), prostaglandins (3), growth factors (5), dressings and topical applications (9), debridement (2) and antibiotics (2) for the treatment of diabetic foot ulcers.

Antimicrobials

Thirty studies were included, 25 with a randomised design. There were nine evaluations of systemic antimicrobials and 21 of topical agents.

Quality of studies

The methodological and reporting quality was generally poor. Commonly encountered problems

of reporting included lack of clarity about randomisation and outcome measurement procedures, and lack of baseline descriptive data. Common methodological weaknesses included: lack of blinded outcome assessment and lack of adjustment for baseline differences in important variables such as wound size; large loss to follow-up; and no intention-to-treat analysis.

Results

Prevention of diabetic foot ulcers

There is some evidence (1 large trial) that a screening and foot protection programme reduces the rate of major amputations. The evidence for special footwear (2 small trials) and educational programmes (5 trials) is equivocal. A single trial of podiatric care reported a significantly greater reduction in callus in patients receiving podiatric care.

Treatment of diabetic foot ulcers

Total contact casting healed significantly more ulcers than did standard treatment in one study.

There is evidence from 5 trials of topical growth factors to suggest that these, particularly platelet-derived growth factor, may increase the healing rate of diabetic foot ulcers. Although these studies were of relatively good quality, the sample sizes were far too small to make any definitive conclusions, and growth factors should be compared with current standard treatments in large, multicentre studies.

Topical ketanserin increased ulcer healing rate in 2 studies, while systemic hyperbaric oxygen therapy reduced the rate of major amputations in 1 study.

Preliminary research into the effects of iloprost and prostaglandin E_1 (PGE_1) on diabetic foot ulcer healing suggests possible benefits. However, good quality, large-scale confirmatory research is needed.

Topical dimethyl sulphoxide (DMSO) (1 trial), glycyl-L-histidyl-L-lysine:copper (1 trial) and topical phenytoin (1 trial) were associated with increased healing. There is no good evidence in favour of any other dressing from 9 small trials, or for skin replacement dressings from 2 trials (the larger of which suffered substantial loss to follow-up).

Antimicrobials

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Venous leg ulcers

DMSO powder produced significantly higher healing rates than placebo, but was equivalent to allopurinol powder. Results were conflicting for silver-based products (silver sulphadiazine and silver-impregnated activated charcoal dressing). There was no evidence in favour of systemic antibiotics, polynoxylin paste, mupirocin 2% impregnated dressing or povidone iodine 10%.

Mixed aetiology wounds

Systemic ciprofloxacin added to a topical regimen produced increased healing rates in 1 trial. Levamisole (primarily used to treat roundworm infection) was associated with significantly higher healing rates than placebo (1 trial). The results for benzoyl peroxide were equivocal. 1% silver–zinc allantoinate cream was more effective than a variety of other topical preparations in a single small study. No differences were found between a hydrocolloid dressing and povidone iodine ointment for complete healing in patients with leg ulcers (aetiology unspecified) or pressure ulcers. No differences were found between an antiseptic spray (eosin 2% and chloroxylenol 0.3%) and an alternative preparation in patients with diabetic foot ulcers or pressure ulcers.

Pressure ulcers

There is no evidence in favour of topical antimicrobials in pressure-sore prevention. Oxyquinoline ointment was significantly more effective than a standard emollient for treating pressure sores in 1 study. No significant difference was detected between a hydrocolloid dressing and povidone iodine ointment, or between a gentian violet preparation and povidone iodine/sugar ointment.

Diabetic foot ulcers

No beneficial effect of topical or systemic antibiotics was identified.

Pilonidal sinuses

Oral metronidazole given after excision resulted in significantly shorter healing time (1 study). Gentamicin-impregnated sponge produced significantly higher rates of primary healing than no sponge.

Conclusions

Much uncertainty remains over the most effective interventions for the prevention and treatment of diabetic foot ulcers. Certain treatments (e.g. growth factors and off-loading techniques such as

total contact casting) show promise but need further, more rigorous evaluation.

There is no existing evidence to support the use of systemic antimicrobial agents for chronic wound healing. Even with interventions that appear to be promising, further, more rigorous evaluation is required before use becomes routine, as existing trials are generally small and many have other methodological problems. Several topical agents may be helpful, but again further research is required to establish effectiveness. Until improved data on relative effectiveness become available, considerations such as cost-minimisation may be used to guide decisions on the use of antimicrobial agents.

Implications for future research

It is likely that most of the included trials have insufficient statistical power to detect a true treatment effect. Most of this research requires replication in larger, well-designed studies, with the incorporation of: adequate sample size, clear inclusion criteria, true randomisation, assessment of baseline comparability, blinded outcome assessment, objective outcome measurement, intention-to-treat protocol and detailed reporting of withdrawals. Details of concomitant interventions and an assessment of the adverse effects associated with interventions should be provided.

Publication

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NHS R&D HTA Programme

The overall aim of the NHS R&D Health Technology Assessment (HTA) programme is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and work in the NHS. Research is undertaken in those areas where the evidence will lead to the greatest benefits to patients, either through improved patient outcomes or the most efficient use of NHS resources.

The Standing Group on Health Technology advises on national priorities for health technology assessment. Six advisory panels assist the Standing Group in identifying and prioritising projects. These priorities are then considered by the HTA Commissioning Board supported by the National Coordinating Centre for HTA (NCCHTA).

This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care. It was identified as a priority by the Pharmaceutical Panel and funded as project number 93/29/01.

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

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Reports are published in the HTA monograph series if (1) they have resulted from work either prioritised by the Standing Group on Health Technology, or otherwise commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

The editors and publisher have tried to ensure the accuracy of this report but do not accept liability for damages or losses arising from material published in this report. They would like to thank the referees for their constructive comments on the draft document.

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