Title: A Systematic review of Dialkylcarbomoylchloride (DACC) impregnated dressings in the management and prevention of wound infection

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Key Messages:

- DACC-coated dressings are a relatively new addition to the wound care arsenal and act to bind and remove bacteria from the wound bed.
- We undertook a systematic review of 17 articles to assess the current level of evidence to support the use of DACC coated dressings in routine clinical practice.
- Current evidence is limited but promising, and further high quality studies are required to further investigate their clinical and cost effectiveness.

Abstract

Introduction: Dialkylcarbomoylchloride (DACC) coated dressings irreversibly bind bacteria at the wound surface that are then removed when the dressing is changed. They are a recent addition to the wound care professionals' armamentarium and have been used in a variety of acute and chronic wounds. This systematic review aims to assess the current evidence supporting the use of DACC coated dressings in the clinical environment.

Methods: We included all reports of the clinical use of DACC coated dressings in relation to wound infection. Medline, Embase, CENTRAL and CINAHL databases were searched to September 2016 for studies evaluating the role of DACC-coated dressings in preventing or managing wound infections.

Results: Seventeen studies with a total of 3408 patients were identified and included in this review. DACC coating was suggested to reduce post-operative infection rates and result in chronic wounds that subjectively looked cleaner and had less bacterial load on microbiological assessments.

Conclusions: Existing evidence for DACC dressing in managing chronic wounds or as a surgical site infection prophylaxis is limited but encouraging with current evidence in support of DACC coated dressings preventing and treating infection without adverse effects.

Key words: Dialkylcarbomoylchloride, DACC, infection, Leukomed, Sorbact

Background

Wound infections are a significant burden to both the individuals suffering the infected wound and to the healthcare systems treating them. The annual incidence of infected chronic wounds is up to 500,000 cases per year[1] and the incidence of surgical site infections (SSI) is reported as between 5-20%[2]. Apart from the morbidity and social implications of living with a wound infection, the financial costs to the NHS are significant, with the costs of SSI alone estimated at £700 million per annum[3 4]. To date various antimicrobial wound dressings using silver, iodine or Polyhexamethylene biguanide have all been employed to try to reduce the microbial burden within wounds. Dialkylcarbomoylchloride (DACC) coated dressings are a recent addition to this group.

DACC is a fatty acid derivative that is highly hydrophobic. Micro-organisms commonly responsible for causing SSI or colonising chronic wounds generally have hydrophobic extra-cellular surfaces, and will therefore irreversibly adhere to the DACC coating on dressings[5]. Subsequent dressing changes will then result in the removal of large numbers of microbes and a decreased bacterial load at the wound site[6]. Mechanical removal of bacteria comes with several additional potential advantages; DACC coated dressings have shown no evidence of wound or systemic absorption of dressing component, or adverse reactions other than to the adhesive component of the dressing[7]. Perhaps most importantly, since the mechanism of antibacterial action is of physical binding and removal, there is no risk of bacteria developing resistance, and the lack of bacteriolysis prevents endotoxin release to the wound bed[8]. Leukomed® Sorbact®, an example of a DACC-coated dressing, is demonstrated in Figure 1.

Objectives

The aim of this review is to assess the current available evidence supporting the clinical use of DACC coated dressings in managing or preventing wound infections.

Methods

Criteria for considering studies for this review

All studies investigating the role of DACC coated dressings in wound care, with primary or secondary outcomes related to infection, were considered for inclusion, including both randomised and non-randomised trials, cohort studies and case series. Only full text reports regarding human subjects and in the English language were included.

Studies were excluded if the report was regarding an in-vitro or basic science study exploring the mode of action of DACC coatings, if DACC was used in conjunction with other advanced dressing systems (such as negative pressure wound therapy), or the article was a case series with less than three cases.

Search Strategy

This systematic review was undertaken in line with recommendations from the PRISMA statement[9]. Medline, Embase, CENTRAL and CINAHL databases were searched from 1946 to September 2016. The full search strategy used is given in table 1. Additional articles were sourced by hand searching the reference lists of relevant articles and via a google scholar search.

Selection of studies and data extraction

Abstracts returned from the above search were assessed for inclusion by three authors acting independently (JT, NB, GS). If felt suitable for inclusion, the full text of the report was

obtained and further assessed against inclusion criteria by the same three authors. Any disagreement was resolved by consensus with input from a fourth author (AH). Study design, patient population, sample size, primary and secondary clinical outcomes and results or clinical impressions of the effects of DACC coated dressings were independently extracted by 3 investigators (JT, NB and GS) and collated using a structured data extraction table for analysis.

Assessment of risk of bias in individual studies

The Cochrane risk of bias tool[10] and JADAD scoring system[11] were used to assess methodological quality of randomised controlled trials (RCTs) and cohort studies included in this review. Two reviewers (NB and JT) assessed the risk of bias of included studies independently and collated results in an assessment of risk bias table.

Results

Results of the search and Included studies

A PRISMA flow diagram is included (Figure 2) displaying the full results of searches. 252 articles were identified by the search strategy outlined above. Of these 252, 34 were considered for inclusion after screening by title and abstract, and the full text sought. After full text reading, 17 were considered to be suitable for inclusion[12-28] (Table 2).

Suitable studies included four RCTs[21 22 27 28], two cohort studies[16 20] and eleven case series[12-15 17-19 23-26].

In general, included studies fell into two types; those investigating DACC coated dressings in chronic wounds with or without signs of infection (One RCT[22], two cohort studies[16 20] and ten case series[12 13 15 17-19 23-26], total 281 patients) and those investigating the use of DACC

coated dressings in the prevention of infection in clean surgical wounds (three RCTs[21 27 28] and one case series[14], total 3133 patients).

Excluded studies

The full reasons for exclusion are shown in figure 2.

Risk of Bias in included studies

The Cochrane risk of bias tool for RCTs[10] together with JADAD[11] scores demonstrated moderate risk of bias in included studies (tables 3 and 4). The cohort study by Kleintjes[20] was deemed to have a low risk of bias. Of the randomised trials, only the trial by Mosti et al[22] had a JADAD score ≥3. Important sources of bias in the three randomised trials examining DACC for prevention of infection[21 27 28] included a lack of true randomisation, with alternating sequence allocation used in all three trials, and a lack of allocation concealment and assessor blinding in trials. Of the three, only the 2016 study by Stanirowski[27] attempted any form of blinding or concealment, with surgeons 'blinded' to the allocation of the patient until the point of dressing application (at which point they became aware of allocation due to the physical appearance of the test dressings).

DACC coated dressings in chronic wound management

The use of DACC coated dressings in chronically infected wounds was reported in one pilot RCT by Mosti et al[22], two cohort studies by Kleintjes et al[20] and Gentili et al[16], and ten case series[12 13 15 17-19 23-26].

Mosti et al[22] performed a pilot RCT comparing the effects of DACC coated dressings and silver impregnated dressings in chronically infected or heavily colonised leg ulcers of vascular origin. The primary outcome measured was a reduction in bacterial load at day 4 of treatment. They found a reduction of bacterial load of 73.1% in the DACC cohort, compared to a reduction of 41.6% in the silver cohort, a statistically significant reduction ($p<0.01$). Although the difference in reduction of bacterial load between the two dressings was statistically significant, there is no comment regarding the clinical significance of this effect.

Kleintjes et al[20] published a cohort study of 13 patients with partial or full-thickness burn wounds, comparing DACC coated dressings with two branded silver impregnated dressings (Acticoat® and Silverlon®). Included wounds were large enough that 2 or 3 dressing types could be applied to different aspects of each wound. Though no statistically significant differences were seen between dressings, authors report that wounds appeared subjectively cleaner, and wound bacterial burden (based on bacterial cultures) was less in swabs from DACC coated dressing sites with 33% positive cultures, compared to the 37.5% in Acticoat and 44% in Silverlon dressing sites.

Gentili et al[16] examined a novel method of testing bacterial load in the context of a cohort study including 19 patients (20 wounds) with chronically infected vascular ulcers. All patients were treated for four weeks with Cutimed® Sorbact® (DACC coated) dressings changed twice weekly. Panbacterial real-time PCR was used to assess bacterial load at a wound site before and after a four-week treatment course with DACC coated dressings. Investigators reported that 10/15 (66%) had a positive outcome in relation to wound size

reduction and that these wounds also demonstrated a reduction in bacterial load measured using real-time PCR.

Ten case series[12 13 15 17-19 23-26] with a total of 209 patients reported mainly subjective results following the use of DACC dressings in chronically infected wounds, with a variety of primary and secondary outcomes including, but not limited to, exudate, erythema, odour, slough and pain. All authors felt that there was significant clinical improvement of the affected wounds (reduction in slough and exudate) seen with DACC coated dressings, but due to the nature of the studies, no quantifiable data could be extracted for synthesis from the studies for the purpose of this review.

DACC coated dressings in the prevention of wound infection in clean surgical wounds

Three RCTs[21 27 28] and one case series[14] examined the use of DACC coated dressings in clean surgical wounds.

Stanirowski et al published both a pilot and a full RCT[27 28] examining post-surgical wound dressing. Patients undergoing caesarean section were randomised to either DACC coated or standard dressings. The pilot study included 142 patients and the full trial 543 patients. Patients were followed up for 14 days and the presence of SSI was assessed using Centre for Disease Control criteria. In the pilot study the investigators reported a SSI rate of 2.8% in the DACC group compared to 9.8% in the standard dressing group ($p = 0.08$). This effect size informed the power calculation for the full RCT, which reported overall SSI rates of 1.8% with DACC compared to 5.2% in standard surgical dressings ($p=0.04$).

Meberg et al[21] recruited 2441 new born infants on an obstetrics ward with the mothers providing consent. Infants were randomised on a 1:1 ratio to either having the umbilical cord stump covered with a DACC coated dressing or daily cleansing with 0.5% chlorhexidine in 70% ethanol solution. Primary outcome was the incidence of new born infection including conjunctivitis, pyoderma, paronychia and omphalitis. Infants were followed up for up to 6 weeks. Overall 377 (15.4%) cases of infection in general were reported. There was no statistical significance in infection rates between the DACC dressing group and the 0.5% chlorhexidine in 70% ethanol solution group (16.3% and 14.6% respectively, $p>0.05$).

Choi et al[14] presented a case series of seven patients in whom skin grafts were fixed with the use of a DACC-coated wound contact layer and tie-over dressing. All wounds were post-excision of lesion in theatre, and so were clean surgical wounds at the point of application of DACC coated dressings. No wounds experienced infection in this small case series.

Synthesis of results

No meta-analysis of trial data was possible for the included studies, due to differences in trial methodology and outcome measures. There were only two trials[27 28] with similar enough outcome measures and methods to consider a meta-analysis, however the 2014 Stanirowski[28] trial used the observed effect size to influence the power calculation of the 2016 study[27]. It was felt by the authors that a meta-analysis of this data would add nothing further to the findings present in the larger scale RCT.

Discussion

Summary and limitations of evidence for DACC in chronic wounds

The evidence examining DACC dressings in chronic wound management is low level (small to medium case studies). In general, the outcomes from these studies is positive however many of the outcome measures were highly subjective. The only randomised controlled evidence in chronic wounds was targeted at the bacterial load within the wound and did not include objective clinical outcomes[20]. This study had a very limited sample size (n=13) and compared dressings in the same wound bed introducing the possibility of contamination. Reports to date are generally encouraging, but there is clearly a need for rigorously designed trials with adequate sample sizes to produce the level 1 or 2 evidence needed to properly determine the efficacy of this technology in chronic wound management.

Summary and limitations of evidence for DACC as prophylaxis against wound infection

The evidence to support DACC dressings use as prophylaxis for SSI in clean surgical wounds is, in theory, of higher quality in that it is based on randomised trials, though the trials reviewed were generally at high risk of bias. Prospective work by Stanirowski et al[28] and earlier work by Meberg[21] did not show a statistically significant difference in infection rates when DACC dressings were used. The design of both studies was sub-optimal including poor treatment allocation and concealment methods, and lack of blinding of participants or investigators.

The full RCT by Stanirowski et al[27] reported a significant reduction in the SSI rates in caesarean section patients receiving DACC compared to standard surgical dressings. However this RCT had significant weaknesses in trial design. There was no allocation concealment and nor was the study truly randomised, since consecutive patients were

simply alternated between study arms. Primary outcome was reported as SSI according to centre for disease control (CDC) definitions of superficial or deep SSI. However, the follow up period was only 14 days long, which is insufficient to capture all SSI according to the CDC definition which includes wound infection up to 30 days post procedure[29]. Trial methods were improved for the larger study in comparison to the pilot, in that the wound assessments for the larger trial were performed by investigators blinded to dressing type. This may account for the improvement in the SSI rate in the control group, which was 9.8% in the pilot but reduced to only 5.2% in the full RCT despite identical surgical methods.

This purpose of this review, as outlined above, was to examine the evidence for the clinical use of DACC-coated dressings. Only one article[27] published data on the cost effectiveness of the intervention, which was not taken into consideration in this review. This is due to a significant disparity between the cost of the intervention reported in the article and the actual cost of the intervention on the UK market (mean cost of Leukomed® Sorbact® dressing in the trial reported as €2.80; mean cost of Leukomed® Sorbact® dressings in the UK (as of Aug 2015) £8.06), making any cost analysis difficult to apply to the reviewer's patient cohort.

All of the available evidence does favour DACC coated dressings over conventional, non-coated dressings, and in some cases over more traditional silver coated dressings. This provides further evidence that more research into this field of study would be beneficial.

Limitations of the review

During the search process, at least one article was identified that was classed as a review of the evidence[30]. This was a non-systematic collection of current evidence written on behalf of the product manufacturer that provided a number of references that were included in the search (additional records identified through other sources, figure 2). Our review, in general, agrees with their findings, however the systematic nature of our review, and the stricter inclusion criteria, meant a much smaller number of studies were included. The product literature did include a large amount of unpublished data presented at conferences, that was not included in our review, raising the possibility that the conclusions of our review have been impacted by this data not being made available.

This review did include a large number of low-level studies (small case studies). This was due to a relative paucity of good quality scientific studies into the effects of DACC-coated dressings in comparison to currently accepted standard practice.

Conclusion

DACC coating of dressings shows promise in both the prevention and treatment of wound infections, though published results are not as yet sufficient to firmly conclude either the clinical or cost effectiveness of its use, and therefore directly impact day-to-day clinical practice. However, the available evidence that is presented is in support of DACC coated dressings, and such promise does allow for the undertaking of further high quality research into their clinical and cost effectiveness.

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Potential Conflict of interests

All authors report no potential conflict of interests relevant to this article.

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Figure 1. Photographs of Leukomed® Sorbact®, a commercially available DACC-coated dressing, against a white background. The coloured nature of the wound contact layer is demonstrated.

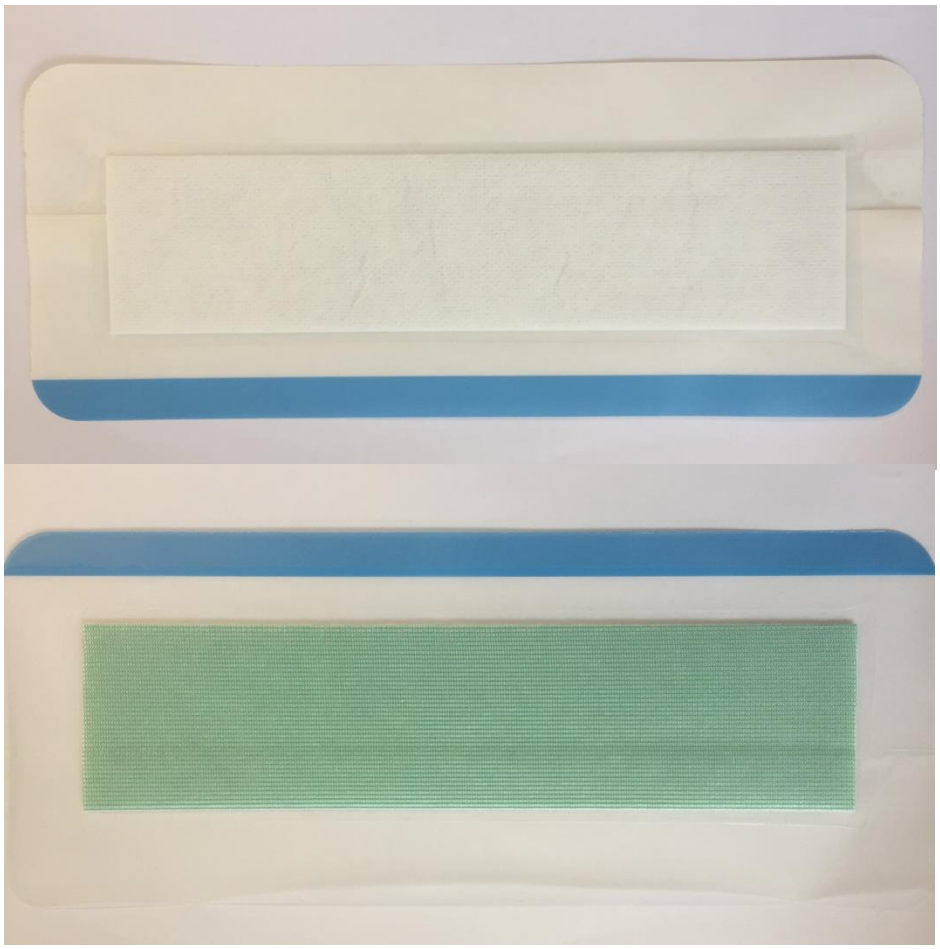

Table 1. Search strategies

Resource Searched: Embase 1974 to 2016 September 13 and Ovid MEDLINE 1946 to Present (All mapped to subject headings)		
Search	**Terms**	**Results**
1	Dialkylcarbamoylchloride.mp	3
2	Dialkylcarbamoyl chloride.mp	5
3	Dialkyl carbamoyl chloride.mp	13
4	DACC.mp	1063
5	leukomed.mp	5
6	cutimed.mp	45
7	sorbact.mp	58
8	hydrophob*.mp	240177
9	dressing.mp	38498
10	8 and 9	179
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 10	1281
12	infect*.mp	4099272
13	wound*.mp	619850
14	surg*.mp	4422074
15	ulcer*.mp	538117
16	12 or 13 or 14 or 15	8790031
17	11 and 16	259
18	limit 17 to human	158
19	limit 18 to English language	150
Resource Searched: CINAHL via EBSCOHost		
Search	**Terms**	**Results**
S1	Dialkylcarbamoylchloride OR Dialkyl carbamoyl chloride OR Dialkylcarbamoyl chloride OR DACC	54
S2	leukomed OR cutimed OR sorbact	21
S3	hydrophob* AND dressing*	16
S4	S1 OR S2 OR S3	85
S5	infect* OR wound*	316031
S6	S4 AND S5 (Limits: English Language)	40
Resource Searched: CENTRAL via Cochrane Collaboration		
Search	**Terms**	**Results**
1	Dialkylcarbamoylchloride	0
2	Dialkyl carbamoyl chloride	1
3	Dialkylcarbamoyl chloride	0
4	DACC	39
5	leukomed OR cutimed OR sorbact	14
6	hydrophob*	374
7	dressing	3069
8	#6 and #7	6
9	#1 or #2 or #3 or #4 or #5 or #8	58
10	wound*	23551
11	infect*	87186
12	#10 or #11	101554
13	#9 and #12	19

Table 2. Summary of included studies

REFERENCE	METHODS	PARTICIPANTS	INTERVENTIONS	OUTCOMES	PRIMARY FINDINGS
STANIROWSKI 2016[27]	Single blinded, randomised control trial	543 Females >18 undergoing planned or emergency caesarean section	Randomised to either DACC coated post-operative dressing or standard surgical dressing	Superficial or deep SSI within the first 14 days after CS (defined as per CDC)	SSI rates of 1.8% in DACC vs 5.2% in control (p=0.04)
STANIROWSKI 2014[28]	Single blinded, randomised, controlled pilot study	142 Females >18 years undergoing planned or emergency caesarean section	Randomised to either DACC coated post-operative dressing or standard surgical dressing	Superficial or deep SSI within the first 14 days after CS (defined as per CDC)	SSI rates of 2.8% in DACC vs 9.8% in control (p=0.08)
CHOI 2015[14]	Case series	7 patients (4 male) requiring skin graft of varying thickness on clean surgical wounds	Skin graft dressed with DACC coated dressing and tie-over dressing for 5 days	Wounds checked for infection at 5 days, 14 days and 30 days post-procedure	No wounds experienced infection
BULLOUGH 2012[13]	Case series	4 patients with complex open abdominal wounds	DACC coated dressings and swabs used as a wound contact layer for the duration of treatment	Wound infection recurrence; wound dimension; wound healing; pain during dressing changes; exudate and odour	3 of 4 wounds healed, and all signs of wound infection had resolved by day 14 of treatment.
GENTILI 2012[16]	Non-comparative, double blind, pilot study	19 consecutive patients with chronic lower limb ulcers	Wounds were treated with a 0.9% NaCl saline solution rinse, surgical debridement and application of DACC dressing. The study was performed during a 4-week period.	Evaluation of wound condition, quality of life, bacterial load	66% of wounds reduced in size. Reduction of bacterial load in all cases.
PIRIE 2009[23]	Case series	3 patients (one male) with chronic non-healing wounds referred to tissue viability services	DACC coated dressing used as a primary wound contact layer in combination with other dressings and therapies	Wound healing, evidence of infection, wound size, exudate levels	All showed clinical improvement (reduced wound size and slough).
KAMMERLANDER 2008[19]	Non-randomised multi-centre evaluation	116 patients (62 male) presenting to one of four European hospitals with a	Patients were treated with Cutimed® Sorbact® as part of their therapeutic regime	study questioned whether it could reduce inflammation; reduce	81% of wounds were successfully treated for infection. 21% of

		wound deemed to be at high risk of infection		infection; improve wound healing; be patient tolerable	wounds healed completely.
HAMPTON 2007[17]	Case Series	21 patients (7 male) with non-healing (>3 months) wounds that were not clinically infected	Patients were treated with Cutimed® Sorbact® as part of their therapeutic regime	Inflammation, exudate, malodour, wound size, pain	60% of wounds healed, 100% had reduced exudate levels and 58% had reduced wound odour
MOSTI 2015[22]	Randomised, comparative, single centre study	40 patients >18 with critically colonised or locally infected vascular ulcers of duration ≥6 months	Patients randomised to Silver containing hydrofibre dressing or DACC-coated dressing	Primary: Ulcer bacterial load	Reduction of bacterial load of 73.1% DACC vs 41.6% Silver (P<0000.1)
SKINNER 2010[26]	Case Series	4 patients (3 male) with diabetic foot ulcers	Patients were treated with Cutimed® Sorbact® as part of their therapeutic regime	Bacterial colonisation, infection, wound healing	One wound healed completely. ¾ progressed towards healing.
POWELL 2009[24]	Case series	6 patients (3 male) with a variety of wounds showing clinical infection or delayed healing	Cutimed® Sorbact® used as a wound contact layer for 2-8 weeks	Inflammation, exudate, odour, wound healing	100% of wounds were reduced in size, exudate and odour. 80% wounds healed completely
MEBERG 1990[21]	Randomised control trial	2441 newborn infants	Patients alternately allocated to umbilical cord stump dressing with either (i) DACC coated dressing or (ii) daily cleansing with 0.5% chlorhexidine in 70% alcohol	Infection in the newborn (conjunctivitis, pyoderma, paronychia and omphalitis)	No significant difference in either to overall rate of infection or in omphalitis
BRUCE 2012[12]	Multi-centre evaluation	13 patients (7 male) with chronic wounds of varying aetiology with signs of infection	Treated with DACC-coated dressings for 28 days or until signs of infection had resolved	Erythema, pain, heat, oedema, odour, exudate	86% reduction in infection; reduction in wound size in 79% of wounds

DERBYSHIRE 2010[15]	Case Series	3 patients with wounds of duration > 4 years.	Patients were treated with Cutimed® Sorbact® as part of their therapeutic regime.	Wound size, wound healing, resource use, pain, exudate levels	All wounds were cleaner, dryer, and required less nursing care/dressing changes
KLEINTJES 2015[20]	Prospective pilot study	13 patients >16 years of age with burn wounds large enough to accommodate three different trial dressings	Burns were dressed with DACC coated dressings, Acticoat® and Silverlon®, three dressings to the same burn	Wound swab MC&S, visual inspection of wounds	Wound areas dressed with DACC-coated dressings appeared subjectively cleaner and has less bacterial growth on MC&S
SIBBALD 2012[25]	Case Series	14 patients with lower limb ulceration (8 diabetic foot ulcers, 6 venous leg ulcers)	Ulcers dressed 3 times a week for 4 weeks with a DACC-coated dressing	Superficial infection (as assessed by NERDS or STONEES criteria), total ulcer surface area, pain	Reduction in total average surface area from 1.74cm^2 to 1.15cm^2 (p=0.337). No significant difference in superficial or deep infection rate.
HAYCOCKS 2011[18]	Case Series	19 patients (13 male) with diabetic foot ulceration up to the age of 80 years, with a total of 29 separate wounds studied	All wounds treated with a DACC-coated dressing as a wound contact layer for 4 weeks	Infection, healing, patient and clinician assessment	By study end, all 29 wounds had reduced signs of infection. 69% of wounds had reduced in size and 27.6% of wounds had healed.

Figure 2. PRISMA Flow Diagram

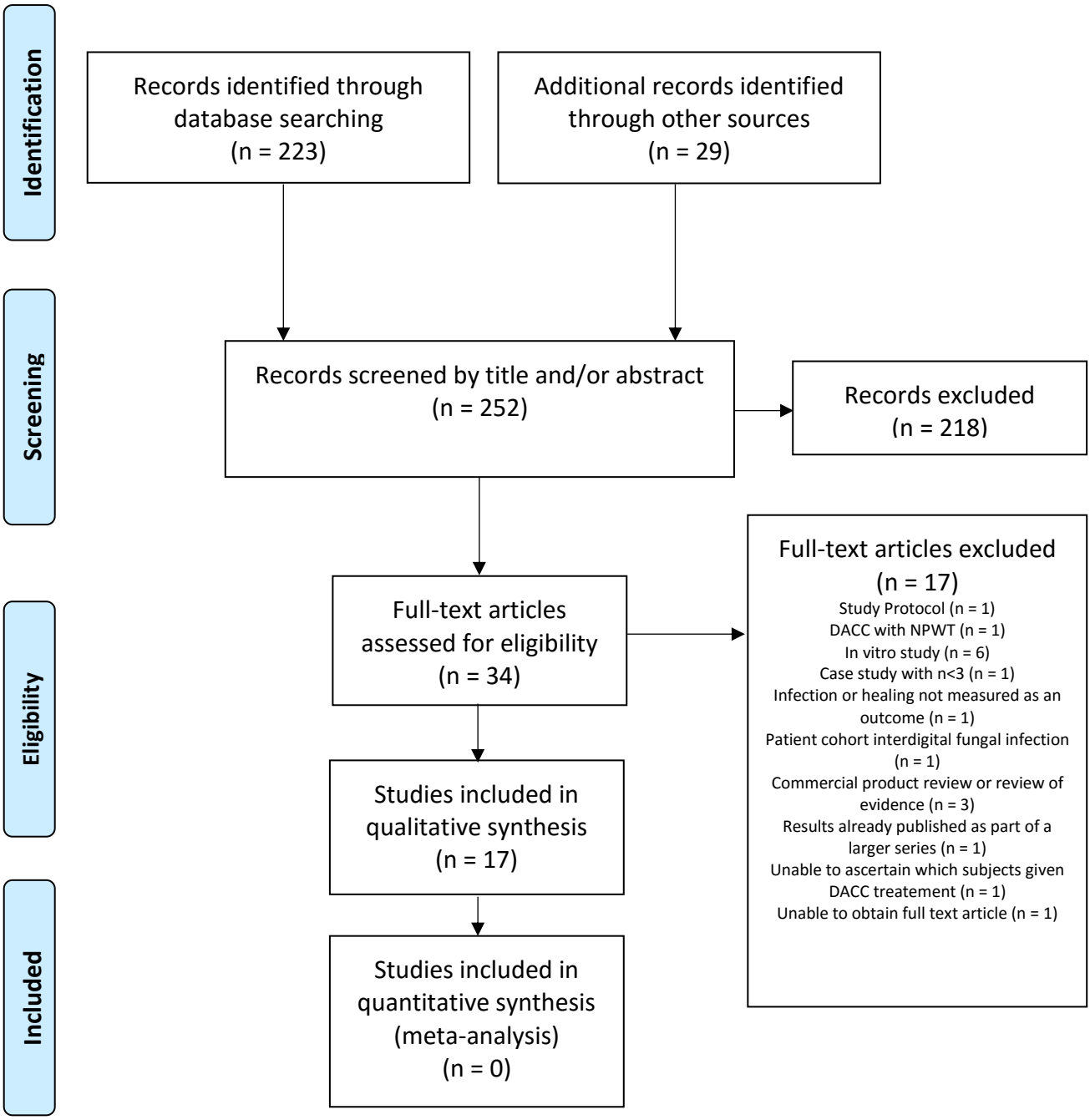

Table 3: Risk of bias assessment in the included randomised studies

Study	Random Sequence Generation (selection bias)	Allocation Concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other Bias	JADAD score
Stanirowski 2014[28]	High	High	High	Low	Low	Low	2
Stanirowski 2016[27]	High	High	High	Low	Low	Low	2
Meberg 1990[21]	High	High	High	Low	Low	Low	2
Mosti 2015[22]	Low	Low	High	Low	Low	Low	3

Table 4: Risk of bias assessment for the included cohort study

Study	Representativeness of the exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cases and controls on the basis of the design or analysis	Assessment of outcome	Adequacy of follow up of cohorts	Were co-interventions similar between groups
Kleintjes (2015)[20]	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Probably yes	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)	Definitely yes (low risk of bias)