TAKE CONTROL of the risk of infection

ACTICOAT range of dressings
Clinical evidence

smith&nephew
ACTICOAT®
Antimicrobial Barrier Dressing
Contents

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Healing in wound care is rarely achieved by one product, with wounds passing through various stages in management determined by the wound bed status at the time of assessment. In some circumstances the objective may be to manage a specific symptom of the wound, such as wound infection or exudate.

Randomised Controlled Trials (RCTs) work best if therapeutic goals can be clearly defined and a single intervention can achieve the desired endpoint (Leaper, 2009). In wound care the desired endpoint is improved wound healing however this is not necessarily achievable with a single dressing or device as highlighted above. To this end, alternative levels and types of evidence are useful to determine the ability of the dressing to manage a specific objective. This has been used, for example, to produce clinical guidelines such as those published by NICE and SIGN relating to surgical site infection and antibiotic prophylaxis (NICE, 2008) and SIGN (2008).

Across the ACTICOAT™ range there has developed a hierarchy of clinical evidence from various care settings to illustrate the impact of the ACTICOAT dressing range on the management of wound infection.

References
**Pyramid of evidence for the ACTICOAT® dressing range in - Acute Wounds**

**Level of evidence as per the SIGN guidance to classify the evidence for each silver product being presented.**

<table>
<thead>
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<td>1+</td>
<td>1 x RCT</td>
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**KEY: SIGN grading system** (http://www.sign.ac.uk/guidelines/fulltext/50/annexb.html):

Levels of evidence

1++  High quality meta analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias and a high probability that the relationship is causal

1+   Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

1 -  Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias

2++  High quality systematic reviews of case control or cohort or studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

2+   Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal

2 -  Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal

3    Non-analytic studies, e.g. case reports, case series, case studies

4    Expert opinion
Childress et al. (2007) conducted a retrospective case-control study comparing ACTICOAT Absorbent with conventional dressings (typically sterile cotton gauze) in the post-operative dressing of surgical wounds for lower extremity re-vascularisation, in a total of 117 ACTICOAT patients with 130 wounds and a total of 99 control group patients with 118 wounds. This study provided significant evidence (p=0.016) of a reduction in wound complications with ACTICOAT in comparison to conventional cotton gauze, with the overall complication rate falling by 64%. The wound complication rate was 14% (17/118) for the control group and 5% (7/130) for the ACTICOAT group. Assuming a 9% reduction in the wound complication rates, 1 wound complication would be prevented for every 11 patients treated with ACTICOAT, resulting in an estimated cost saving of $5,595 in the treatment of infection for every $110 invested in ACTICOAT dressings. This assumes the material cost of treating a patient with ACTICOAT would be $10 and the cost of treating infection $5,595.

Ozaki et al. (2015) measured surgical site complications after 30 days post-op. Wound complication rates were statistically identical between treatment groups (p=0.87) ACTICOAT Absorbent did not improve Surgical Site Complications (SSC) in this study overall, however most of these wounds (93%) were classified as clean. There was significantly lower rate of complications in a small sub-group of non-clean wounds with ACTICOAT compared to Gauze (p=0.048). Accordingly this sub-group data (7% of patients) suggest ACTICOAT Absorbent may be useful in reducing SSC in contaminated wounds, which is in alignment with the recent silver consensus document (Ayello 2012).

Management of infection and common wound pathogens

Clinical
- Management of post-cardiac surgery mediastinitis and reduction in persistently positive microbiological cultures (Totaro 2009).

In-vivo
- Faster healing and lower bioburden with ACTICOAT 7 vs PHMB (Wright et al., 2003).

*ACTICOAT 7 is not indicated in surgical incision
Bhattacharyya and Bradley (2006) successfully used Standard ACTICOAT to manage an ongoing wound infection caused by MRSA and Beta-haemolytic streptococcus following a complex knee surgery. This case study used antibiotics to successfully treat systemic infection but found them unable to resolve the persistent superficial infection at the wound site. A subsequent regime of irrigation of the wound, and application of ACTICOAT secured with OPSITE™ resulted in a reduction in exudate and appearance of healthy granulation tissue leading to complete healing with no recurrence in the infection at 3 years post-surgery follow up. The author also suggests that the continuous bactericidal activity provided by the silver dressing negated the need for frequent hospital admissions for systemic antibiotic treatment.

Bhattacharyya and Bradley (2008) report the use of ACTICOAT 7 to treat complications and wound breakdown following a knee surgery revision procedure,* to prevent localized skin necrosis due to infection, thereby avoiding skin grafting as a secondary procedure. In this case study, two patients were successfully treated with ACTICOAT 7 dressings without using systemic antimicrobials after developing methicillin-resistant Staphylococcus aureus infection in the surgical site. Successful bacterial clearance helped to reduce the spread of cutaneous infection and subsequent wound necrosis without the use of systemic antibiotics.

Totaro (2009) reported four cases of patients presenting with post-sternotomy mediastinitis. All patients were initially treated for an average of 9 days with NPWT however persistent positive wound cultures remained. Standard ACTICOAT was then used under NPWT in two patients and alone (no NPWT) in the other two cases. Following an average treatment period of 56 hours, microbiological wound cultures were negative in all patients. NPWT was then continued in 3/4 patients with subsequent wound closure surgically or with secondary closure.

Wright et al. (2003) conducted an assessment of ACTICOAT 7 against gauze dressing impregnated with polyhexamethylene biguanide (PHMB) using in-vitro and in-vivo (porcine wound models) to test antimicrobial and bactericidal efficacy respectively. Both dressings were demonstrated to have potent in-vitro bactericidal effects. However in zone of inhibition tests PHMB did not have any activity beyond its borders. The three-week in-vivo experiments demonstrated that wounds dressed with the ACTICOAT 7 dressing healed considerably faster than those dressed with the PHMB dressing and also demonstrated a lower wound bioburden.

References

*ACTICOAT 7 is not indicated in surgical incision
Pyramid of evidence for the ACTICOAT™ dressing range in - Burns

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<tr>
<td>1+ 5 x RCTs</td>
<td>Huang Y <em>et al.</em>, A randomized comparative trial between ACTICOAT and SD-Ag in the treatment of residual burn wounds, including safety analysis. Burns (2007); 33(2): 161-6.</td>
</tr>
<tr>
<td>2++ 4 x Cohort Studies</td>
<td>Cuttle L <em>et al.</em>, A retrospective cohort study of ACTICOAT versus Silvazine™ in a paediatric population. Burns (2007); 33 701-707.</td>
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<tr>
<td></td>
<td>Peters D A and Verchere C. Healing at Home: Comparing Cohorts of Children with Medium–Sized Burns Treated as Out-Patients With In-Hospital Applied ACTICOAT to Those Children Treated As In-Patients With Silver Sulfadiazine. Journal of Burn Care and Research; (2006) 27.198-201.</td>
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<tr>
<td><strong>2++</strong></td>
<td>1 x Case Control Study</td>
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<td></td>
<td>1 x Systematic Review</td>
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<td></td>
<td>Demling, R and DeSanti, M. The rate of re-epithelialization across meshed skin grafts is increased with exposure to silver. Burns (2002); 28(3): 264-6.</td>
</tr>
<tr>
<td><strong>2+</strong></td>
<td>3 x Cohort/ case control studies</td>
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<td><strong>3</strong></td>
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- **4** Expert opinion
The ACTICOAT dressing range

evidence summary - Burns

Health Economics

- Reduction in the frequency of dressing change with Standard ACTICOAT vs Silvazine™ (Cuttle et al. 2007) and Standard ACTICOAT vs Sulfamylon™-soaked EXU-DRY™ (p=0.01) (Silver et al. 2007).
- Reduction in cost of dressings (p=0.024), ancillary products (p=0.072), labour (p=0.010) and average total treatment costs (p=0.043), with Standard ACTICOAT vs Sulfamylon-soaked EXU-DRY (Silver et al. 2007). Reduction in the costs of treatment with Standard ACTICOAT vs Silvazine (Cheng et al. 2004) and (Fong et al. 2005).
- Significantly fewer patients requiring antibiotics with Standard ACTICOAT vs SSD (p=0.016) (Tonkin and Wood, 2006).

Surgical Procedures

- Fewer patients requiring debridement/graft procedures with Standard ACTICOAT vs Silvazine (p<0.001) (Cuttle et al. 2007) and Standard ACTICOAT vs SSD (p=0.03) (Peters and Verchere 2006).

Hospital Stay

- Length of hospital stay reduced with Standard ACTICOAT vs SSD (p=0.045) (Tonkin and Wood 2005), (p<0.001) (Peters and Verchere 2006).
- Strand (2010) highlighted reduced hospitalisation costs of up to 64% as a result of significantly reduced (p<0.001) length of hospital stay following the introduction of a new treatment protocol, which included Standard ACTICOAT, for paediatric burns.
- A recent review and subsequent value analysis of studies using either SSD or Standard ACTICOAT for treatment of paediatric scalds reported a 9 day reduction in mean hospital stay using Standard ACTICOAT compared to SSD. (Malic 2014)

Resource Use

Numerous studies have demonstrated the ACTICOAT dressing range to be more cost effective that Silvazine/Silver Sulfadiazine in the treatment of various types of burns.

Cuttle et al. (2007) conducted a retrospective study on paediatric burns. They audited 328 patients treated with Silvazine between January 2000 – June 2001 and compared the results with 241 patients treated with Standard ACTICOAT between July 2002 – July 2003. The authors found that ACTICOAT was only required to be changed every 3-4 days compared to the labour intensive daily bathing and dressing changes required with Silvazine. This resulted in a reduction in the cost of treatment in terms of nursing time and decreased pain medication (although this was not directly measured). The authors also found that the expenditure on pressure garments had reduced to $164,000 when the treatment regime had changed to ACTICOAT in contrast with $210,000 for when the treatment regime was Silvazine.

Cheng et al. (2004) study of 447 paediatric patients estimated the cost saving as between 21%-28% for smaller burn wounds (1%-5% TBSA) and between 15%-18% for larger burn wounds (15%-25% TBSA) with Standard ACTICOAT (241 patients) compared to Silvazine (206 patients).

Fong et al. (2005) conducted an audit comparing Standard ACTICOAT (19 patients) with Silvazine (51 patients) in patients with burns and found antibiotic usage was reduced with ACTICOAT (5.2%) compared with Silvazine (57%). In addition, in an analysis of treatment costs, 4 ACTICOAT patients were selected and matched with 4 Silvazine patients. This analysis revealed a $30,450 saving in treatment costs when comparing the costs of the 4 ACTICOAT patients ($78,907) with the 4 Silvazine ($109,357) patients, resulting in an average saving per patient for ACTICOAT (excluding antibiotics, staffing and surgery) of $7,613. The average dressing cost per patient for the ACTICOAT group was also lower ($946) compared with Silvazine ($1533).
The ACTICOAT° dressing range evidence summary - Burns

In an investigation of four periodic clinical audits comparing SSD (36 patients) with Standard ACTICOAT (36 patients), Tonkin and Wood (2006) found antibiotic usage to be significantly lower in the ACTICOAT group whereby 11.1% of patients received antibiotics in the ACTICOAT group compared with 61.1% for the SSD group (p=0.016).

Silver et al. (2007) compared Standard ACTICOAT and Sulfamylon™-soaked EXU-DRY™ in the treatment of burns patients. The authors also found that ACTICOAT patients required significantly fewer dressing changes (p=0.01). This amounted to a significant reduction in cost of dressings, (p=0.024), costs of ancillary products (p=0.072), labour costs (p=0.01) and average total treatment costs (p=0.043) which was $2343 for the ACTICOAT group compared to $3866 for the Sulfamylon-soaked EXU-DRY group.

Surgical Procedures

Cuttle et al. (2007) found that the percentage of children requiring grafting was significantly less (p<0.001) in the Standard ACTICOAT group (15.4% ACTICOAT vs 25.6% Silvazine™). Cheng et al. (2004) found that the skin graft rate was also lower with ACTICOAT (15% with ACTICOAT vs 27% with Silvazine, p=0.001).

Tonkin and Wood’s study (2006) showed 25% of Standard ACTICOAT patients had surgery in contrast to 67% of SSD patients. In addition, only 6% of ACTICOAT patients experienced a wound breakdown compared to 25% of SSD patients.

Peters and Verchere (2006) compared Standard ACTICOAT with SSD in the treatment of medium sized paediatric burns (> 20% TBSA) in 30 prospective ACTICOAT patients with 73 matched historical controls treated with SSD. They showed the mean number of debridements/graft procedures were lower for ACTICOAT compared with SSD (ACTICOAT 0.3±0.466 vs 0.54±0.65 for SSD, p=0.03).

Hospital Length of Stay

Cuttle et al. (2007) found that over the time period 2002–2003 where Standard ACTICOAT was being administered, the number of inpatient bed days in comparison to Silvazine decreased, even though the total number of new patients had increased.

Tonkin and Wood (2006) reported a significant (p=0.045) saving in the length of hospital stay required in the treatment of burns patients. The mean length of stay for Standard ACTICOAT was 8.8 days compared with 15.1 days for SSD patients.

Peters and Verchere (2006) also reported a significant reduction in the length of stay with Standard ACTICOAT in the treatment of medium-sized paediatric burn wounds (>20% TBSA) when compared to SSD. Their results showed that patients in the ACTICOAT group required a mean stay of 0.83 days compared to 13.85 days with SSD (p<0.001), amounting to a saving of 13 days.

Strand (2010) performed a retrospective case review of paediatric burns before and after implementation of a new care protocol which included Standard ACTICOAT, INTRASITE® Gel and ALLEVYN® Adhesive. Significant reductions in length of hospital stay (12.5 to 4.5 days (p<0.001)) and also reduction in antibiotic usage (70% to 25% (p<0.001)) were observed in the post protocol change group. The resulting reduction in hospitalisation costs provided a saving of up to 64% compared to the previous treatment regime.

Malic (2014) and colleagues performed a review and subsequent value analysis of studies using either SSD or Standard ACTICOAT for treatment of paediatric scalds spanning over a 25 year period. Mean time to healing was 14.9 days for ACTICOAT and 17.2 days for SSD studies. The mean duration of hospital stay was 14.9 days for SSD and 5.9 days for ACTICOAT. A potential cost saving of $43,920 (Canadian Dollars) per patient was identified when using ACTICOAT, calculated using a bottom-up microcosting model.
The ACTICOAT® dressing range evidence summary - **Burns**

### Healing

- Faster healing times with Standard ACTICOAT vs Silver Sulfadiazine (SSD) (Huang et al. 2007)
  - Saving of 3.35 days with ACTICOAT.
- Faster re-epithelialisation times with Standard ACTICOAT vs Silvazine™ (Cuttle et al. 2007)
  - Saving of 3.4 days with Standard ACTICOAT (p=0.047).
- Faster rate of wound closure with Standard ACTICOAT vs gauze dressings used with an antimicrobial solution (Demling and Desanti 2002)
  - Rate of wound closure 40% more with ACTICOAT compared with gauze/antimicrobial dressings.

A recent RCT study by Huang et al. (2007) evaluated 166 wounds in 98 burns patients comparing the clinical efficacy of Standard ACTICOAT and Silver Sulfadiazine (SSD). They found that healing time was 12.42 days for the ACTICOAT group in contrast with 15.79 days for the SSD group, resulting in a significant saving of over 3.3 days.

Cuttle et al. (2007) conducted a retrospective study of 328 paediatric patients treated with Silvazine between January 2000 - June 2001 and contrasted it with 241 patients treated with Standard ACTICOAT between July 2002 - July 2003. All patients had partial or full thickness burns. Their results showed that for patients not requiring grafting, the time to re-epithelialisation was significantly less (p=0.047) for ACTICOAT patients compared with Silvazine; ACTICOAT patients achieved a mean re-epithelialisation time of 14.9 days in contrast with 18.3 days for Silvazine, amounting to a mean saving of 3.4 days for ACTICOAT patients.

Demling and Desanti (2002) studied 20 patients with deep burn wounds (15%-40% TBSA) with meshed skin grafts, investigating the re-epithelialisation rate of Standard ACTICOAT and gauze dressings continually moistened with an antimicrobial solution (neomycin and polymyxin solution) over 10 days. Each patient presented with 2 wounds; one was treated with ACTICOAT and the other with the standard gauze dressing treatment. The authors found a significant increase in the re-epithelialisation rate for the ACTICOAT group at day 4 and day 7. This resulted in a 40% increase in the rate of re-epithelialisation for the ACTICOAT group; at the end of 7 days, 100% of wounds were closed in the ACTICOAT group in contrast with just 55±10% for the antibiotic solution.

### Management of infection

- Significantly reduced antibiotic use (p<0.001) to manage local wound infection was reported by Strand and colleagues (2010) following the introduction of a new treatment protocol, which included ACTICOAT, compared to previous treatment for paediatric burns.*

Huang et al. (2007) found the bacterial clearance rate on the 6th and 12th days after application of treatment for Standard ACTICOAT patients were significantly higher than Silver Sulfadiazine (SSD) patients (p<0.05). The clearance rates were 16.7% (day 6) and 26.7% (day 12) for the ACTICOAT group in contrast with 11.5% and 19.2% respectively for the SSD group.

Strand (2010) performed a retrospective case review of paediatric burns before and after implementation of a new care protocol which included Standard ACTICOAT, INTRASITE® Gel and ALLEVYN® Adhesive. Significant reductions in length of hospital stay (12.5 to 4.5 days (p<0.001)) and also reduction in antibiotic usage (70% to 25% (p<0.001)) were observed in the post protocol change group. The resulting reduction in hospitalisation costs provided a saving of up to 64% compared to the previous treatment regime.

* ACTICOAT is not a pharmaceutical. It should be emphasised that the dressing has a local not systemic effect.
The ACTICOAT™ dressing range
evidence summary - **Burns**

**Pain**

- Less pain during dressing change with Standard ACTICOAT vs patients treated with older silver formulations (Silver Nitrate and Silver Sulfadiazine) (p<0.001) (Gravante et al. 2009).
- Less pain on dressing removal with Standard ACTICOAT vs Silver Nitrate (p<0.05) (Tredget et al. 1998).
- Less pain during wear and on dressing removal with ACTICOAT vs Silver Sulfadiazine (SSD) (p<0.0001) (Varas et al. 2005).

In a meta analysis of the 3 RCTs (Tredget et al., 1998; Muangman et al., 2006; Varas et al., 2005) mentioned below which included 112 patients (56 ACTICOAT dressings and 56 patients treated with older silver formulations, namely Silver Nitrate and Silver Sulfadiazine) Gravante et al. (2009) found significant evidence (p<0.001) that Standard ACTICOAT patients experienced less pain than older silver formulation patients during dressing change.

An RCT conducted by Tredget et al. (1998) compared Standard ACTICOAT with gauze dressings moistened with 0.5% solution of silver nitrate in terms of patient comfort and ease of use. The authors studied 30 patients, each with 2 study wounds. Using a 10 point Visual Analogue Scale (VAS) to assess pain, they found ACTICOAT to be significantly less painful on dressing removal where a mean VAS pain score of 2.6 was recorded for ACTICOAT compared with 3.9 for the Silver Nitrate (p<0.05). The authors also observed no difference in pain up to 2 hours after dressing application.

Standard ACTICOAT has been shown to be less painful than SSD (1%) in the treatment of partial thickness burns. Muangman et al. (2006) conducted an RCT of 50 patients (25 ACTICOAT and 25 1% SSD). Using a 10 point VAS scale, the authors found the average pain score for ACTICOAT patients to be less than the SSD group (4±0.6 for ACTICOAT vs 5±0.7 for SSD).

The study showed similar results to the Varas et al. (2006) study of 14 patients. Each patient had 2 burns assessed, one randomised to Standard ACTICOAT and the other randomised to SSD. The authors compared the pain associated with dressing changes using a 10 point VAS scale. The results showed that there was less pain associated with dressing changes with ACTICOAT compared with SSD (mean pain score 3.2 for ACTICOAT vs 7.9 for SSD, p>0.0001).

**Prevention of Infection**

- Incidence of infection significantly lower (p<0.001) for Standard ACTICOAT vs older silver formations (Silver Nitrate and Silver Sulfadiazine) (Gravante et al. 2009).
- Incidence of burn wound sepsis (>10^5 organisms per gram of tissue) and secondary bacteraemia arising from wound infection less for Standard ACTICOAT vs Silver Nitrate gauze dressings (Tredget et al. 1998).
- Incidence of burn wound cellulitis lower for Standard ACTICOAT vs Silvazine™ (Fong et al. 2005).
- Less antibiotic usage with Standard ACTICOAT vs SSD (Tonkin and Wood, p=0.016), Standard ACTICOAT vs Silvazine (Fong et al. 2005) and Standard ACTICOAT vs. Mepitel™ (Strand 2010).
- Wound infections and wound colonisations developed in fewer patients with Standard ACTICOAT vs SSD (Muangman et al. 2006).
- Less complications with Standard ACTICOAT vs SSD (p=0.035) (Peters and Verchere 2006).
Gravante et al. (2009) found in a meta analysis of five RCT’s including 285 patients (105 Standard ACTICOAT patients and 180 older silver formulation patients treated with Silver Nitrate and Silver Sulfadiazine) that ACTICOAT patients had a significantly lower incidence (p<0.0001) of infection (9.5% infected) than the patients treated with older silver formulations (27.8% patients).

Tredget et al. (1998) found that the incidence of burn wound sepsis (>10^5 organisms per gram of tissue) was less for Standard ACTICOAT patients compared with patients treated with Silver Nitrate gauze dressings. The authors found burn wound sepsis in 5 out of 25 biopsies for ACTICOAT compared with 16 out of 25 biopsies for the Silver Nitrate group. Secondary bacteraemia arising from infected wounds was also less frequent in the ACTICOAT group compared with Silver Nitrate (1 vs 5 respectively, with 17 wounds in each group).

Fong et al. (2005) study of 70 patients (19 Standard ACTICOAT, 51 Silvazine™) showed a reduction in the incidence of burn wound cellulitis for ACTICOAT patients (10.5%) when compared with Silvazine patients (55%). Furthermore, the authors showed a reduction in antibiotic use for ACTICOAT patients where only 5.2% of patients required antibiotics compared with 57% of Silvazine patients. In another study, Tonkin and Wood’s (2005) study of 72 patients also saw similar results, where antibiotic usage was significantly (p=0.016) lower in the Standard ACTICOAT group where 11.1% patients received antibiotics in contrast with 61.1% of SSD patients.

Muangman et al. (2006) compared 50 patients (25 treated with Standard ACTICOAT, 25 with SSD) in terms of clinical efficacy. The authors found that fewer ACTICOAT patients developed wound colonisation compared with SSD (64% for ACTICOAT vs 88% for SSD). Furthermore, fewer ACTICOAT patients developed a wound infection (12% for ACTICOAT vs 16% for SSD).

Peters and Verchere (2006) compared 30 Standard ACTICOAT patients prospectively with 73 SSD patients retrospectively. The authors found significant evidence that fewer patients experienced complications with Standard ACTICOAT compared with SSD (where only 3.3% of ACTICOAT patients experiencing complications vs 20.5% for SSD; p=0.035).
The ACTICOAT° dressing range evidence summary - Burns

Safety

- Serum silver levels less with Standard ACTICOAT vs. maximum levels reported with Silver Sulfadiazine in small/medium (Vlachou 2007) to large (Moieman 2011)% TSBA burns.
- No association between Standard ACTICOAT use and clinical, biochemical or haematological signs of toxicity (Vlachou 2007; Moieman 2011).
- No significant differences between Standard ACTICOAT and SSD with routine blood tests, liver and renal function tests (Huang et al. 2007).
- No side effects found with Standard ACTICOAT usage (Huang et al. 2007).

Moieman et al. (2011) evaluated serum silver levels, biochemistry and haematology in 6 patients with burns greater than 20% total body surface area (TBSA) before, during and after the application of Standard ACTICOAT dressings. The median maximum serum silver level recorded, 200.3 μg/L, reached at a median of 9.5 days following initial silver dressing application. This decreased to a median of 164.8 μg/L at the end of the treatment period and to a median of 8.2 μg/L at the end of follow-up. There were no adverse events due to haematological or biochemical abnormalities. In this small study, serum silver levels were elevated but remained similar to that reported following the use of silver sulfadiazine. The authors confirmed that ACTICOAT is safe to use on patients with burns, even when they are extensive.

Vlachou et al. (2007) assessed silver levels of Standard ACTICOAT in 30 patients with skin grafts, donor sites and residual burn sites. The study showed that the levels of serum silver for ACTICOAT patients were less than the maximum level reported in literature for patients treated with Silver Sulfadiazine cream. The authors concluded that the use of ACTICOAT was not associated with clinical, biochemical or haematological signs of toxicity and was safe for treating people with burns.

Huang et al. (2007) found no significant difference between Standard ACTICOAT and SSD with routine blood tests, liver and renal function tests. Additionally, no side effects were found relevant with the use of Standard ACTICOAT.

References
### Pyramid of evidence for the ACTICOAT® dressing range in - Chronic Wounds

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| 1+                | 1 x RCT  
| 2++               | 1 x Cohort Study  
| 2+                | 2 x Case control  
| 3                 | 1 x Case series  
| 4                 | 1 x Review  

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- **2 -** Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
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- **4** Expert opinion
**The ACTICOAT dressing range evidence summary - Chronic Wounds**

### Management of infection

- ACTICOAT significantly more effective in resolving clinical signs of infection vs Aquacel™ Ag and Comfeel™/Biatain™ Silver \(p<0.05\) (Gago *et al.* 2008)
  - After 2 weeks, resolution of clinical signs of infection for 60% of Standard ACTICOAT patients vs less than 10% from Aquacel Ag and Comfeel/Biatain Silver.

- ACTICOAT 7 shown to significantly reduce \(\log_{10}\) bacterial count in a clinical setting \(p=0.011\) (Sibbald *et al.* 2007).

- Standard ACTICOAT dressings were found to provide a complete, or almost complete, barrier to the penetration/spread of MRSA in 95% of readings (Strohal *et al.* 2005)
  - 67% of all wound observations showed a decrease in the MRSA load with an eradication rate of 11%.

- ACTICOAT and IODOSORB™ were both found to effective in treatment of leg ulcers with high bioburden in a recent RCT by Miller *et al.* (2010); similar wound healing rates were reported across the 12 week study, with the exception of the initial 2 weeks where ACTICOAT had a significantly faster healing rate \(p<0.01\).

Numerous studies in the literature performed *in-vitro* and *in-vivo* provide evidence for the ACTICOAT dressing range's antimicrobial efficacy. In a clinical study of 75 patients with a mixture of venous leg ulcers (50) pressure ulcers (15), diabetic foot ulcers (7) and post-traumatic ulcers (3), Gago *et al.* (2008) found Standard ACTICOAT to be significantly \(p<0.05\) more effective than both Aquacel Ag and Comfeel/Biatain Silver in resolving clinical signs of infection. After 2 weeks, clinical signs of infection were resolved in 60% of ACTICOAT patients in contrast with less than 10% for both Aquacel Ag and Comfeel/Biatain Silver.

Sibbald *et al.* (2007) study of 15 venous leg ulcer patients treated with ACTICOAT 7 suggested that the antimicrobial efficacy of ACTICOAT is also applicable in the clinical setting. They reported a significant reduction in \(\log_{10}\) bacterial count between baseline and final biopsies \(p=0.011\). The authors commented that it was likely that the antimicrobial effects of the ACTICOAT dressings sufficiently reduced the bacterial burden for healing to begin.

Strohal *et al.* (2005) conducted a study on 7 patients with a total of ten MRSA colonised wounds. At each dressing change (after 1, 24, 48 and 72 hours), swabs were taken from the upper side of the dressing and the wound bed. None of the dressings showed heavy MRSA load (++++) breakthrough on the upper side over the 72 hour observation period. Furthermore, no bacterial penetration through the dressing was shown in seven wounds. Of the remaining three wounds, two dressings had a ++ MRSA colonisation and one wound had minor colonisation (+) of the upper side. Standard ACTICOAT dressings were found to provide a complete, or almost complete, barrier to the penetration/spread of MRSA in 95% of readings. In addition, 67% of all wound observations showed a decrease in the MRSA load with an eradication rate of 11%.

Miller *et al.* (2010) carried out a 12 week randomised control trial in 281 community patients with leg ulcers compromised by bacterial burden. They assessed the effectiveness of either ACTICOAT or IODOSORB dressings* with respect to healing rate and clinical signs of critical colonization and infection. No significant difference in the number of wounds healed between the antimicrobial treatment groups was reported; 64% from the silver group and 63% from the iodine group. Mean wound healing rates were similar for the silver and iodine groups with silver recording a marginally higher healing rate (average 2.10; SD 1.89) compared with iodine (average 1.69; SD 2.46). Further analysis of each two-weekly period showed no significant difference between the treatment groups in the overall wound healing rate in the 12 weeks, nor for any of the 2-week healing rates with the exception of the first 2 weeks where silver dressings were shown to have a significantly higher healing rate \(p<0.01\) compared to the iodine dressing.

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*The nanocrystalline silver product range included ACTICOAT, ACTICOAT Absorbent, and ACTICOAT 7. Options in the cadexomer iodine product range were IODOSORB ointment and IODOSORB powder. For brevity, these products are collectively referred to as silver and iodine in this paper. ACTICOAT Absorbent is no longer available.*
Gago et al. (2008) found that patients in the Standard ACTICOAT group healed significantly faster than both Aquacel Ag (p=0.027) and Comfeel/Biatain Silver (p=0.042) patients. At the end of 8 weeks, 56% of ACTICOAT patients had healed in contrast with 28% of Aquacel Ag and 24% of Comfeel/Biatain Silver patients.

Former-Cordero (2007) also showed Standard ACTICOAT to be efficacious in the healing of chronic lower limb lymphoedema ulcers in a study of 8 patients. All ulcers in the study were healed between 1 - 9 weeks of treatment with ACTICOAT, with a mean healing time of 26.6 days.

Miller et al. (2010) carried out a 12 week randomised control trial in 281 community patients with leg ulcers compromised by bacterial burden. They assessed the effectiveness of either ACTICOAT* or IODOSORB™ dressings* with respect to healing rate and clinical signs of critical colonization and infection. No significant difference in the number of wounds healed between the antimicrobial treatment groups was reported: 64% from the silver group and 63% from the iodine group. Mean wound healing rates were similar for the silver and iodine groups with silver recording a marginally higher healing rate (average 2.10; SD 1.89) compared with iodine (average 1.69; SD 2.46). Further analysis of each two-weekly period showed no significant difference between the treatment groups in the overall wound healing rate in the 12 weeks, nor for any of the 2-week healing rates with the exception of the first 2 weeks where silver dressings were shown to have a significantly higher healing rate p < 0.01 compared to the iodine dressing.

Sibbald et al. (2007) analysed 43 blood samples from 11 venous leg ulcer patients. Serum samples were obtained at baseline, 4 weeks, 8 weeks and final assessment. The authors found no clinically relevant changes occurred in serum silver concentrations or haematology and biochemistry results. The median silver concentration was 0.3 ng/ml at baseline (range, 0.2-1.9 ng/mL) and 0.7 ng/mL at final assessment (range, 0.2-3.1 ng/ml). All blood silver levels remained within the normal range (0-14.9 ng/ml) for all patients throughout the study.

*The nanocrystalline silver product range included ACTICOAT, ACTICOAT Absorbent, and ACTICOAT 7. Options in the cadexomer iodine product range were IODOSORB ointment and IODOSORB powder. For brevity, these products are collectively referred to as silver and iodine in this paper. ACTICOAT Absorbent is no longer available.
Combination therapy - The ACTICOAT® dressing range with Negative Pressure Wound Therapy (NPWT)

- Increasing evidence for the ACTICOAT dressing range use in combination with NPWT to manage bioburden or prevent infection in high risk wounds although higher level evidence is required.

**Clinical evidence**

A recent systematic review of the use of NPWT on incisional wounds highlighted infection as the most reported complication of these wounds (described in 9/10 studies reviewed [Ingargiola 2013]).

Evidence supporting the combined use of NPWT and the ACTICOAT dressing range is currently limited to mainly cohort/case studies or care bundle implementations across a variety of indications and range from chronic [Goldstein 2010], burns [Goldstein 2010, Psinos 2009, González 2013], surgical wounds [Hickson 2015] including sternal wounds [Keppa 2013, Agarwal 2005, Totaro 2009] or various trauma wounds [Pour 2011, Chariker 2012, Richards 2011, Belek 2010]. In addition, many of the studies identified have used this combination over dermal substitutes, flaps or grafts [Goldstein 2010, González 2013, Belek 2010] where the therapy package was reported to be useful for selected wounds that are infected and problematic.

Furthermore, co-use of PICO® system and ACTICOAT Flex has been described by [Hickson 2015]. This study described the introduction of a care bundle for Caesarean section incisions in patients with high co-morbidities, particularly in obese patients. Interventions included the introduction of rigorous pre and post-operative procedures, patient education, initiation of a low-risk dressing bundle consisting of ACTICOAT Flex under OPSITE® Post-Op Visible dressing, and finally inclusion of a high-risk package of ACTICOAT Flex in combination with PICO. These interventions were shown to reduce infection rates by 96% between 2007 and 2012.

**References**


Combination therapy - The ACTICOAT° dressing range with Negative Pressure Wound Therapy (NPWT)


## Treatment of antimicrobial resistant organisms

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Supporting citation for the ACTICOAT™ dressing range in Chronic wounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+</td>
<td>Huang, Y. et al., A randomized comparative trial between ACTICOAT and SD-Ag in the treatment of residual burn wounds, including safety analysis. Burns 33, 161–6 (2007).</td>
</tr>
</tbody>
</table>

**KEY**: SIGN grading system (http://www.sign.ac.uk/guidelines/fulltext/50/annexb.html):

- **Levels of evidence**
  - 1++: High quality meta analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias and a high probability that the relationship is causal
  - 1+: Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
  - 1 -: Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
  - 2++: High quality systematic reviews of case control or cohort or studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
  - 2+: Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
  - 2 -: Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
  - 3: Non-analytic studies, e.g. case reports, case series, case studies
  - 4: Expert opinion

*ACTICOAT 7 is not indicated in surgical incision*
• Reduction of MRSA in burn wounds (Huang 2007) and surgical wounds (Bhattacharyya 2006, 2008)** following ACTICOAT* dressing use.

• Newton and colleagues (2010) describe implementation of a care bundle which included ACTICOAT* and aseptic no-touch technique leading to a reduction in MRSA associated bacteraemia (wound origin).

• Reduced need for antibiotic therapy to manage local wound infection was reported in surgical wounds with ACTICOAT 7 (Bhattacharyya 2008)** and burns with Standard ACTICOAT (Huang 2007, Strand 2010), although further more controlled studies would be required to confirm this.

A recent review suggests that the clinical emergence of resistance to silver can be minimized if the level of silver ions released from products is high and bactericidal activity is rapid (Chopra 2007). Clinical evidence to support use of Standard ACTICOAT against resistant organisms is increasing; (Huang et al., 2007) performed a randomized controlled trial (RCT) of Standard ACTICOAT treatment compared to silver sulphadiazine cream (SSD) on residual burn wounds, primarily to investigate the effectiveness of each treatment. However, on analysis of bacteria in the wound throughout the 12 week treatment period, both the ACTICOAT and SSD treatment showed that those colonised with MRSA initially became 100% clear of this organism. Interestingly, the clearance rate of this antibiotic resistant organism was found to be higher by 6 days of treatment for the ACTICOAT group versus the SSD treatment (33% and 20% respectively). Furthermore, patients at risk of delayed healing and untreated local infection could progress to systemic sepsis; this was highlighted by Newton (2010) who reported the benefit of ACTICOAT dressings* as part of a strategic treatment plan to reduce the number of MRSA infected wounds progressing to MRSA bacteraemias.

MRSA has also been implicated in the recurrent infection and delayed healing in an orthopaedic revision wound (Bhattacharyya 2006). This case study used antibiotics to successfully treat systemic infection but found them unable to resolve the persistent superficial infection at the wound site. Subsequent management of the wound infection with Standard ACTICOAT silver dressings allowed progression to healing. At 3 years follow up no deep infection was observed in this patient. The author also suggests that the continuous bactericidal activity provided by the silver dressing negated the need for frequent hospital admissions for systemic antibiotic treatment.

Additional case studies by (Bhattacharyya 2008)** further support the use of ACTICOAT 7 silver dressings to treat MRSA where wounds had broken down following orthopaedic revision surgery. Successful bacterial clearance helped to reduce the spread of cutaneous infection and subsequent wound necrosis. This was achieved without the use of systemic antibiotics.

A reduction in antibiotic usage and was also attributed to introduction of Standard ACTICOAT dressings into a paediatric burns unit in Sweden (Strand 2010). This retrospective study demonstrated a reduction in the number of patients requiring antibiotics from 70% to 25% (p<0.001) between 2001 and 2007 combined with a significant reduced length of stay (12.5 to 4.5 days (p<0.001)) following the new protocol introduction. Similar findings were reported by Tonkin (2005) following a clinical audit of burns patients comparing wound dressing regimes using SSD or Standard ACTICOAT. A 50% reduction in antibiotic use (p=0.016) was reported with ACTICOAT dressings compared to SSD in addition to a significant reduction in hospital length of stay (15.1 and 8.8 days for SSD and ACTICOAT respectively, p=0.045).

*The dressing used was standard ACTICOAT, ACTICOAT 7 and ACTICOAT Absorbent. ACTICOAT Absorbent is no longer available.

**ACTICOAT 7 is not indicated in surgical incision
References


Huang, Y. et al. (2007). A randomized comparative trial between ACTICOAT™ and SD-Ag in the treatment of residual burn wounds, including safety analysis. Burns 33, 161–6.


TAKE CONTROL
of the risk of infection

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