WALDNER
TECNOLOGIE MEDICALI

Spett.le
**Agenzia Intercent-ER**
Via dei Mille, 21
40121 Bologna

Trento, 25 gennaio 2018

**Oggetto:** Offerta Nr. **181400160**
*Rif. da citare in qualsiasi comunicazione relativa alla presente offerta*

PROCEDURA APERTA PER LA FORNITURA DI MATERIALE DA MEDICAZIONE AVANZATA 2

**LOTTO N. 27 - CIG N. 7275284A46**

OFFERTA
**TECNICA**

WALDNER
TECNOLOGIE MEDICALI

## ELENCO DELLA DOCUMENTAZIONE PRESENTATA

A) Scheda tecnica;

B) Certificato CE e Dichiarazione di conformità;

C) Dichiarazione Latex Free;

D) Brochure;

E) Relazione di Servizio Post Vendita e Formazione;

F) Studi clinici.

Systagenix
An Acelity Company

Acelity

# SCHEDA TECNICA
# SILVERCEL™

<table>
<tr><td>CATEGORIA</td><td>Medicazione antisettica</td></tr>
<tr><td>DESCRIZIONE</td><td>Medicazione a base d'idroalginato con argento</td></tr>
<tr><td>COMPOSIZIONE e CARATTERISTICHE</td><td>La medicazione SILVERCEL™ presenta la seguente composizione:<br>• 60% fibre di alginato di calcio e carbossimetilcellulosa (51% alginato di calcio ricco di acido guluronico, 9% CMC)<br>• 40% fibre di argento tecnologia X-Static ( nylon 32% e argento 8% di cui l'1% di ossido di argento ed il 99% di argento metallico )<br><br>Svolge azione antisettica ad ampio spettro attraverso il rilascio di argento. Rilascia argento in maniera bilanciata e controllata, a livelli battericidi per il tempo di permanenza in situ della medicazione. Non colora il fondo della lesione. Crea un ambiente umido ideale per la guarigione della ferita favorendo la proliferazione cellulare. Assorbe verticalmente elevate quantità di essudato minimizzando la macerazione. Non si sfalda a contatto con l'essudato ma rimane integro e compatto, garantendo una rimozione sicura e facile. Può essere ritagliato. Si adatta alla forma ed alla misura della ferita. È adatto per lesioni sia superficiali che profonde e sottominate.</td></tr>
<tr><td>CAPACITÁ DI ASSORBIMENTO (ABS)</td><td>28g/g<br>21,61 g/100cm$^2$/0.5hrs<br>23,31 g/100cm$^2$/1 hrs</td></tr>
<tr><td>CAPACITÁ ed AZIONE ANTIBATTERICA</td><td>Rapida Efficacia antimicrobica contro più di 150 microorganismi isolati clinicamente compresi ceppi antibiotico resistenti quali MRSA,VRE,MRSE. Il rilascio degli ioni argento è controllato, bilanciato, prolungato ed efficace. L'eventuale combinazione con garza grassa vaselinata non inficia l'efficacia antibatterica.</td></tr>
<tr><td>FORMATI</td><td><table><tr><th>CODICE</th><th>DIMESIONI</th></tr><tr><td>CAD050</td><td>cm 5 x cm 5</td></tr><tr><td>CAD011</td><td>cm 11 x cm 11</td></tr><tr><td>CAD020</td><td>cm 10 x cm 20</td></tr><tr><td>CAD230</td><td>cm 2, 5 x cm 30, 5</td></tr></table></td></tr>
<tr><td>SPESSSORE</td><td>+/- 1,5 mm</td></tr>
<tr><td>DITTA PRODUTTRICE</td><td>Advanced Medical Solutions Group Ltd, UK</td></tr>
<tr><td>CLASSE DI APPARTENENZA</td><td>Secondo la Direttiva CE 93/42; Classe III, CND M04040802 NID 460045/R</td></tr>
<tr><td>MARCHIO CE</td><td>70851</td></tr>
<tr><td>DESTINAZIONE D'USO</td><td>SILVERCEL™ e' indicato per la gestione di tutte le lesioni croniche infette o fortemente</td></tr>
</table>

| | |
|---|---|
| | colonizzate, superficiali o cavitarie, con una quantità di essudato elevata. Tali lesioni includono Idd, lesioni vascolari, lesioni diabetiche, siti donatori, lesioni chirurgiche e traumatiche. |
| **MECCANISMO D'AZIONE** | L'idroalginato, grazie alla sua composizione consente:<br>• **Assorbimento e gestione degli essudati elevati:** l'idroalginato assorbe elevate quantità di essudato tipiche delle lesioni infette, minimizzando la macerazione e creando un gel che mantiene l'ambiente umido per favorire la proliferazione cellulare. Le fibre di alginato gelificano e non rilasciano l'essudato che hanno assorbito<br>• **Incrementata resistenza alla trazione in ambiente umido**: grazie all'acido guluronico, SILVERCEL™ aumenta notevolmente la resistenza alla trazione in ambiente umido (+56% rispetto ad asciutto): quando inumidita si modifica in un gel fibroso, che rimane **compatto, integro e di facile rimozione, non si sfalda a contatto con gli essudati e non traumatizza il tessuto alla rimozione**. Le eventuali fibre di alginato di calcio, che potrebbero rimanere in situ, vengono facilmente asportate con un semplice lavaggio con soluzione fisiologica.<br>**Le fibre di Nylon rivestite di Argento (tecnologia X-Static)** consentono:<br>• **Azione antisettica rapida e ad ampio spettro:** il rilascio di ioni di argento contrasta ed abbatte la carica batterica, riducendo l'infezione. Dimostrata rapida efficacia antimicrobica in vitro e ampio spettro di azione (>150 microorganismi umani testati isolati clinicamente) anche verso ceppi antibiotico-resistenti isolati clinicamente (MRSA, VRE, MRSE).<br>• **Rilascio di Argento bilanciato, controllato e prolungato:** Grazie all'esclusiva tecnologia X-Static™ e alla riserva di argento elementare di SILVERCEL™, viene garantito un rilascio di ioni argento efficace a livello battericida, bilanciato, controllato in base alle necessità della lesione e prolungato, fino a 7 giorni garantendo l'attività antimicrobica efficace per la riduzione dell'infezione per un tempo longevo, e consentendo la riduzione al minimo della frequenza dei cambi di medicazione. |
| **MODALITA' D'USO** | **APPLICAZIONE:** lavare con soluzione fisiologica la lesione e tamponarla, assicurandosi che la cute perilesionale sia asciutta. Scegliere la misura e il formato di medicazione che è più adatta alla ferita.Applicare direttamente sul letto della ferita conformandola alle dimensioni della lesione.<br>**RIMOZIONE della MEDICAZIONE:** rimuovere delicatamente il prodotto che si è gelificato a contatto con l'essudato |
| **TEMPO DI APPLICAZIONE** | Può rimanere in situ fino a 7 giorni. |
| **COMPATIBILITA'** | È compatibile con tutti i prodotti della linea medicazioni avanzate della Systagenix Wound Management. |
| **STERILIZZAZIONE** | Sterilizzato con radiazioni. Non risterilizzabile |
| **CONFEZIONAMENTO** | 1° Confezionamento - Busta sterile<br>2° Confezionamento - Scatola di cartone<br>3° Confezionamento – Scatola di cartone |
| **ETICHETTATURA** | Sul confezionamento vengono riportate tutte le informazioni previste al punto 13 allegato 1 Direttiva CE 93/42 Dlgs 46/97. |

<table>
<tr><td>CONFEZIONE DI VENDITA</td><td>
<table>
<tr><th>CODICE</th><th>Misure</th><th>Confezionamento primario</th><th>Confezionamento secondario</th><th>Confezionamento terziario</th></tr>
<tr><td>CAD050</td><td>cm 5 x cm 5</td><td>singolo pezzo</td><td>10 pezzi</td><td>5 scatole (50 pezzi)</td></tr>
<tr><td>CAD011</td><td>cm 11 x cm 11</td><td>singolo pezzo</td><td>10 pezzi</td><td>5 scatole (50 pezzi)</td></tr>
<tr><td>CAD020</td><td>cm 10 x cm 20</td><td>singolo pezzo</td><td>5 pezzi</td><td>5 scatole (25 pezzi)</td></tr>
<tr><td>CAD230</td><td>cm 2,5 x cm 30,5</td><td>singolo pezzo</td><td>5 pezzi</td><td>5 scatole (25 pezzi)</td></tr>
</table>
</td></tr>
<tr><td>LATTICE</td><td>Il prodotto non contiene costituenti in lattice.</td></tr>
<tr><td>PRODUZIONE</td><td>La medicazione SILVERCEL™ viene prodotta negli stabilimenti della Advanced Medical Solutions Group Ltd. (Uk) certificati a norma ISO/EN 13485:2003 dalla BSI British Standard Institution. Detti sistemi di Qualità richiedono controlli di qualità per materie prime, intermedi, e prodotti finiti, sia dal punto di vista chimico-fisico che biologico.</td></tr>
<tr><td>CONTROLLI</td><td>Ogni lotto di parti componenti viene ispezionato prima che ciascun componente venga accettato per la produzione. Il singolo prodotto finito è sottoposto a ispezioni visive e, ove applicabile, automatizzate di carattere dimensionale, fisico, biologico e chimico. Viene effettuata una prova di corretto funzionamento prima del confezionamento e della sterilizzazione. Detto prodotto è stato preventivamente sottoposto ai test di allergenicità e tossicità prima dell'immissione sul mercato.</td></tr>
<tr><td>CONSERVAZIONE</td><td>Conservare a temperatura inferiore a 25°C.</td></tr>
<tr><td>VALIDITA'</td><td>2 anni</td></tr>
</table>

bsi.

By Royal Charter

# EC Design-Examination Certificate

Directive 93/42/EEC on Medical Devices, Annex II Section 4

**No.** **CE 70851**

Issued To: **Advanced Medical Solutions Ltd**
**Premier Park**
**33 Road One**
**Winsford Industrial Estate**
**Winsford**
**Cheshire**
**CW7 3RT**
**United Kingdom**

In respect of:

**Hydro-Alginate Antimicrobial Wound Dressing with Silver**

BSI has performed a design examination on the above devices in accordance with the Council Directive 93/42/EEC, Annex II Section 4. The design conforms to the requirements of this directive. For marketing of these products an additional Annex II excluding Section 4 certificate is required.

For and on behalf of BSI, a Notified Body for the above Directive (Notified Body Number 0086):

Frank Lee, EMEA Compliance & Risk Director

First Issued: **28 January 2005** Date: **24 April 2015** Expiry Date: **27 January 2020**

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bsi.

By Royal Charter

# EC Design-Examination Certificate

**Supplementary Information to CE 70851**

Issued To:

**Advanced Medical Solutions Ltd**
**Premier Park**
**33 Road One**
**Winsford Industrial Estate**
**Winsford**
**Cheshire**
**CW7 3RT**
**United Kingdom**

**Hydro-Alginate Antimicrobial Wound Dressing with Silver**

**Brand Name:**

| | |
|---|---|
| **SILVERCEL** | Hydro-Alginate Antimicrobial Dressing/Packing with Silver |
| **SILVERCEL** | Non-Adherent Hydro-Alginate Antimicrobial Dressing/Packing with Silver |
| **RELEASE Ag** | Non-Adherent Hydro-Alginate Antimicrobial Dressing with Silver |

| |
|---|
| Flat Felt Dressings to a maximum size of 200cm$^2$ |
| Rope Dressings to a maximum size of 77cm$^2$ |

| Dressing type | Size (cm) | Area (cm$^2$) |
|---|---|---|
| Flat | 5 x 5 | 25 |
| Flat | 11 x 11 | 121 |
| Flat | 10 x 20 | 200 |
| Rope | 2.5 x 30.5 | 76.25 |

First Issued: **28 January 2005** Date: **24 April 2015** Expiry Date: **27 January 2020**

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By Royal Charter

# EC Design-Examination Certificate

**Supplementary Information to CE 70851**

Issued To:

**Advanced Medical Solutions Ltd**
**Premier Park**
**33 Road One**
**Winsford Industrial Estate**
**Winsford**
**Cheshire**
**CW7 3RT**
**United Kingdom**

## Certificate History

| Date | Reference Number | Action |
|---|---|---|
| 28 January 2005 | 10043943 | First issue |
| 16 December 2005 | 10075428 | Change from brand name to product name as brand names are specific to the market where the product is sold |
| 23 November 2006 | 10081761 | Amendment to Indications |
| 21 October 2009 | 10101149 | Packaging specification change; addition of Non-Adherent variant; IFU changes; supplementary information updated to include brand names and new variants |
| 19 March 2010 | 10113547 | Certificate renewal |
| 20 April 2010 | 10114122 | Addition of new packaging line at Premier Park manufacturing facility |
| 29 July 2011 | 10124073 | Addition of new spinning and carding lines at Premier Park manufacturing facility. Change of manufacturer address to Premier Park |

First Issued: **28 January 2005** Date: **24 April 2015** Expiry Date: **27 January 2020**

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# EC Design-Examination Certificate

**Supplementary Information to CE 70851**

Issued To:

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**33 Road One**
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**Winsford**
**Cheshire**
**CW7 3RT**
**United Kingdom**

## Certificate History

| Date | Reference Number | Action |
|---|---|---|
| 11 October 2012 | 10135782 | Change in EMA film raw material resin from LOTRYL 14MGC02 (Skymed 600 EMA film) to LOTRYL 18MA02 resin (Skymed 601 EMA film) for non-adherent variants; removal of Release Ag Hydro-Alginate Antimicrobial Dressing with Silver from certificate |
| 23 January 2015 | 10152003 | Certificate renewal |
| 24 April 2015 | 10155177 | Addition of new MultiVac packing machine for rope variant |

First Issued: **28 January 2005** Date: **24 April 2015** Expiry Date: **27 January 2020**

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Advanced Medical Solutions Ltd
Premier Park, 33 Road One
Winsford Industrial Estate
Cheshire. CW7 3RT. UK
**Tel :** +44 (0)1606 863500 **Fax :** +44 (0)1606 545669
**Web** : www.admedsol.com
Registered in England 2666957

DD01-003, rev.04

# EC DECLARATION OF CONFORMITY

## IN RELATION TO HYDRO-ALGINATE ANTIMICROBIAL WOUND DRESSING WITH SILVER (DESIGN DOSSIER 01)

Advanced Medical Solutions Ltd. (Premier Park, 33 Road One, Winsford Industrial Estate, Winsford, Cheshire, CW7 3RT, United Kingdom) declares that the Class III medical devices manufactured by Advanced Medical Solutions and described hereafter as

| Product Name | Size (cm) | AMS Product Code (*previous code*) | Systagenix Product Code |
|---|---|---|---|
| SILVERCEL® Non-Adherent Hydro-Alginate Antimicrobial Dressing with Silver | 5 x 5 | 10012456 *(10010785)* | CAD7050 |
| SILVERCEL® Non-Adherent Hydro-Alginate Antimicrobial Dressing with Silver | 11 x 11 | 10012457 *(10010786)* | CAD7011 |
| SILVERCEL® Non-Adherent Hydro-Alginate Antimicrobial Dressing with Silver | 10 x 20 | 10012458 *(10010787)* | CAD7020 |
| SILVERCEL® Non-Adherent Hydro-Alginate Antimicrobial Packing with Silver | 2.5 x 30.5 | 10012475 *(10010788)* | CAD7230 |
| SILVERCEL® Non-Adherent Hydro-Alginate Antimicrobial Dressing with Silver | 11 x 11 | 10012380 | CAD7011P3 |
| SILVERCEL® Non-Adherent Hydro-Alginate Antimicrobial Packing with Silver | 10 x 20 | 10012381 | CAD7020P3 |
| RELEASE® Ag Non-Adherent Hydro-Alginate Antimicrobial Dressing with Silver | 11 x 11 | 10009638 | DAC711FH |
| RELEASE® Ag Non-Adherent Hydro-Alginate Antimicrobial Dressing with Silver | 10 x 20 | 10009639 | DAC720FH |
| RELEASE® Ag Non-Adherent Hydro-Alginate Antimicrobial Dressing with Silver | 11 x 11 | 10009640 | DAC711F |
| RELEASE® Ag Non-Adherent Hydro-Alginate Antimicrobial Dressing with Silver | 10 x 20 | 10009641 | DAC720F |
| RELEASE® Ag Non-Adherent Hydro-Alginate Antimicrobial Dressing with Silver | 11 x 11 | 10010250 | DAC011E |
| RELEASE® Ag Non-Adherent Hydro-Alginate Antimicrobial Dressing with Silver | 10 x 20 | 10010251 | DAC020E |
| SILVERCEL® Hydro-Alginate Antimicrobial Dressing with Silver | 5 x 5 | 10012464 *(10010793)* | CAD050 |
| SILVERCEL® Hydro-Alginate Antimicrobial Dressing with Silver | 11 x 11 | 10012464 *(10010794)* | CAD011 |
| SILVERCEL® Hydro-Alginate Antimicrobial Dressing with Silver | 11 x 11 | 10011992 | CAD011DE |
| SILVERCEL® Hydro-Alginate Antimicrobial Dressing with Silver | 10 x 20 | 10012466 *(10010795)* | CAD020 |
| SILVERCEL® Hydro-Alginate Antimicrobial Packing with Silver | 2.5 x 30.5 | 10012467 *(10010796)* | CAD230 |
| SILVERCEL® Hydro-Alginate Antimicrobial Packing with Silver | 2.5 x 30.5 | 10011993 | CAD230DE |



**CONFIDENTIAL**

Certificate No. MD78010

Advanced Medical Solutions Ltd
Premier Park, 33 Road One
Winsford Industrial Estate
Cheshire. CW7 3RT. UK
**Tel :** +44 (0)1606 863500 **Fax :** +44 (0)1606 545669
**Web** : www.admedsol.com
Registered in England 2666957

are in conformity with the essential requirements and provisions of Council Directive 93/42/EEC (Medical Devices Directive) amended by Directive 2007/47/EC, as transposed into UK Regulations (Statutory Instrument 2002 No. 618 and Statutory Instrument 2012 No. 1426) subject to and in conformity with the applicable provisions of Annex II (including Section 4), Full Quality Assurance Certificate (CE 01699) and EC Design Examination certificate (CE 70851), under the supervision of our Notified Body the British Standards Institution (0086).

Standards Applied: Refer to relevant section of Design Dossier 01 (DD01).

Issued in Winsford, UK.

Rose Guang
Quality Assurance and Regulatory Affairs Director

26 January 2015
Date



**CONFIDENTIAL**

Certificate No. MD78010

WALDNER
TECNOLOGIE MEDICALI

Spett.le
**Agenzia Intercent-ER**
Via dei Mille, 21
40121 Bologna

Trento, 25 gennaio 2018

**Oggetto: Gara per la fornitura di materiale da medicazione avanzata 2.**
**Allegato offerta nr. 181400160 – Lotti 2 – 22 – 24 – 27 – 28 – 30 – 31 – 33 – 39.**

**ARTICOLO 6 DEL DISCIPLINARE DI GARA "*OFFERTA TECNICA*" – PAGINA 19**

Il sottoscritto Giuseppe Waldner, nato a Borgo Valsugana (TN) il 12.06.1966 e residente a Trento (TN) in Via Eremo nr. 22, in qualità di Amministratore Unico della Società **Waldner Tecnologie Medicali S.r.l. a Socio Unico (facente parte di Gruppo Waldner)** con Sede Legale in Verona (VR), Via Sabotino, 2/C e Sede Amministrativa in Trento (TN), Via della Cooperazione 149, P.IVA e C.F. 01542210222, codice attività 46.46.3, nr. tel. 0461/949898, nr. fax 0461/942108, e-mail: woundcare@waldner.co, Pec: commerciale@pec.waldner.co

*Consapevole delle sanzioni penali in caso di dichiarazioni false e della conseguente decadenza dei benefici eventualmente conseguiti (ai sensi degli artt. 75 e 76 del D.P.R. 28 dicembre 2000, n. 445) sotto la propria responsabilità*

**DICHIARA**

- Ai fini della partecipazione alla presente procedura, che la traduzione di seguito allegata è conforme all'originale.

In fede,

**Waldner Tecnologie Medicali S.r.l. a Socio Unico**

WALDNER
Giuseppe Waldner
Amministratore Unico
Waldner Tecnologie Medicali S.r.l., a Socio Unico
**Sede Legale:** Via Sabotino, 2/C - 37124 Verona
**Sede Operativa:** Via della Cooperazione, 149 - 38123 Trento
Cod. Fisc. e Part. IVA: 01542210222

CERTIFICATO EC-DESIGN EXAMINATION

NUMERO CE 70851

EMESSO IN FAVORE DI: Advanced Medical Solutions Limited
Premier Park
33 Road One
Winsford Industrial Estate
Winsford
Cheshire
CW7 3RT
United Kingdom

Relativo a:

Hydro-Alginate Antimicrobial Wound Dressing with Silver

BSI ha eseguito una valutazione della progettazione sul dispositvo sopra secondo le norme della direttiva 93/42 / CEE, allegato II, punto 4. Il design è conforme ai requisiti della presente direttiva. Per la commercializzazione di questi prodotti è necessario un ulteriore certificato relativo all allegato II con l'esclusione della sezione 4.

In nome e per conto di BSI, ente notificato per la direttiva di cui sopra (Numbero 0086)

Prima emissione: 28 gennaio 2005
Data: 24 aprile 2015
Scadenza: 27 gennaio 2020

Informazioni supplementari a CE 70851

EMESSO IN FAVORE DI: Advanced Medical Solutions Limited
Premier Park
33 Road One
Winsford Industrial Estate
Winsford
Cheshire
CW7 3RT
United Kingdom

Hydro-Alginate Antimicrobial Wound Dressing with Silver

Nome del Brand:
SILVERCEL Hydro-Alginate Antimicrobial Dressing/Packing with Silver
SILVERCEL Non-Adherent Hydro-Alginate Antimicrobial Dressing/Packing with Silver
RELEASE Ag Non-Adherent Hydro-Alginate Antimicrobial Dressing with Silver

| Tipo di medicazione | Dimensione | Area |
|---|---|---|
| Piatta | 5x5 | 25 |
| Piatta | 11x11 | 121 |
| Piatta | 10x20 | 200 |
| Rope | 2.5x30.5 | 76.25 |

Prima emissione: 28 gennaio 2005
Data: 24 aprile 2015
Scadenza: 27 gennaio 2020

EC DECLARATION OF CONFORMITY

In relazione al prodotto HYDRO-ALGINATE ANTIMICROBIAL WOUND DRESSING WITH SILVER

(DESIGN DOSSIER O1)

Advanced Medical Solutions Ltd. (Premier Park, 33 Strada One, Winsford Industrial Estate, Winsford, Cheshire, CW7 3RT, Regno Unito) dichiara che i dispositivi medici di classe III prodotti da Advanced Medical Solutions e descritto qui di seguito:

| Product Name | Size (cm) | AMS Product Code (*previous code*) | Systagenix Product Code |
|---|---|---|---|
| SILVERCEL® Non-Adherent Hydro-Alginate Antimicrobial Dressing with Silver | 5 x 5 | 10012456 *(10010785)* | CAD7050 |
| SILVERCEL® Non-Adherent Hydro-Alginate Antimicrobial Dressing with Silver | 11 x 11 | 10012457 *(10010786)* | CAD7011 |
| SILVERCEL® Non-Adherent Hydro-Alginate Antimicrobial Dressing with Silver | 10 x 20 | 10012458 *(10010787)* | CAD7020 |
| SILVERCEL® Non-Adherent Hydro-Alginate Antimicrobial Packing with Silver | 2.5 x 30.5 | 10012475 *(10010788)* | CAD7230 |
| SILVERCEL® Non-Adherent Hydro-Alginate Antimicrobial Dressing with Silver | 11 x 11 | 10012380 | CAD7011P3 |
| SILVERCEL® Non-Adherent Hydro-Alginate Antimicrobial Packing with Silver | 10 x 20 | 10012381 | CAD7020P3 |
| RELEASE® Ag Non-Adherent Hydro-Alginate Antimicrobial Dressing with Silver | 11 x 11 | 10009638 | DAC711FH |
| RELEASE® Ag Non-Adherent Hydro-Alginate Antimicrobial Dressing with Silver | 10 x 20 | 10009639 | DAC720FH |
| RELEASE® Ag Non-Adherent Hydro-Alginate Antimicrobial Dressing with Silver | 11 x 11 | 10009640 | DAC711F |
| RELEASE® Ag Non-Adherent Hydro-Alginate Antimicrobial Dressing with Silver | 10 x 20 | 10009641 | DAC720F |
| RELEASE® Ag Non-Adherent Hydro-Alginate Antimicrobial Dressing with Silver | 11 x 11 | 10010250 | DAC011E |
| RELEASE® Ag Non-Adherent Hydro-Alginate Antimicrobial Dressing with Silver | 10 x 20 | 10010251 | DAC020E |
| SILVERCEL® Hydro-Alginate Antimicrobial Dressing with Silver | 5 x 5 | 10012464 *(10010793)* | CAD050 |
| SILVERCEL® Hydro-Alginate Antimicrobial Dressing with Silver | 11 x 11 | 10012464 *(10010794)* | CAD011 |
| SILVERCEL® Hydro-Alginate Antimicrobial Dressing with Silver | 11 x 11 | 10011992 | CAD011DE |
| SILVERCEL® Hydro-Alginate Antimicrobial Dressing with Silver | 10 x 20 | 10012466 *(10010795)* | CAD020 |
| SILVERCEL® Hydro-Alginate Antimicrobial Packing with Silver | 2.5 x 30.5 | 10012467 *(10010796)* | CAD230 |
| SILVERCEL® Hydro-Alginate Antimicrobial Packing with Silver | 2.5 x 30.5 | 10011993 | CAD230DE |

sono conformi ai requisiti essenziali e alle disposizioni della direttiva 93/42 / CEE (Direttiva sui Dispositivi Medici) modificata dalla direttiva 2007/47 / CE, come recepita nella normativa del Regno Unito

(Statutory Instrument 2002 N0. 618 e Statutory Instrument 2012 Numero 1426 ) nel rispetto e in conformità con le disposizioni dell'allegato II(inclusa la sezione 4), Full Quality Assurance Certificate (CE01699) e delcertificato EC Design Examination (CE70851) sotto la supervisione del nostro Organismo Notificato British Standards Institution (0086).

Spett.le
**Agenzia Intercent-ER**
Via dei Mille, 21
40121 Bologna

Trento, 25 gennaio 2018

**Oggetto: Gara per la fornitura di materiale da medicazione avanzata 2.**
**Allegato offerta nr. 181400160 – Lotti 2 – 22 – 24 – 27 – 28 – 30 – 31 – 33 – 39.**

**DICHIARAZIONE "*LATEX FREE*"**

Il sottoscritto Giuseppe Waldner, nato a Borgo Valsugana (TN) il 12.06.1966 e residente a Trento (TN) in Via Eremo nr. 22, in qualità di Amministratore Unico della Società **Waldner Tecnologie Medicali S.r.l. a Socio Unico (facente parte di Gruppo Waldner)** con Sede Legale in Verona (VR), Via Sabotino, 2/C e Sede Amministrativa in Trento (TN), Via della Cooperazione 149, P.IVA e C.F. 01542210222, codice attività 46.46.3, nr. tel. 0461/949898, nr. fax 0461/942108, e-mail: woundcare@waldner.co, Pec: commerciale@pec.waldner.co

**COMUNICA**

- Che la caratteristica relativa all'assenza di lattice è riportata all'interno delle schede tecniche dei prodotti offerti e all'interno dell'apposita dichiarazione allegata.

In fede,

**Waldner Tecnologie Medicali S.r.l. a Socio Unico**

Giuseppe Waldner
Amministratore Unico

Waldner Tecnologie Medicali S.r.l. a Socio Unico
Sede Legale: Via Sabotino, 2/C - 37124 Verona
Sede Operativa: Via della Cooperazione, 149 - 38123 Trento
Cod. Fisc. e Part. IVA: 01542210222

An Acelity Company

Milano, 25 novembre 2016

C.A. a chi di competenza

Oggetto: Dichiarazione Latex Free prodotti Systagenix

Il sottoscritto Maingonnat Franck nato a Thiais Francia il 16/12/1972, residente per la carica a Milano Viale Enrico Forlanini, 21 edificio 23, in qualità di Amministratore Delegato della ditta KCI Medical s.r.l. con sede in Milano Viale Enrico Forlanini, 21 edificio 23 n° tel. 0271098034 n° fax 0271098020 con codice fiscale n. 10804870151 e con partita I.V.A. n. 10804870151,

Ai sensi del D.P.R. 445/2000
DICHIARA

Che l'unico prodotto conosciuto che contiene gomma di lattice naturale nel dispositivo o nel confezionamento è DYNAFLEX® Multi-Layer Compression System.
Tutti i prodotti commercializzati da Systagenix Wound Management Ltd. Subiscono una revisione sistematica dei loro materiali costituenti e del confezionamento. Questa revisione ha richiesto di ottenere informazioni dai fornitori quando necessario.
Il risultato della revisione ha portato alla conclusione che i prodotti ed il relativo confezionamento dei prodotti elencati sotto non sono fabbricati con gomma di lattice naturale.
Questa dichiarazione è in linea con le attuali linee guida in ambito regolatorio.
L'elenco sotto è corretto al momento in cui si scrive e sarà aggiornato non appena ulteriori informazioni saranno rese disponibili.

- ACTISORB® Plus 25 Activated Charcoal Dressing with Silver
- ACTISORB® Silver 220 Activated Charcoal Dressing with Silver
- ACTISORB® Silver 220 Antimicrobial Binding Dressing
- ACTISORB® Activated Charcoal Dressing
- ACTISORB® SILBERFREI Activated Charcoal Dressing
- ADAPTIC® Non-Adhering Dressing
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- ADAPTIC TOUCH® Non-Adhering Silicone Dressing
- BIOCLUSIVE® PLUS Transparent Film Dressing
- BIOCLUSIVE® Select Transparent Dressing

An Acelity Company

- BIOCLUSIVE® Transparent Dressing
- FIBRACOL® Plus Collagen Wound Dressing with Alginate
- INADINE® PVP-I Non Adherent Dressing
- N-A® Knitted Viscose Primary Dressing
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- PROMOGRAN PRISMA® Wound Balancing Matrix
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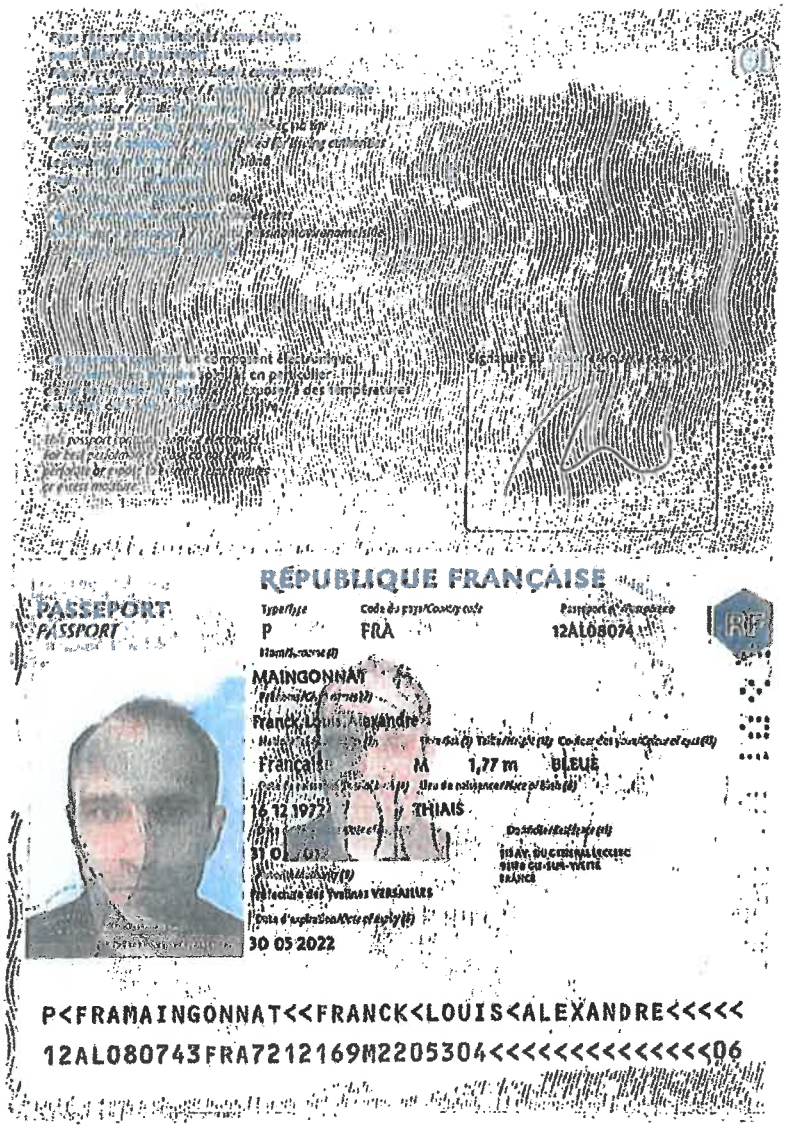
- REGAL® Filmated Dressing Swabs
- RELEASE® Non-Adherent Absorbent Dressing
- RELEASE® CONTROL Reinforced Alginate Dressing
- SOFNET® Medical Cleaning Swabs
- TIELLE® All Codes
- TOPPER® Swabs
- TOPPER® Xtra Swabs All codes (conosciuto comes SURGIPAD®)

In fede,

KCI Medical S.r.l
Patrick Mainsonnat
Legale Rappresentante

Acelity

KCI Medical srl -- Viale Enrico Forlanini 21, Edificio 23, 20134 Milano
tel: + 39 (0) 2 71098034 | fax + 39 (0) 71098017 www.acelity.com



RÉPUBLIQUE FRANÇAISE

PASSEPORT
PASSPORT

Type/Type: P
Code du pays/Country code: FRA
Passeport n°/Passport No: 12AL08074

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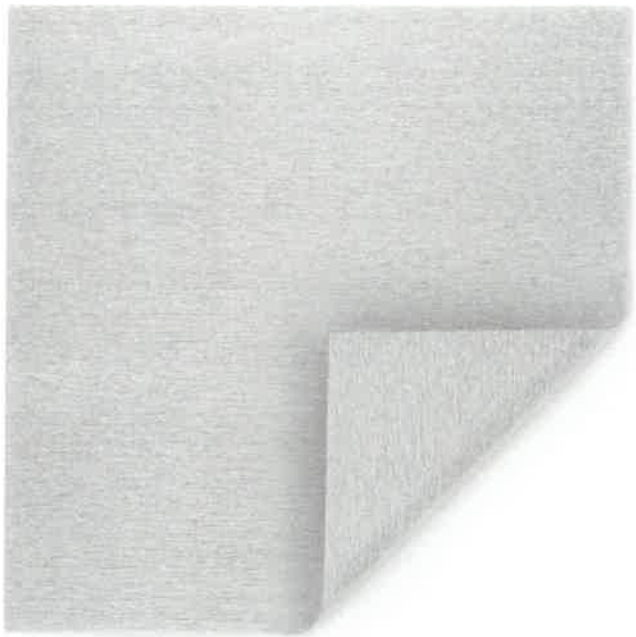
# EFFICACIA
# ANTISETTICA PROLUNGATA



## SILVERCEL®

Acelity

Systagenix
An Acelity Company

www.systagenix.it

## COS' E'?

SILVERCEL® è una medicazione antisettica composta da alginato di calcio ad elevata percentuale di acido guluronico, Carbossimetilcellulosa (CMC) e fibre in nylon con rivestimento di argento.

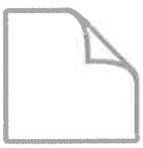
## COME AGISCE?

Grazie all'ottimale gestione dell'essudato ed all'azione antisettica prolungata SILVERCEL® è una medicazione ideale per il trattamento delle ulcere croniche[1-3].

### Gestione dell'essudato

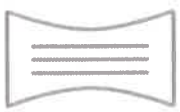
La composizione unica di SILVERCEL® consente la gestione di livelli di essudato da moderato ad abbondante, creando un ambiente ottimale per la guarigione della lesione.

**Gestione efficace dell'essudato** anche sotto compressione[3,4]



Rimozione integra della medicazione

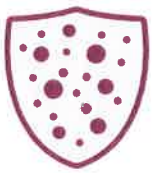
Minimizza il rischio di macerazione[5,6]



Maggiore resistenza alla trazione (+56%) in ambiente umido[5]

### Azione Antisettica

Capacità antimicrobica controllata prolungata ed efficace:

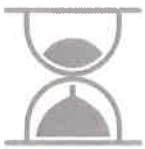


150+

**Protezione efficace** contro più di 150 agenti patogeni[7,8] tra cui:

- MRSA
- MRSE
- VRE
- Pseudomonas aeruginosa
- Escherichia Coli
- Streptococcus pyogenes
- Klebsiella pneumoniae
- Candida albicans


Rilascio prolungato di ioni d'argento fino a 7 giorni (14 giorni *in vitro*)[5,7]



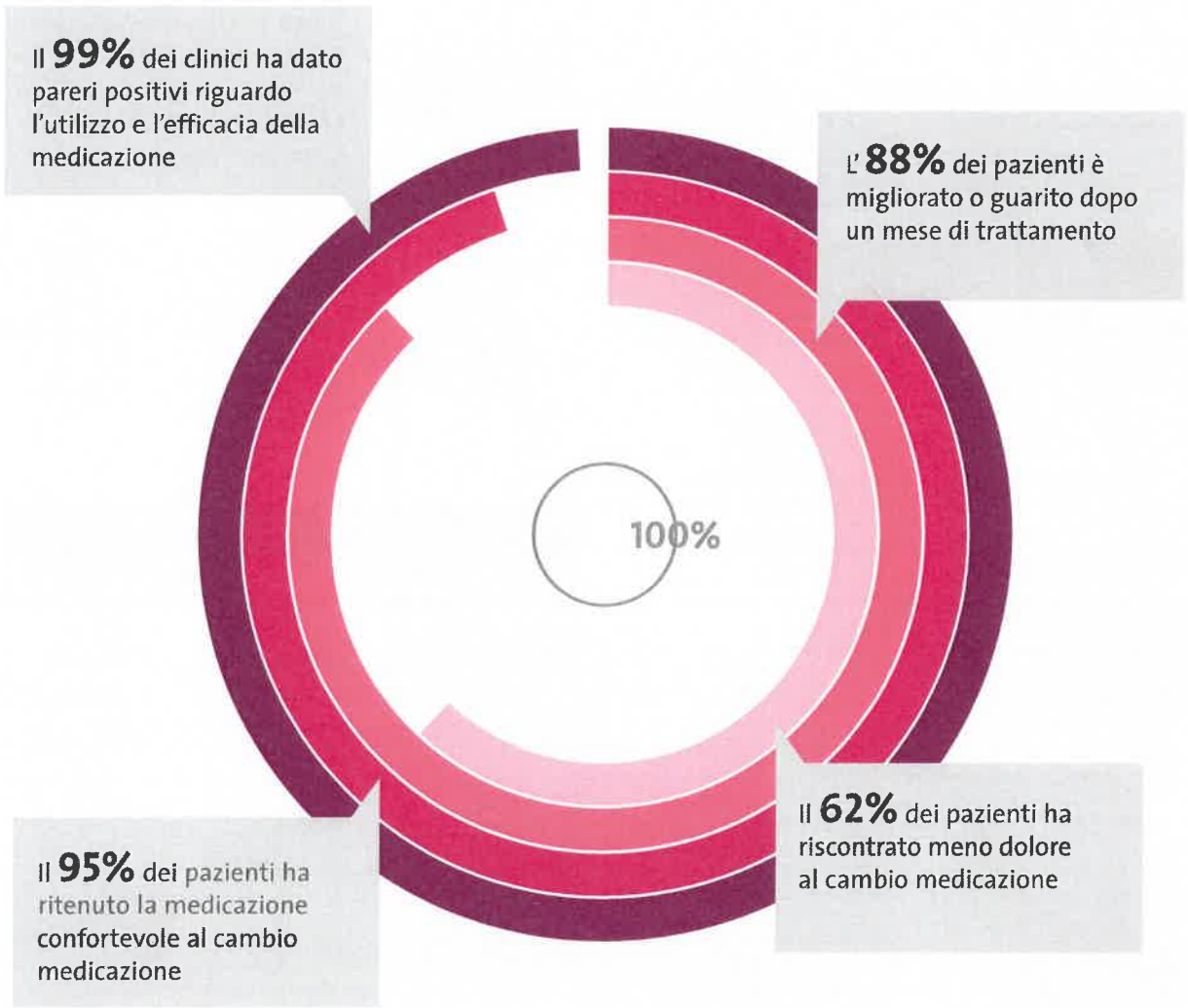
Protezione antisettica continua durante la permanenza in situ della medicazione, in funzione del livello di essudato[3,8]

## Evidenze Cliniche

Studio *in vivo*[9]:

- In presenza di livelli elevati di essudato, SILVERCEL® ha mostrato integrità e resistenza meccanica alla rimozione
- SILVERCEL® è significativamente più efficace di Aquacel Ag nella gestione dell'essudato
- Le ulcere trattate con Aquacel Ag evidenziano una maggiore presenza di residui di medicazione che generano maggiori reazioni e discontinuità tessutali

Studio multicentrico - Case study[10]:



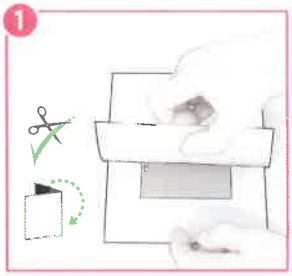

I dati sono supportati anche da uno studio RCT[11].

# MODALITA' D'USO

## PRIMA DELL'APPLICAZIONE

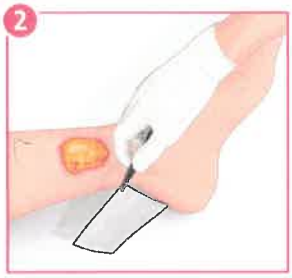
Fare riferimento al foglietto illustrativo per le istruzioni complete. Scegliere un formato di SILVERCEL® che sia leggermente più grande della dimensione della lesione. Detergere la lesione secondo i protocolli standard di trattamento. Assicurarsi che la cute circostante la ferita sia asciutta.

### Preparazione della medicazione




1. Rimuovere delicatamente la medicazione dalla confezione.
2. Se necessario tagliare o piegare **SILVERCEL®** in funzione della forma e dimensione della lesione.

### Applicazione della medicazione




1. Per lesioni cavitarie zaffare la medicazione assicurandosi che non debordi dai margini della lesione.
2. Con il migliorare delle condizioni della lesione e la riduzione dell'essudato, inumidire la medicazione con soluzione fisiologica prima di applicarla.

### Applicazione della medicazione secondaria


1. Applicare sopra **SILVERCEL®** una medicazione secondaria non occlusiva, ad esempio una schiuma di poliuretano **TIELLE®**.

### Cambio e rimozione della medicazione


1. Riapplicare **SILVERCEL®** quando la medicazione secondaria è satura o quando si ritiene opportuno un cambio medicazione
2. Rimuovere delicatamente la medicazione secondaria. Se la lesione appare asciutta, irrigare la medicazione con soluzione fisiologica prima di procedere alla rimozione.
3. Rimuovere **SILVERCEL®** dal letto della ferita e detergere la lesione prima di eseguire una nuova medicazione.

# QUANDO SI USA

SILVERCEL® è indicata nel trattamento di tutte le lesioni acute e croniche infette con essudato da moderato ad elevato, a tutto spessore o a spessore parziale, tra cui:

- Piaghe da decubito
- Ulcere vascolari
- Ulcere diabetiche
- Siti donatori di innesto, lesioni traumatiche e chirurgiche

La presenza di alginato di calcio nella medicazione può facilitare il controllo del sanguinamento nelle ferite.

SILVERCEL® può essere utilizzato sotto bendaggio compressivo[5] ed è efficace sia asciutto che preventivamente bagnato con soluzione fisiologica[6]

Uno studio clinico ha dimostrato che SILVERCEL® è efficace anche nel trattamento di ustioni gravi, gestendo sia l'essudato che il sanguinamento e creando un ambiente umido ottimale per la guarigione[7]

| SILVERCEL® | | |
|---|---|---|
| Misura | Confezionamento | Codice |
| 5cm x 5cm | 5 scatole da 10 pz | CAD050 |
| 11cm x 11cm | 5 scatole da 10 pz | CAD011 |
| 10cm x 20cm | 5 scatole da 5 pz | CAD020 |
| 2.5cm x 30.5cm | 5 scatole da 5 pz | CAD230 |


Per saperne di più sui benefici della medicazione SILVERCEL®, potete contattare il vostro Product Specialist Systagenix di zona o visitare il sito internet www.systagenix.it


References

1. Ieot, L et al. The management of wounds using SILVERCEL™ Hydro-Alginate. Wounds UK Supplement 2005; 1(2). 2. Addison, D et al. An Antimicrobial Dressing for moderate to heavily exuding infected and critically colonised wounds. Poster, EWMA 2003. 3. Addison D et al. Evaluation of the Antimicrobial Properties, Silver Release Profile & Absorbency Characteristics of an Antimicrobial Silver Hydro-Alginate Wound Dressing. Poster, 2005 (In vitro). 4. Kennison, T et al. Simulated In-Use Tests to Evaluate an Elemental Silver Hydro-Alginate Wound Dressing. Poster, ETRS 2006 (In vitro). 5. Stephens, S et al. Evaluation of an Elemental Silver Hydro-Alginate Wound Dressing. Poster, 2007. 6. Addison, D et al. SILVERCEL Alginate: A new silver dressing. Poster, WUWHS 2004. 7. Di Leonardo A et al. The use of Silvercel 1st-dress excision wounds following burns surgery. Wounds UK 2006; Vol 2(4):122-124.

WALDNER
TECNOLOGIE MEDICALI

*Servizio*

# POST VENDITA

*e*

*Proposta*

# FORMATIVA

*Linea prodotti: SYSTAGENIX*

## LA NOSTRA AZIENDA

*Waldner Tecnologie Medicali* si pone come obiettivo primario quello di rispondere alle diverse esigenze dei propri Clienti fornendo soluzioni tecnologicamente quanto più evolute per il settore.

Ci impegniamo a garantire un servizio che possa supportare con la propria presenza e l'alta qualità dei servizi offerti tutti i Clienti e i Partner che fanno parte del nostro network. Lavoriamo, ogni giorno, con il massimo impegno e rispetto a fianco di chi, come noi, ambisce agli standard più elevati.

L'attuale struttura della *Waldner Tecnologie Medicali* è in grado di garantire le dimensioni, l'organizzazione e la copertura globale necessarie per soddisfare pienamente le esigenze di un mercato in continua evoluzione come la Sanità.

UN **SERVIZIO** COMPLETO

UNA **PRESENZA** CAPILLARE

UN **INGRANAGGIO** SINERGICO

UN **TEAM** INTEGRATO


- TRENTINO ALTO-ADIGE
- VENETO
- FRIULI-VENEZIA GIULIA
- EMILIA-ROMAGNA
- TOSCANA
- MARCHE
- LOMBARDIA
- PIEMONTE
- VALLE D'AOSTA
- LIGURIA

**SEDE UFFICI**

*VERONA - via Sabotino, 2/C - 37124*

*TRENTO - via della Cooperazione, 149 – 38123*

Per maggiori info

**www.waldner.co**

## LE NOSTRA SPECIALITÀ

*Waldner Tecnologie Medicali* offre un servizio specializzato e completo che ricopre le principali specialità ospedaliere:


## LA BUSINESS UNIT "WOUND CARE"

Il *Team Wound Care* offre una vasta gamma di soluzioni per la cura delle ferite. Il portfolio prodotti comprende dispositivi e apparecchiature per la guarigione di ferite acute, croniche, di origine incisionale fino alla medicina rigenerativa con prodotti per la chirurgia della parete addominale e la chirurgia ricostruttiva.

I prodotti trattati sono nello specifico

- *Terapia a Pressione Negativa - KCI Medical*
- *Medicazioni tradizionali ed avanzate - Systagenix*

## Ufficio Back Office e Forza Vendita dedicata

La Business Unit Wound Care vanta un Ufficio Back-Office dedicato incaricato di rispondere alle singole esigenze dei Clienti e una Forza Vendita capillare sul territorio.

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*e-mail* woundcare@waldner.co

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|---|---|---|
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## Approvvigionamento e Logistica

Il Magazzino è sede di stoccaggio di materiale di consumo, nonché di nuove apparecchiature, strumentari e muletti.

**Tempi di consegna:**
Per merce presente a magazzino, i tempi di consegna sono di 5 giorni lavorativi dalla comunicazione dell'ordine, e, in casi eccezionali di estrema urgenza di 48 ore solari dal ricevimento dell'ordine.
Per merce non disponibile, si stima la consegna di quanto ordinato entro 10 (dieci) giorni lavorativi dalla data dell'ordine e, comunque, ci si impegna, nel caso di impossibilità di consegna del materiale richiesto, di darne comunicazione al Servizio ordinante.

**Controlli merce:**
I controlli in entrata e in uscita della merce sono rappresentati da:

- *verifica integrità imballo*
- *verifica integrità prodotto*
- *verifica data di scadenza*
- *verifica presenza marchio CE*
- *verifica codice e quantità*
- *rintracciabilità del prodotto tramite numero del lotto*

Il Magazzino garantisce il proprio servizio in orario d'ufficio **dal lunedì al venerdì dalle ore 08.00 alle ore 18.00** ai seguenti recapiti:

*Telefono* 0461 949898 – *Fax* 0461 942108
*e-mail* magazzino@waldner.co

## Tracciabilità di Lotto/Numero di Serie

*Waldner Tecnologie Medicali* è dotata di un ERP che consente la tracciabilità di lotto/numero di serie all'interno di tutti i processi aziendali, sia nel ciclo attivo (DDT, fattura, reso merce da Cliente, nota di credito), sia nel ciclo passivo (fattura fornitore, reso merce a fornitore).

Il Sistema Gestionale traccia i prodotti dall'ingresso in azienda alla loro uscita attraverso un Terminale RFID che li identifica in maniera puntuale e univoca applicando il relativo lotto o numero di serie. L'informazione è riportata nei documenti; in tal modo i Dispositivi Medici sono sempre identificabili.

La garanzia di tracciabilità offerta da Waldner Tecnologie Medicali facilita la gestione delle movimentazioni, agevola l'amministrazione dei magazzini propri e di quelli dei Clienti (esempio: realizzazione inventari) e offre uno strumento di tutela in casi particolari, come possono essere i Recall.

## Conservazione del prodotto

*Waldner Tecnologie Medicali* tratta e conserva i prodotti, secondo le specifiche del fornitore, in spazi opportunatamente protetti e ottimizzati. La mappatura degli stessi agevola il controllo capillare di ogni fase di processo, dall'accettazione delle merci allo stoccaggio fino all'uscita, e garantisce una rapida evasione degli ordini.

Qualora esistano particolari modalità di conservazione (temperatura controllata, riparo dalla luce, ecc.), *Waldner Tecnologie Medicali* dispone di spazi adeguati ed è dotata dei necessari dispositivi.

## *Gestione Recall*

*Waldner Tecnologie Medicali* è particolarmente attenta al tema della vigilanza per i dispositivi medici, considerando fondamentale il principio del Sistema di Vigilanza internazionale: *migliorare la protezione della salute e della sicurezza dei pazienti, utilizzatori e terzi, mediante la riduzione della probabilità che lo stesso tipo di incidente si ripeta in presenza di altre circostanze.*

*Waldner Tecnologie Medicali* prevede una Procedura Gestione Reclami nel rispetto delle normative vigenti e secondo gli standard ISO 9001, atta a valutare l'incidente segnalato, trasmettere rapidamente i dati al Fabbricante e facilitare il chiarimento delle possibili cause e l'applicazione delle eventuali azioni correttive.

In caso di Recall segnalati dal Fornitore *Waldner Tecnologie Medicali* agisce per quanto di propria competenza, secondo i termini di legge e seguendo le indicazioni del Fabbricante, sui Clienti interessati a supporto delle azioni intraprese dal Fabbricante stesso: ritiro di un Dispositivo, o sua modifica o sostituzione o distruzione, il tutto a carico del Fornitore.

## Formazione tecnico scientifica

In uno scenario che muta rapidamente, *Waldner Tecnologie Medicali* si impegna costantemente nel dedicare tempo e risorse all'aggiornamento professionale dei Medici e del Personale sanitario e non.

Per questo offriamo a *Dirigenti, Medici, Capo Sala, Infermieri, Tecnici, Farmacisti, Responsabili amministrativi e Ingegneri clinici* l'opportunità di partecipare a programmi scientifici nazionali e internazionali, con personale docente altamente qualificato, e a eventi formativi promossi e organizzati direttamente da *Waldner Tecnologie Medicali.*

Di seguito un format standard sulla base del quale ogni singolo corso viene studiato sulle specifiche esigenze del Cliente, analizzando il contesto operativo rispetto alla tematica formativa.

### TARGET

***DIRIGENTI, MEDICI, CAPO SALA, INFERMIERI, TECNICI, FARMACISTI, RESPONSABILI AMMINISTRATIVI***

### TIPOLOGIA DI EVENTI FORMATIVI

***CONGRESSI SCIENTIFICI, CORSI TEORICI, WORKSHOP, WORKSHOP IN REPARTO***

*Esempio Corso* **PERSONALE MEDICO E INFERMIERISTICO**

***Programma BASE***

- OBIETTIVO:
  I partecipanti a fine sessione saranno in grado di valutare una ferita, scegliere la medicazione più appropriata da applicare in base alla tipologia di lesione, valutare il tempo di cambio della medicazione stessa.

- CONTENUTI TEORICI

  Principi base, illustrazione delle principali caratteristiche di ciascun tipo di medicazione, linee guida aggiornate. Inoltre al termine del corso sarà distribuito materiale didattico/bibliografico a supporto di quanto esposto.

- SESSIONE WORKSHOP

  Analisi casi clinici, prova pratica di utilizzo delle medicazioni.

- SESSIONE FORMATIVA IN AMBULATORIO/REPARTO
  Su richiesta e autorizzazione della Direzione Sanitaria delle Aziende si garantisce la presenza in Ambulatorio di un Product Specialist altamente specializzato a disposizione per assistenza tecnica durante gli interventi, sia in occasione della prima medicazione, sia nei successivi follow-up, a scopo formativo e non pratico, con esclusione di qualsiasi tipo di partecipazione attiva all'attività.

- VALUTAZIONE
  Al termine della formazione sarà proposto un questionario di valutazione per verificare il livello

di preparazione raggiunto ed eventuali argomenti da approfondire. Infine, a ogni corso, potrà essere rilasciato un attestato di partecipazione.

***Programma AVANZATO***

Basato sul format BASIC, il corso analizza le casistiche più complesse, mettendo a disposizione l'ampia gamma di letteratura scientifica esistente. Attraverso un confronto interattivo con i partecipanti, saranno identificare le idonee soluzioni e approcci. Gli operatori, inoltre, potranno servirsi della preparazione del Personale Docente per la definizione di *Protocolli* da osservare nella gestione delle ferite.

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La responsabilità sociale è parte del nostro modo di essere impresa. Siamo impegnati a promuovere sostenibilità e innovazione, prestando attenzione alla qualità della vita in Azienda e agli standard di lavoro, offrendo un servizio snello ed efficace per il Paziente.
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Da sempre l'Azienda presidia, con particolare attenzione, le aree di rischio per i propri Collaboratori in termini di sicurezza sul lavoro e prevenzione degli infortuni. Si garantisce, pertanto, l'adeguata formazione allo scopo di aumentare la consapevolezza di ogni Livello e al contempo accrescere la tutela delle Risorse. Nel 2015 è stato modificato il DVR introducendo rischi anche se latenti a tutela del Collaboratore. Sottostando al Decreto legislativo 231/2001, l'Azienda si è imposta protocolli rigidi che sono soggetti a continuo presidio da parte di personale altamente qualificato.

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**Agenzia Intercent-ER**
Via dei Mille, 21
40121 Bologna

Trento, 25 gennaio 2018

**Oggetto: Gara per la fornitura di materiale da medicazione avanzata 2.**
**Allegato offerta nr. 181400160 – Lotti 2 – 22 – 24 – 27 – 28 – 30 – 31 – 33 – 39.**

**DISCIPLINARE DI GARA – SEZIONE 9.1 *"MODALITA' DI ATTRIBUZIONE DEL PUNTEGGIO TECNICO"* - CRITERIO DI VALUTAZIONE *"AZIONE ANTIBATTERICA RISPETTO AI TEMPI DI AZIONE DEL PRODOTTO"***

Il sottoscritto Giuseppe Waldner, nato a Borgo Valsugana (TN) il 12.06.1966 e residente a Trento (TN) in Via Eremo nr. 22, in qualità di Amministratore Unico della Società **Waldner Tecnologie Medicali S.r.l. a Socio Unico (facente parte di Gruppo Waldner)** con Sede Legale in Verona (VR), Via Sabotino, 2/C e Sede Amministrativa in Trento (TN), Via della Cooperazione 149, P.IVA e C.F. 01542210222, codice attività 46.46.3, nr. tel. 0461/949898, nr. fax 0461/942108, e-mail: woundcare@waldner.co, Pec: commerciale@pec.waldner.co

**ALLEGA**

- Ai fini della partecipazione alla presente procedura, gli studi clinici a supporto della valutazione dell'azione antibatterica rispetto ai tempi di azione del prodotto.

In fede,

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# Evaluation of two absorbent silver dressings in a porcine partial-thickness excisional wound model


• **Objective:** To investigate and compare the performance of two widely used silver-containing, fibre-based dressings (Silvercel and Aquacel Ag) in terms of exudate management, wound-site adherence, dressing integrity, retention of dressing debris within wounds, frequency of debris-associated foreign body reactions and the impact of both debris and tissue reactions on wound-tissue integrity.

• **Method:** The dressings were evaluated in a porcine partial-thickness exudating wound model (an *in vivo* model of moderate to high exudation up to post-wounding day 4, and low exudation from days 4 to 7). Dressing performance was assessed using a panel of semi-quantitative scales. Wound-exudate retention, dressing structure following exposure to exudate, and adherence to wound tissues were compared macroscopically; the extent of trapped dressing debris, any ensuing tissue reactions and the level of resulting tissue disruption were compared histologically.

• **Results:** Silvercel was found to be significantly more effective in terms of wound exudate management than Aquacel Ag. On exposure to high levels of wound exudate, Silvercel retained its shape and mechanical strength, and remained at the site of application. In contrast, Aquacel Ag formed a fluid (semi-fibrous) gel, with minimal mechanical integrity and variable retention at the wound site. Silvercel was significantly more adherent to wound tissues than Aquacel Ag, but the level of trapped dressing debris, the frequency of ensuing foreign body reactions and the level of consequent wound-tissue disruption was lower, although not statistically, in the Silvercel-treated wounds.

• **Conclusion:** These results suggest that the potential adverse clinical consequences of unmanaged wound exudate may be less likely in Silvercel than Aquacel Ag-treated wounds. In addition, the adverse effects of dressing adherence may be less likely in Aquacel Ag-treated wounds, although such benefits may be negated by the potentially deleterious effects of elevated dressing debris deposition. In view of these findings, further development of absorbent fibre-based dressings should be directed at maximising exudate management, minimising dressing adherence and preventing dressing-debris entrapment.



• **Declaration of interest:** This study was funded by Johnson & Johnson Wound Management. Cica Biomedical is an independent contract research company, and neither author has any interest in the sponsor's commercial activities.

*in vivo* study; exudate management; dressing adherence; dressing debris; foreign body reactions


Silver-containing, fibre-based, absorbent dressings are widely used in the management of exuding infected wounds and those at risk of infection.[1-3] While *in vitro* laboratory studies have investigated and compared certain clinically relevant dressing characteristics, such as bactericidal activity, silver release and fluid handling,[4] other equally important characteristics have been largely overlooked.

Anecdotal reports from clinicians concerning excessive adherence of certain silver-containing, fibre-based dressings, and the retention of dressing fibres on the wound surface after dressing removal, have highlighted the need for further experimental investigation of the performance of such dressings in an appropriate, clinically relevant, test system.

Excessive adherence of dressing materials to wound and marginal tissues is associated with patient discomfort on dressing removal, and may in extreme circumstances cause localised tissue damage, especially to particularly fragile tissues.[5] To minimise the likelihood of these adverse effects, pre-clinical investigation of dressing adherence, under test conditions that most closely approximate to the clinical wound setting, should be undertaken as a matter of course.

Fibre-based dressings have the propensity to inadvertently introduce dressing debris into wound tissues.[6-8] As the presence of foreign materials, such as trapped dressing fibres, within wounds has the potential to delay resolution of inflammation and adversely affect healing,[6,9-12] it is important that the level of fibre entrapment and any resulting detrimental effects are fully determined, and dressings reformulated as required.


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Information from studies in animal models is central to our understanding of the wound-repair process. Such studies have been invaluable in developing and validating a range of highly effective wound management strategies[13] and screening out inappropriate therapies.[14]

Of all the animal species available to biomedical research, the pig is widely accepted as the most appropriate for wound-healing studies, reflecting the close correlation in outcomes between porcine wound-healing investigations and subsequent clinical studies.[15] Previous work by others supports the use of porcine wound models to evaluate absorbent dressings in terms of wound-fluid management, dressing adherence and the histological determination of dressing debris entrapment within wound tissues.[6,9,11,16-19] Porcine partial-thickness wounds produce moderate to high levels of exudate during the first four days post-injury and become less exudative thereafter, paralleling the range of wound exudation observed in the clinical setting. This characteristic allows dressing performance to be evaluated under a range of wound exudate levels.

In this study the porcine partial-thickness exudating wound model was used to investigate and compare two widely used silver-containing, fibre-based, absorbent dressings, Silvercel (Johnson & Johnson Medical, UK) and Aquacel Ag (ConvaTec, UK), in terms of wound exudate management and adherence to the wound site. The deposition of dressing debris (fibres), cellular/tissue reactions to that debris and the impact of those reactions on wound-tissue integrity were also examined in histological sections of both Silvercel and Aquacel-Ag treated wounds.

## Materials and method

### Dressings

Silvercel is a hydroalginate dressing containing silver (8% w/w); the hydroalginate component is a high-content guluronic acid calcium alginate combined with carboxymethyl cellulose. Aquacel Ag is a sodium carboxymethyl cellulose Hydrofiber dressing with silver (1.2% w/w).

Both dressings were provided to the investigators in a blinded (coded) sterile form by the study sponsor, who removed them from their packaging, cut them into 2.5 x 2.5cm squares and individually packaged and coded them under sterile conditions.

### Animals and husbandry

Four young Yorkshire large white pigs (30–35kg) were used. The animals were housed and maintained at an ambient temperature of 18–24°C, with 12-hour light/dark cycles. They were fed once daily with standard pig diet and provided with water *ad libitum*. Before experimentation, they were housed for seven days with minimal disturbance to allow them to acclimatise to their surroundings. Each animal was clearly marked with an identification code using a permanent marker.

The general health and well-being of the animals were monitored in accordance with Home Office guidelines at least twice daily during their stay in the facility. They were continually monitored after each anaesthetic episode until full recovery.

All *in vivo* procedures were undertaken by appropriately experienced and Home Office-licensed individuals, and were overseen by a veterinary officer experienced in the care of large animals.

### Anaesthetics, analgesics and antibiotics

Animals were fasted for 12 hours before each anaesthetic episode, but were given free access to drinking water during this period.

The pigs were sedated using a pre-med consisting of azaperone (Stresnil) (2mg/kg intramuscularly), midazolam (Hypnovel) (0.3mg/kg intramuscularly) and atropine sulphate (Atrocare) (40µg/kg intramuscularly). General anaesthesia was then induced using 2% xylizine (Rompun) (1mg/kg intramuscularly) and ketamine (Ketaset) (15mg/kg intramuscularly), and maintained using isoflourane (1.5%) and oxygen. Animals under anaesthesia were given eye protection in the form of chlortetracycline (Aureomycin).

On the day of surgery the antibiotic amoxycillin (Amoxypen LA) (1.5mg/kg intramuscularly) was given. Local anaesthetic (bupivacaine HCl, Marcaine 0.5%) was administered before wounding, with 1–2ml injected around each wound margin. Analgesics in the form of buprenorphine (Vetergesic) (0.01mg/kg intramuscularly) and carprofen (Rimadyl) (2–4mg/kg subcutaneously) were given immediately post-wounding and on post-wounding day 1 (and at other times according to perceived clinical need).

### Creation of standardised experimental wounds

Under anaesthesia, hair on the back and flanks of the animals was removed with clippers and safety razor, and the area thoroughly cleansed with an aseptic cleanser (5% chlorhexidine).

Areas to be wounded were then swabbed with 70% alcohol. Anatomically similar sites, located parallel to and approximately 10cm from the spine, were marked on the skin (sites over the fore and hind limbs were excluded to limit any effects of skin flexure on dressing performance).

At each site a single 2 x 2cm partial-thickness excisional wound (0.6mm deep) was created using a dermatome (Zimmer, Ohio, US). Any overt bleeding post-wounding was stemmed using sterile gauze pads and light pressure.

After injury, wounds were irrigated with sterile physiological saline and carefully swabbed dry with sterile gauze to remove any tissue debris and blood.

**Fig 1. The five-point semi-quantitative scale used to assess the level of free exudate on the surface of wounds**


### Dressing application

Two wounds on each animal (one on each flank) were treated with Silvercel, and a further two wounds were treated with Aquacel Ag. A sheet of a moisture-vapour-permeable adherent transparent film dressing (Bioclusive, Johnson & Johnson Medical, UK) was applied over the absorbent dressings. Topper gauze (Johnson & Johnson Medical, UK) was laid over the absorbent dressings and the film, and was secured with adhesive tape (Sleek, Smith & Nephew, UK). All dressing materials were held in place with Surgifix 6 elastic netting (Cistema d'Asti, Italy).

Each animal was then returned to its pen and monitored for any adverse effects of anaesthesia and/or surgery, until full recovery.

### Assessment of dressing performance

The pigs were re-anaesthetised (as described above) on post-wounding days 2, 4 and 7, and the outer dressings (Sugifix 6 and Topper gauze) were removed.

Exudate management at each wound site was assessed using a five-point semi-quantitative scale: the level of free (unabsorbed) exudate under the Bioclusive film and the extent of leakage away from the injury site onto the overlaid Topper gauze was scored, where 1 = no free exudate/leakage, 2 = minimal free exudate/leakage, 3 = moderate free exudate/leakage, 4 = significant free exudate/leakage, and 5 = very significant free exudate/leakage (Fig 1).

Next, the film dressing was removed and, while still *in situ*, the absorbent dressings' appearance, consistency and retention of structure were visually examined. All wound sites were then irrigated with sterile saline, and saline-soaked gauze (Topper) was applied.

After five minutes the saline-soaked gauze was lifted off and the absorbent dressings were gently removed with forceps. The force required to remove the dressings was assessed using a five-point semi-quantitative scale: 1 = no/very light adherence; 2 = light adherence; 3 = moderate adherence; 4 = strong adherence; 5 = very strong adherence.[16]

In view of reports on the possible leaching of silver from silver dressings and subsequent wound/periwound staining,[20] wound sites were also examined for the presence of wound and periwound discolouration.

### Histological investigations

On post-wounding day 7 all animals were euthanised and each wound, together with the surrounding marginal skin, was excised and fixed in 10% buffered formalin (Bios Europe, UK). A central 5mm (approx.) strip of tissue, including wound and marginal tissue, was cut (perpendicular to the dorsal midline) from each fixed specimen. The strips were processed to paraffin wax, and 6µm sections were taken and stained with haematoxylin and eosin (H&E).

Sections were initially viewed under low magnification (x40 total magnification) to investigate the overall characteristics of the neo-dermal and neo-epidermal tissues and to detect gross abnormalities within these tissues. Wound-tissue disruption was scored using a four-point scale: 1 = normal appearance; 2 = low-level disruption; 3 = moderate disruption; 4 = significant disruption to wound tissue organisation (Fig 2).

Sections were then viewed under higher magnifications (x100 and x200) to assess the level of trapped dressing debris and the tissue reaction to that debris (in terms of frequency of giant cell – foreign body reactions, which is discussed below). Level of trapped debris was scored on a four-point scale: 1 = no debris; 2 = low levels of debris; 3 = moderate levels of debris; 4 = high levels of trapped debris (Fig 3). Tissue reaction to trapped debris was scored on a five-point scale: 1= no foreign-body reactions; 2 = occasional foreign-body reactions; 3 = moderate numbers of foreign-body reactions; 4 = abundant foreign-body reactions, 5 = very abundant foreign-body reactions (Fig 4).

While undertaking the histological investigations, all identifying features (treatment codes) of wound sections were taped over and sections 'read' blind. Tissue sections were scored by a single rater (with extensive experience of wound-tissue histology) on two occasions (separated by 48 hours) and mean scores were calculated.

### Statistical analysis

Statistical evaluation was performed using SPSS version 11.0. Non-parametric two-sample Mann Whitney U-test was used to investigate the significance of the differences observed between the two dressings for each assessment (live phase and histological).

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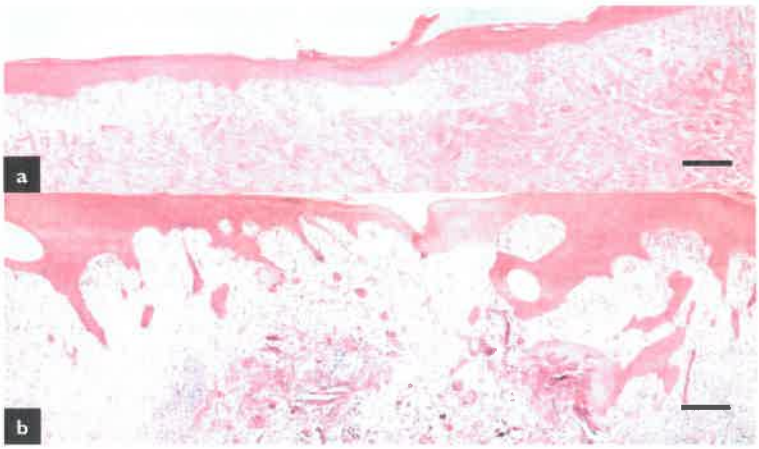


**Fig 2. Examples of the semi-quantitative scale used to assess tissue disruption associated with the presence of dressing debris within wounds. (a) normal appearance (score 1) and (b) significantly disrupted (score 4) (Scale = 200µm)**

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Differences were considered statistically significant when p values were 0.05 or less. Results are indicated as means ± SEM.

Selection of a four-animal, eight-replicate (per dressing) model was based on previous pig wound-healing studies (undertaken by the investigators), in which statistically significant differences were detected.

## Results

The results of this investigation are divided in to live phase and histological findings. Summary data for all assessments undertaken are detailed in Table 1.

### Live phase findings

- ***Exudate management*** At days 2 and 4, higher levels of free (unabsorbed) exudate were observed in wounds dressed with Aquacel Ag compared with Silvercel; this was statistically significant (p=0.021) on day 2 (Fig 5). No free exudate was observed in any wound on day 7.

Pooled exudate (over the wound and periwound skin) was observed in Aquacel Ag-treated wounds on day 2 (two wounds) and day 4 (three wounds). Exudate pooling was not observed in any Silvercel-treated wound at any time.

- ***Dressing characteristics after use*** The two dressings responded differently to application to wound sites and exposure to wound exudate.

Silvercel, which on removal from packaging presents as a soft 'open weave', pale grey-brown, fibrous pad, retained its structure throughout the study. On exposure to high levels of wound exudate (during the first four days after wounding), it darkened and became heavier/firmer, probably reflecting the absorption of wound exudate, but retained its shape and fibrous structure, and remained at the wound site (Fig 6a). When exposed to low exudate conditions (on day 7 following application on day 4), it was largely indistinguishable in appearance to its initial application.

Aquacel Ag's ability to retain its dressing structure depended on the level of wound exudate. On removal from its packaging, it presents as a soft, pale purple-grey, stippled, 'lint-like' pad. When exposed to high levels of exudate, it formed a highly fluid gel (with a variable fibrous component) that spread under the film dressing onto wound marginal tissues. On removal of the film dressing, the fluid component drained away from the wound site, leaving the more fibrous component on the wound surface and marginal skin (Fig 6b and 6d). Under moderate exudate conditions, it formed a more viscous amorphous gel with an increased fibrous component. Under low exudate conditions, it retained more of its original structure, with less gelling, and did not spread beyond the application site.

- ***Dressing adherence to wound tissues*** For Silvercel, dressing removal effectively entailed removing the main bulk of the dressing originally applied. For Aquacel Ag, it meant removing any remaining fibrous (non-gelled) material.

Dressing adherence to wound tissues was greatest for both dressings on day 2, after which it tended to

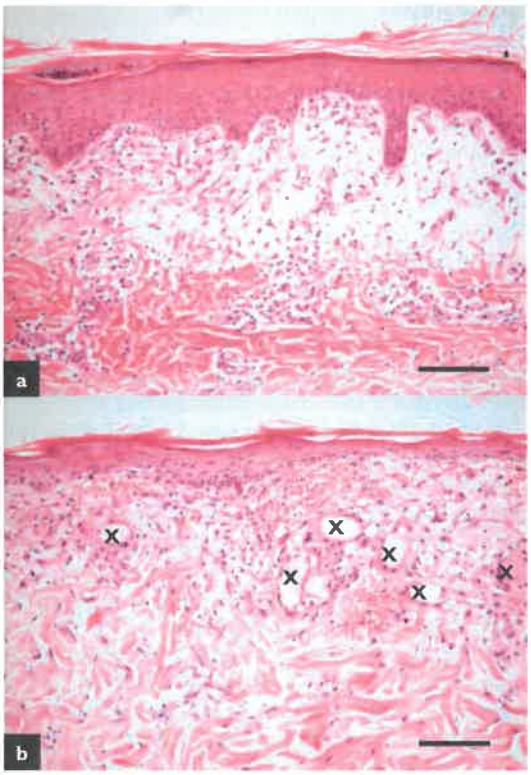



**Fig 3. Examples of the semi-quantitative scale used to assess the level of debris within wound tissues: (a) no debris apparent (score 1) and (b) high levels of trapped debris (score 4). Debris indicated by X. (Scale = 100µm)**

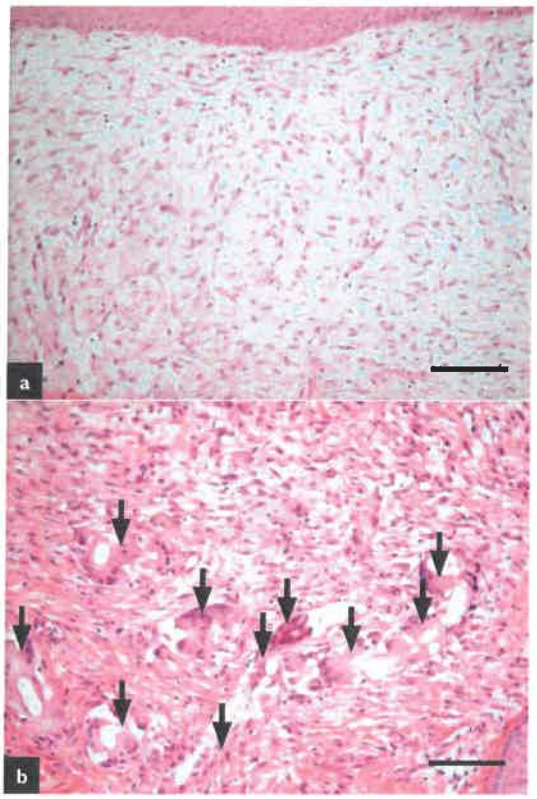



**Fig 4. Minimal (score 1) (a) and maximal (score 5) (b) of the five-point semi-quantitative scale used to measure the frequency of foreign body reactions within wound tissues (arrows = foreign body reactions) (Scale = 100µm)**

reduce. Aquacel Ag was significantly less adherent than Silvercel on day 2 (p=0.021), marginally less adherent on day 7 and similar on day 4 (Fig 7).

Following hydration with saline and the removal of the bulk of the used dressings, some dressing debris was found firmly attached to the wound surface in both groups. Adherent debris of Silvercel took the form of clearly defined individual dark grey fibres that appeared to be inserted into the wound (Fig 8a). With Aquacel Ag, this took the form of pale, barely visible fibres and semi-fibrous mats attached to the wound surface (Fig 8b).

Extended hydration with saline-moistened gauze removed most of the remaining debris from the two dressings. Debris that proved resistant to this was left in place as further, more physical, attempts at removal had the potential to cause re-injury. No incidence of dressing removal-associated re-injury was recorded in this study.

It should also be noted that wound and peri-wound discolouration, associated with the deposition of silver by dressing materials, was not observed in this investigation.

**Table 1. Summary of results for all study assessments**

| Assessment | Silvercel | Aquacel Ag |
|---|---|---|
| Unabsorbed exudate: | | |
| • Day 2 | 1.25 (0.16) | 2.50 (0.46) |
| • Day 4 | 1.50 (0.19) | 2.38 (0.53) |
| • Day 7 | 1.00 (0.00) | 1.00 (0.00) |
| Dressing adherence to wound: | | |
| • Day 2 | 4.63 (0.18) | 3.25 (0.41) |
| • Day 4 | 2.25 (0.49) | 2.25 (0.49) |
| • Day 7 | 3.00 (0.42) | 2.13 (0.35) |
| Trapped dressing debris within wound tissue | 1.86 (0.24) | 2.25 (0.31) |
| Frequency of dressing debris-associated foreign body reactions | 2.14 (0.32) | 3.00 (0.27) |
| Wound disruption score | 1.57 (0.30) | 2.13 (0.30) |

Data are presented as mean (SEM)

## Histological findings

• ***Trapped dressing debris within wound tissues*** Dressing-derived debris was observed in seven out of eight wounds treated with Aquacel Ag and in five of the seven given Silvercel (one Silvercel tissue sample was damaged during processing).

Trapped debris from the two dressings was very different in appearance and distribution. Silvercel debris took the form of sparsely distributed, clearly defined, individual fibres that were invariably cut in cross-section (Fig 9a). The fibres had a pale (white/grey) appearance and were predominantly located in the mid to upper regions of granulation tissue and within the epidermis.

Aquacel Ag debris was pale pink (having taken up eosin stain) and had a more amorphous structure. It was distributed throughout the full depth of the wounds, being found within the wound base, the mid-wound and trapped in pockets within new epithelial tissue (Fig 9b). It was often found in aggregates within neo-dermal tissue.

Using the four-point semi-quantitative scoring system described above, Aquacel Ag-treated wounds were found to contain more trapped dressing debris than Silvercel-treated wounds, although this was not statistically significant.

• ***Tissue reaction to trapped dressing debris*** When the host's phagocytic cells, such as neutrophils and macrophages, are unable to rapidly degrade a foreign material, additional phagocytes are invariably recruited to assist in this process. Where phagocytotic clearance is frustrated by the indigestibility of materials, large complexes of fused macrophages form. These multinucleate complexes are termed giant cell - foreign body reactions (GC-FBRs). Such foreign body reactions are sites of ongoing inflammation, and when present in high numbers can impede the healing process.[9, 12,21]

Giant cell – foreign body reactions to trapped

dressing debris were observed in all wounds with dressing debris. As the GC-FBRs effectively encircle trapped dressing debris, the distribution of these giant cell reactions was largely similar to that of the debris itself. In the Silvercel-treated wounds, GC-FBRs were primarily located in the upper granulation tissue and epidermis, while in Aquacel Ag-treated wounds they tended to be arranged in aggregates throughout the full depth of wounds.

When the appearance of GC-FBRs was compared, those encircling Silvercel fibres were noticeably smaller (they involved fewer macrophages) than those attempting to digest Aquacel Ag debris (Fig 9a and b).

Blind assessment of GC-FBR frequency found higher numbers of GC-FBRs in Aquacel Ag-treated wounds compared with Silvercel. This difference was not statistically significant.

• ***Wound tissue disruption consequent to debris entrapment*** Wound-tissue disruption and the degree of loss of normal wound architecture were considered in terms of the presence of dressing debris-associated discontinuities within wound granulation tissue, and were assessed semi-quantitatively as described above.

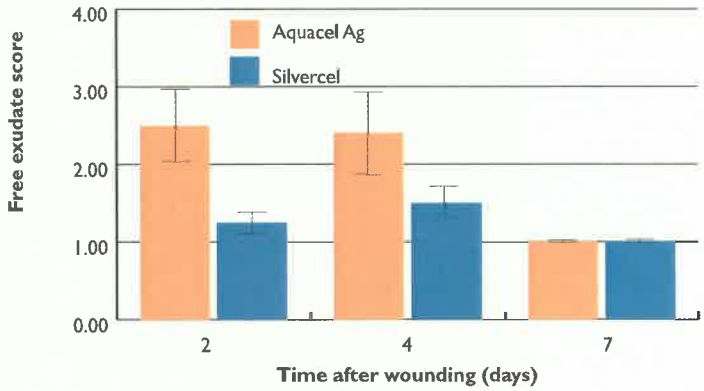
Four of the seven Silvercel-treated wounds examined (57%) were normal in appearance, two (29%) displayed low-level disruption and one (14%) was moderately disrupted. Two of the eight Aquacel Ag-treated wounds (25%) had a normal appearance, three (37.5%) displayed low-level disruption and three (37.5%) were moderately disrupted. This tendency towards higher levels of wound-tissue disruption in Aquacel Ag-treated wounds translated into a noticeably, although not significantly, higher mean wound-tissue disruption score when compared with Silvercel-treated wounds.

## Discussion

While there is no defined optimal level of wound hydration, it is widely accepted that, for most wounds, moist wound-healing conditions are preferred to excessive hydration or desiccation.[22] While the limited generation of fluid from cutaneous injury sites is considered normal, being a consequence of the loss of skin barrier function and wound-site inflammation, chronic production of excessive wound fluid can impair healing and macerate periwound tissues,[23,24] negatively affecting patients' quality of life.[25]

Exudate levels produced by porcine partial-thickness wounds vary with time after experimental injury. Significant volumes of exudate are generated over the first two to four days, after which exudation reduces as wounds steadily re-epithelialise. While the duration of exudation and healing time may be short — significantly shorter than in certain chronic wound-healing states — this model does provide a clinically relevant range of wound exudate levels for the evaluation of absorbent wound dressing performance.

**Fig 5. Comparison of Silvercel and Aquacel Ag in terms the level of free exudate at the wound surface (mean ± SEM).**




In this study, Silvercel was found to be significantly more effective than Aquacel Ag in terms of its ability to absorb and retain wound fluid. This suggests that any adverse consequences of unabsorbed exudate, such as periwound maceration and delayed healing, may be less likely in wounds treated with this dressing in the clinical setting. It also suggests that Silvercel may be more effective in the management of wounds that produce large volumes of wound exudate. In this study, free 'unmanaged' exudate was assessed subjectively using an 'in-house' five-point semi-quantitative scale, whereas others have measured the volume of exudate aspirated from the wound surface.[16] Reflecting the widely perceived superiority

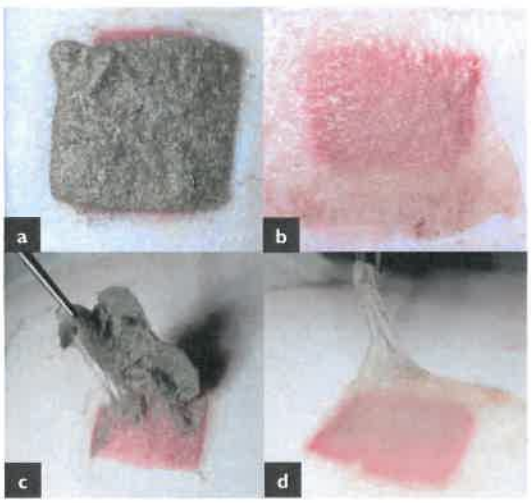
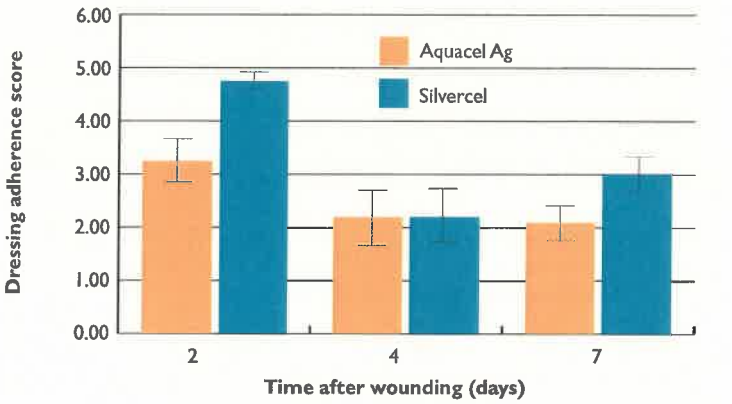



**Fig 6. The appearance and consistency of the dressing materials on post-wounding day 2: Silvercel (a and c); Aquacel Ag (b and d)**

**Fig 7. Comparison of Silvercel and Aquacel Ag in terms of wound site adherence (mean ± SEM).**




of such objective quantitative data, this approach will be adopted in future studies.

The degree to which a dressing adheres to a wound surface determines its ease of removal, the level of associated patient discomfort and the degree of damage to wound tissue.[5] Silvercel was found to be more adherent than Aquacel Ag — an observation that proved statistically significant on day 2.

This may reflect Silvercel's greater ability to retain its dressing structure and preserve the mechanical strength of its individual fibres. We suggest that individual adherent Silvercel fibres bind the main bulk of the dressing to the wound site, whereas similarly bound Aquacel Ag fibres, whose tensile strength is limited, break when minimal force is applied. While this reduces dressing adherence, and the potential for discomfort and wound site re-injury at dressing change, it may also increase debris entrapment within wound tissues.

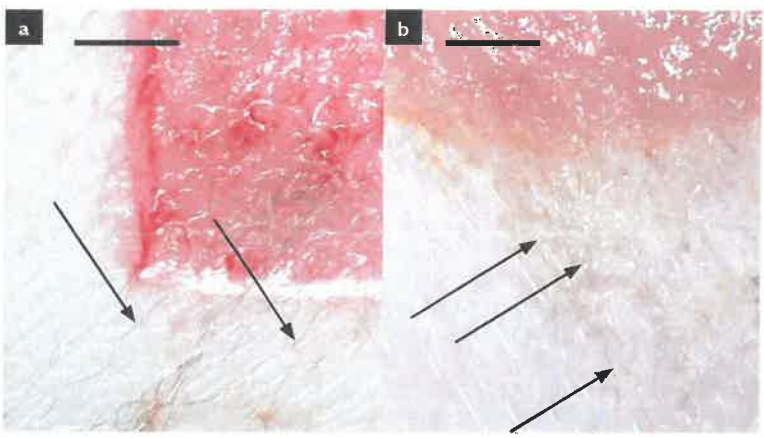



**Fig 8. Appearance residual debris on the surface of wounds: Silvercel-treated wound at post-wounding day 2 (note fine dark fibres) (a); Aquacel Ag-treated wound at post wounding day 4 (note pale debris including fibres) (b). (Scales = 5mm)**

Small amounts of adherent debris were found on the wound surface after the removal of both dressings. However, the visibility of dressing debris on the wound surface varied between the dressings. Due to their dark grey colour and singular form, Silvercel fibres were clearly visible, whereas the Aquacel Ag debris, which tended to take on the colouring of the wound surface (presumably reflecting the uptake of wound exudate) and lacked any defined shape, was more difficult to detect. Such detection difficulties were not experienced on histological examination, where debris was found in most wounds. The relative ease by which dressing debris was located in wound tissues highlights the benefits of histological investigation over macroscopic observation.

Histological assessment of harvested wound tissues demonstrated that the amount of trapped dressing debris, the frequency of foreign body reactions to that debris and the level of associated wound disruption were lower (although not significantly so) in Silvercel-treated wounds. Silvercel debris tended to be located near the wound surface, within the epidermis and upper granulation tissue, whereas Aquacel Ag debris was more widely distributed, being found throughout the full wound depth. This finding may be due to differences in the dressings' ability to retain their structure and the tensile strength of individual dressing fibres. We suggest that as Silvercel fibres are firmly bound to the main body of the dressing, this limits their incorporation into deeper tissues and facilitates their extraction when the main body of the dressing is removed from the wound surface. Given Aquacel Ag's limited ability to retain its dressing structure and its loss of fibre strength, no restriction is placed on the deposition of debris into wound tissues, for which no mechanism of extraction is available.

The differential distribution of debris from the two dressings may also be explained by the timing of its incorporation into the wound. The presence of Aquacel Ag debris throughout the full wound depth suggests entrapment started shortly after injury. While the presence of Silvercel debris in upper wound tissues suggests the debris was incorporated later in the wound-healing process.

Effective wound healing depends on the timely progression of wounds through the phases of the healing process. Factors that interrupt this normal progression — for example, by prolonging wound-site inflammation — have the propensity to impair the healing process.[26] Where foreign materials become lodged in tissues, an inflammatory response occurs to remove that material, a process that involves the recruitment of inflammatory phagocytic cells. The level of this inflammatory response is dictated by the physical and chemical properties of the trapped material. Where phagocytosis is prevented by the indigestibility of the material, these

inflammatory cells fuse together to form GC-FBRs around the material. As these foreign body reactions are sites of ongoing inflammation, they may prolong wound inflammation, thereby delaying the healing process.[6,9,11,21] As these foreign body reactions are normally closely spatially restricted to the site of the indigestible material, occasional short-lived GC-FBRs within wounds are thought to have a limited impact on the healing of the wound as a whole.[6,11] Where GC-FBRs are more numerous, due to higher levels of indigestible material, the level of supplemental inflammation is greater and delayed healing more likely.[6,10-12,18,27] The lifespan of GCs-FBRs depends on a wide range of physical and chemical characteristics of the foreign material concerned, with some reactions to particularly indigestible dressing fibres being found 16 months after tissue implantation.[6] While the clinical consequences of foreign body reactions to dressing materials have yet to be fully determined, it is generally accepted that deposition of foreign materials (such as dressing debris) within wounds has the potential to adversely affect the wound-healing process, and should be avoided.

The observation of GC-FBRs in wounds treated with Silvercel and Aquacel Ag suggests the trapped debris derived from both dressings was to some degree indigestible over the limited test period. As the frequency of foreign body reactions depends on the amount of foreign material present, it is not surprising that such reactions were more prevalent in Aquacel Ag-treated wounds, in which the amount of debris also tended to be greater.

The observation that individual Aquacel Ag foreign body reactions tended to be larger and involved greater numbers of fused macrophages than those encircling Silvercel debris may be explained by differences in either the chemical composition of the two dressings or the physical form of the debris within the wound site.

The site of dressing debris deposition has some influence on its retention at the wound site and its potential to affect healing. Dressing debris within the epidermis is removed from the wound site during normal epidermal desquamation. However, debris trapped within the dermis may give rise to more long-term issues such as ongoing inflammation and, where significant amounts of debris are trapped, delayed wound healing.

Histological assessment showed noticeably (but not significantly) more tissue disruption in Aquacel Ag-treated wounds, with larger areas of granulation tissue occupied by trapped dressing materials and foreign body reactions. While the histological appearance of wound tissues in which dressing debris has become trapped is clearly abnormal compared with wounds without debris, the impact of this debris-associated disruption on key functional wound-healing parameters has yet to be fully determined. Further investigation of the impact of dressing debris reactions using clinically relevant wound-healing endpoints, such as granulation-tissue formation and wound re-epithelialisation, may help to determine the clinical significance of the observations made here.

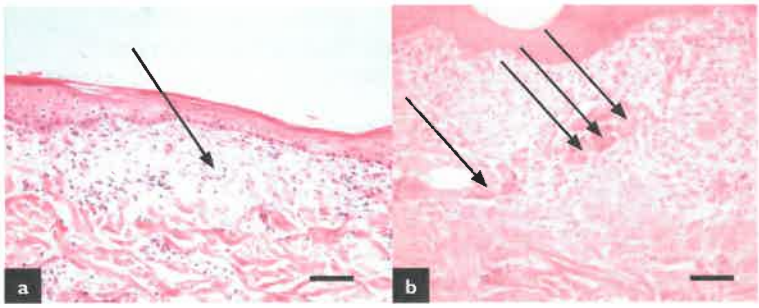



**Fig 9. Photomicrographs of haematoxylin and eosin stained sections from Silvercel (a) and Aquacel Ag-treated wounds (b). Representative examples of the appearance and distribution of dressing debris within wounds, and the tissue reactions to that debris. (Scale = 100µm)**

This study investigated the presence of dressing debris, associated foreign body reactions and wound tissue disruption in wound tissues harvested one week after wounding. In view of this limited time frame, it is impossible to state the likely duration of debris residence, the possible lifespan of foreign body reactions to it, or predict the long-term impact on the healing process. Longer-term studies are clearly warranted.

## Conclusion

This study compared the performance of two absorbent silver dressings in an *in vivo* model of moderate to high wound exudation. Silvercel was found to be significantly more effective in terms of wound exudate handling than Aquacel Ag, but was significantly more adherent to wound tissues. Interestingly, this elevated adherence was paralleled by lower levels of trapped dressing debris, reduced foreign body reaction frequency and reduced wound-tissue disruption, when compared with Aquacel Ag.

Based on these findings, we suggest that the potential adverse clinical consequences of unmanaged wound exudate may be less likely in Silvercel than Aquacel Ag-treated wounds. In addition, the adverse effects of dressing adherence may be less likely in Aquacel Ag-treated wounds, although such benefits may be negated by the potentially deleterious effects of elevated dressing debris deposition in Aquacel Ag-treated wounds.

In view of these findings, we suggest that further development of absorbent, fibre-based dressings should be directed at maximising exudate management, minimising dressing adherence and preventing dressing debris entrapment. ■

# Comparative evaluation of silver-containing antimicrobial dressings and drugs

Joseph J Castellano, Susan M Shafii, Francis Ko, Guillermo Donate, Terry E Wright, Rudolph J Mannari, Wyatt G Payne, David J Smith, Martin C Robson

Castellano JJ, Shafii SM, Ko F, Donate G, Wright TE, Mannari RJ, Payne WG, Smith DJ, Robson MC. Comparative evaluation of silver-containing antimicrobial dressings and drugs. Int Wound J 2007;4:114–122.

## ABSTRACT

Wound dressings containing silver as antimicrobial agents are available in various forms and formulations; however, little is understood concerning their comparative efficacy as antimicrobial agents. Eight commercially available silver-containing dressings, Acticoat® 7, Acticoat® Moisture Control, Acticoat® Absorbent, Silvercel™, Aquacel® Ag, Contreet® F, Urgotol® SSD and Actisorb®, were tested to determine their comparative antimicrobial effectiveness in vitro and compared against three commercially available topical antimicrobial creams, a non treatment control, and a topical silver-containing antimicrobial gel, Silvasorb®. Zone of inhibition and quantitative testing was performed by standard methods using *Escherichia coli*, *Pseudomonas aeruginosa*, *Streptococcus faecalis* and *Staphylococcus aureus*. Results showed all silver dressings and topical antimicrobials displayed antimicrobial activity. Silver-containing dressings with the highest concentrations of silver exhibited the strongest bacterial inhibitive properties. Concreet® F and the Acticoat® dressings tended to have greater antimicrobial activity than did the others. Topical antimicrobial creams, including silver sulfadiazine, Sulfamylon and gentamicin sulfate, and the topical antimicrobial gel Silvasorb® exhibited superior bacterial inhibition and bactericidal properties, essentially eliminating all bacterial growth at 24 hours. Silver-containing dressings are likely to provide a barrier to and treatment for infection; however, their bactericidal and bacteriostatic properties are inferior to commonly used topical antimicrobial agents.

**Key words:** Antimicrobial agents • Quantitative culture • Silver dressings • Wound treatment

**Key Points**

- the use of silver in the treatment of burns and chronic wounds has been used for centuries

## INTRODUCTION

The use of silver in the treatment of burns and chronic wounds has been used for centuries. The antimicrobial properties of silver made water potable as early as 1000 BC (1). Used in its solid form, silver nitrate is known in several languages by different terms. 'Lunar caustic', an English term, was derived in the Middle Ages from silver's association with the moon. 'Lapis infernalis' in Latin and 'pierre infernale' in French are also descriptive terms for silver nitrate (2). There are different suggestions regarding the first use of silver nitrate, with most referring to the Middle Ages as the period of its beginning, while others refer to the discovery of silver nitrate in the 15th century by Basilius Valentinus (2). John Woodall

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published the use of Lapis infernalis in 'The Surgeon's Mate' in 1617, with uncertainty that his description was that of silver nitrate because he considered it the same as the 'hard causticke stone' used for opening abscesses (2).

In the 1700s, venereal diseases were treated with silver nitrate, as well as fistulae from the salivary glands, from bone and from perianal abscesses (2,3). Although its astringent properties were recognised, silver nitrate was also considered an alternative to the cauterising iron (2). In the 19th century, silver nitrate was used to remove granulation tissue therefore allowing epithelization, and to promote crust formation on the surface of the wound for large surface wounds that healed by epithelization from the edges and contraction (2). Varying concentrations of silver nitrate were also used in the 19th century for the treatment of fresh burns. Ophthalmia neonatorum was prevented with the introduction of silver nitrate eye drops by Carl S.F. Credé in 1881 (2,3). Halsted reported the use of silver wire for suturing, covered by silver foil in a description of a hernia operation (2,4). He referred to the inhibitory effect of silver foil on *Staphylococcus aureus* as well (2,4). C.S.F. Credé's son, B. Credé, created dressings with silver impregnated in them, the 'white silver dressing' which was wide-mesh cotton in which silver foil was mounted, and the 'grey silver dressing' which was sterilised cotton with metallic silver powder, both of which were applied to skin grafts (2).

In 1967, Moyer revived the interest in silver nitrate as a treatment of burns with his introduction of continual irrigation of 0·5% silver nitrate solution (5–7). He reported that 0·5% silver nitrate aqueous solution does not interfere with epidermal proliferation that occurs with a 1% aqueous solution, yet affords the bacteriostatic properties against *S. aureus*, β-hemolytic streptococci, *Pseudomonas aeruginosa* and *Escherichia coli* (4). The hypotonic silver nitrate solution can cause electrolyte disturbances, which Moyer describes as the sodium sink (5,8,9). Mafenide acetate, Sulfamylon®, was introduced by Lindberg, Moncrief and Mason modified from the mafenide hydrochloride which had been used widely during World War II in Germany as topical treatment of wounds (7,8,10). Although it has a broad antibacterial spectrum and an ability to penetrate the eschar, mafenide acetate was found to cause pain on application of partial thickness burns (6,9). Because it is a carbonic anhydrase inhibitor, hyperpnea and hyperchloremic acidosis can develop (9). Despite these adverse effects, the 0·5% silver nitrate solution and Sulfamylon® became the mainstay of burn therapy until the introduction of silver sulfadiazine. Silver sulfadiazine, Silvadene®, was found effective as a topical antimicrobial treatment against *Enterobacter*, *Klebsiella*, *E. coli*, *Proteus*, *Staphylococcus*, *Streptococcus* and *Pseudomonas*, with some antifungal and antiviral properties, painless on application, and non irritating to tissues (6,10).

The antimicrobial effects of silver products appear to be directly related to the amount and rate of silver released (3). Chemically, although silver in its metallic state is inert, when it interacts with moisture from the skin and with fluid from a wound, silver is ionised leading to antimicrobial effects (3). The ionised silver moity is highly reactive, binding to tissue proteins and causing structural changes in the bacterial cell wall and intracellular and nuclear membranes, ultimately leading to cellular distortion and loss of viability (3,11). Additionally, the silver ion further exhibits its bacteriostatic properties by binding to and denaturing bacterial DNA and RNA, and thereby inhibiting bacterial replication (3).

Silver's mechanism of action is attributed to its strong interaction with thiol groups present in cell respiratory enzymes in the bacterial cell. The mechanism of action of silver sulfadiazine is believed to be by binding to cell membranes and to the bacterial cell wall rather than by interacting with cellular DNA (8). Products such as Acticoat® release both silver ions and silver radicals, causing impaired electron transport, bacterial DNA inactivation and other cell membrane damage (3). Silver radicals are gaining favour as a mechanism of action because of their high potency for reactivity due to the presence of unpaired electrons in the outer orbits (3).

Infection is a leading cause of morbidity and mortality from extensive burn injury, traumatic injuries and surgical procedures (12–15). Therefore, silver has drawn much attention as a treatment and prophylaxis for burn and wound care. Topical silver creams and solutions, and other topical antimicrobial preparations have a broad spectrum of antimicrobial activity, low development of resistance, few adverse reactions and a low risk of systemic toxicity, but require frequent application, are

**Key Points**

- the mechanism of action of silver sulfadiazine is believed to be binding to cell membranes and to the bacterial cell wall rather than by interacting with cellular DNA and RNA, thereby inhibiting bacterial replication
- topical silver creams and solutions, and other topical antimicrobial preparations have a broad spectrum of antimicrobial activity, low development of resistance, few adverse reactions and a low risk of systemic toxicity, but require frequent application, are care intensive to apply and remove and are sometimes painful

**Key Points**

- The purpose of this experiment is to comparatively evaluate eight silver dressings: Urgotul® SSD, Acticoat® 7, Acticoat® Moisture Control, Acticoat® Absorbent, Silvercel™, Contreet® F, Aquacel® Ag, Actisorb®, two silver agents: Silver Sulfadiazine and SilvaSorb® Gel, Sulfamylon® and Gentamicin Sulfate cream to determine their antimicrobial effectiveness against *S. aureus*, Streptococcus faecalis, *P. euruginosa* and *E. coli*

care intensive to apply and remove and are sometimes painful. In contrast to these topical silver agents, wound dressings containing silver as antimicrobial agents have been introduced in various designs by the wound care industry in recent years, however. The dressings are designed to control the release of silver to the wound allowing the dressings to be changed with less frequency. The purpose of this experiment is to comparatively evaluate eight silver dressings: Urgotul® SSD, Acticoat® 7, Acticoat® Moisture Control, Acticoat® Absorbent, Silvercel™, Contreet® F, Aquacel® Ag, Actisorb®, two silver agents: Silver Sulfadiazine and SilvaSorb® Gel, Sulfamylon® and Gentamicin Sulfate cream to determine their antimicrobial effectiveness against *S. aureus*, *Streptococcus faecalis*, *P. aeuruginosa* and *E. coli*.

## MATERIALS AND METHODS

The eight silver-impregnated dressings and topical silver antimicrobial agents used are described below.

### Silver-impregnated dressings

#### *Acticoat® Absorbent (Smith and Nephew)*

Acticoat® Absorbent uses the Silcryst™ Nanocrystals and consists of a silver-coated calcium alginate fabric. The manufacturer states that there is sustained release of ionic silver activity, as well as the ability to absorb excess exudates via the alginate to form a gel maintaining a moist environment.

#### *Acticoat® 7 (Smith and Nephew)*

Acticoat® 7, like all Acticoat® products, contains Silcryst™ Nanocrystals. This dressing consists of two rayon/polyester non woven inner cores laminated between three layers of silver-coated high density polyethylene mesh, designed to be the barriers against the bacterial invasion.

#### *Acticoat® Moisture Control (Smith and Nephew)*

Acticoat® Moisture Control also uses Silcryst™ Nanocrystals. This dressing consists of an absorbent three layer dressings of a nanocrystalline silver-coated polyurethane layer, a white polyurethane foam layer and a blue waterproof polyurethane film layer. It also maintains a moist environment in the presence of exudate.

#### *Aquacel® Ag (Squibb and Son, UK; ConvaTec)*

The dressing contains 1·2% ionic silver in a Hydrofiber®, a fibrous non woven felt of sodium carboxymethylcullulose fibres. It absorbs moisture to form a gel, binding sodium ions and releasing silver ions (16). In addition, the manufacturer states that by utilising the Hydrofiber® technology, the dry Aquacel® Ag fibers gel on contact with wound fluid, locking exudates that contains bacteria away from the wound, as well as forming a cohesive gel that reduces dead space.

#### *Urgotul® SSD (Laboratory Urgo, France)*

This gauze dressing is coated in a Vaseline paste containing hydrocolloid and silver sulfadiazine particles (15).

#### *ACTISORB® (Johnson and Johnson)*

The ACTISORB dressing consists of an activated charcoal cloth impregnated with silver within a spun-bonded nylon envelope. The manufacturer states that there is 220 mg silver per 100 g activated charcoal cloth, approximating 33 μg silver per square centimetre cloth. In addition, it is claimed by the manufacturer that the porous charcoal layer binds toxins and odour-causing molecules.

#### *Contreet® foam (Coloplast Corporation)*

The Contreet® foam dressing is silver-impregnated based on Biatain foam technology. The manufacturer states that it combines both sustained silver release and manages exudates, stating that the more exudate the wound produces the more silver released by the dressing.

#### *Silvercel™ (Johnson and Johnson)*

The Silvercel™ dressing is a non woven felt composed of calcium alginate carboxymethylcellulose fibres. It is blended with a metallic silver-coated nylon fibre (15).

### Topical silver antimicrobial agents

#### *SilvaSorb® Gel (Medline)*

SilvaSorb® is a microlattice synthetic hydrogel matix that contains silver chloride (15). It is claimed to maintain a moist environment and hold a significant amount of exudate due to its hydrogel matrix.

#### *Silvadene® Cream 1% (King Pharmaceuticals)*

Silvadene®, silver sulfadiazine, is a white, non staining anti-infective cream.

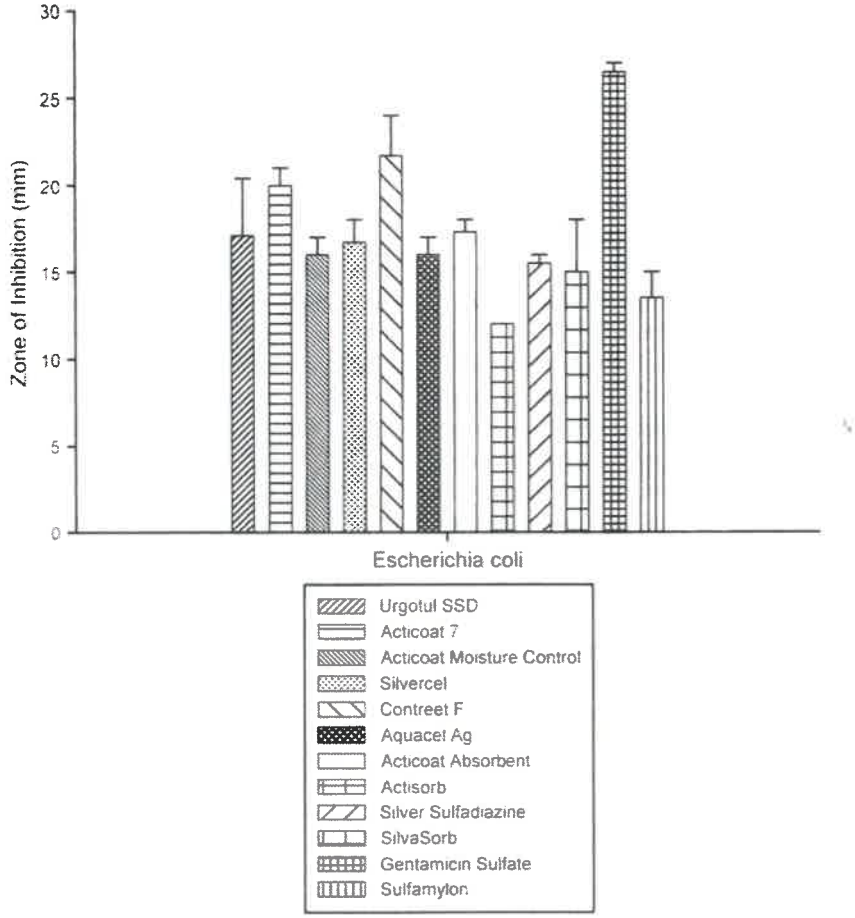


**Figure 1.** Average zone of inhibition of eight silver dressings and antimicrobial creams *Escherichia coli*.

**Key Points**

- the disc diffusion test was used to determine the zone of inhibition and was performed in triplicate
- the average zones of inhibition were calculated between the triplicate runs which showed close approximation

## Topical antimicrobial agent

### *Sulfamylon® (Mylan-UDL Laboratories, Inc.)*

Sulfamylon® cream is a white, non staining, anti-infective cream containing mafenide acetate (10%).

### *Gentamicin Sulfate Cream 0·1% (Fougera)*

Gentamicin sulfate is a white cream base 0·1% by weight.

## Zone of inhibition determination

The disc diffusion test was used to determine the zone of inhibition and was performed in triplicate. Six-millimetre diameter samples of each of the eight silver dressings and each of the topical antimicrobial silver agents were prepared. Each inoculation was adjusted to 0·5 McFarland turbidity standards to ensure reproducibility and prepared on unsupplemented Mueller–Hinton agar plates within 15 minutes of preparation of the inoculum in accordance with National Committee for Clinical Laboratory Standards recommendations (16). The accuracy of the adjusted density of the inoculum was verified using a spectrophotometer. Multiple 6-mm diameter circular samples of each silver dressing and each topical agent were placed evenly at least 24 mm apart on the plates by using sterilised forceps within 15 minutes of inoculation of the agar plates. The prepared plates were incubated at 37°C in a humidified atmosphere of 5% carbon dioxide for 24 hours. The zone of inhibition was calculated by measuring the diameter to the nearest whole millimetre using sliding callipers of the inhibited growth around the dressing disk. Because the unsupplemented Mueller–Hinton agar was used, the measuring device was held to the inverted illuminated petri dish. Average zones of inhibition were calculated between the triplicate runs which showed close approximation.

**Key Points**

- all silver dressings and topical antimicrobial non dressing agents showed inhibition of bacterial populations to some extent. Contreet® F and the various Acticoat® dressings showed the largest zones of inhibition
- bacterial death after 72 hours of incubation showed the susceptibility of the bacteria to the specific agent, be it a silver-impregnated dressing or topical silver agents

### Quantitative analysis of antimicrobial activity

Quantitative analyses were performed in triplicate by the following method: Bacterial suspensions were generated by inoculating 3 ml Tryptic Soy broth with $5 \times 10^8$ of the following four bacterial species: *S. aureus* (ATCC 29213), *S. faecalis* (ATCC 29212), *P. aeruginosa* (ATCC 27853) and *E. coli* (ATCC 25922). Turbidity equivalent was adjusted to a 0·5 McFarland standard using a spectrophotometer. One square centimetre sample of each of the eight silver dressings or one millilitre of the two topical antimicrobial silver agents or the two other (non silver) topical antimicrobial agents was added to the bacterial suspensions and allowed to inoculate at 37°C in a humidified atmosphere of 5% carbon dioxide. After the initial 24-hour incubation, the suspensions were quantitatively cultured on blood agar plates and MacConkey agar plates and incubated for 48 hours at 37°C in a humidified atmosphere of 5% carbon dioxide. Colony counts were manually performed and expressed as CFU/ml. The bacterial suspension with the silver dressings or topical agents continued to incubate for a total of 48 and 72 hours, with the previously described procedure performed to determine their respective colony counts.

## RESULTS

The zone of inhibition test (Figures 1–4) showed considerable variation in the ability to inhibit the growth of the four bacterial organisms: *S. aureus* (ATCC 29213), *S. faecalis* (ATCC 29212), *P. aeruginosa* (ATCC 27853) and *E. coli* (ATCC 25922). All silver dressings and topical antimicrobial non-dressing agents showed inhibition of bacterial populations to some extent (Figures 1–4). Contreet® F and the various Acticoat® dressings showed the largest zones of inhibition.

Bacterial death after 72 hours of incubation showed the susceptibility of the bacteria to the specific agent, be it a silver-impregnated dressing or topical silver agents. Quantitative analysis, shown in Table 1, *E. coli* was 100%

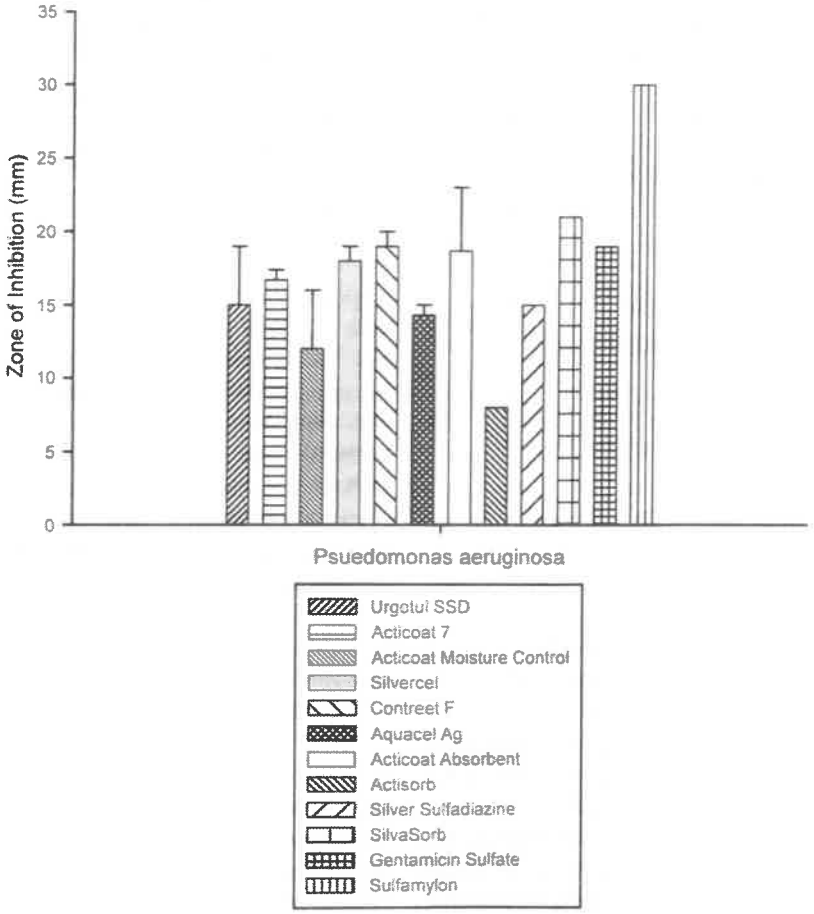


**Figure 2.** Average zone of inhibition of eight silver dressings and antimicrobial creams *Psuedomonas aeruginosa*.

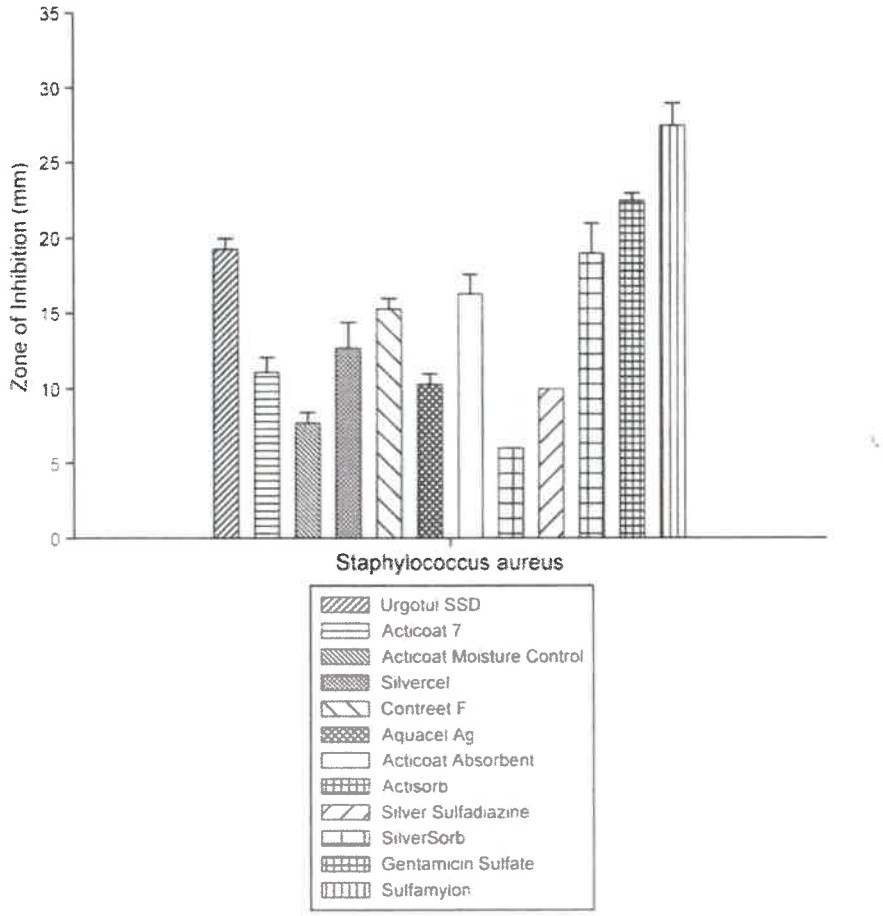


**Figure 3.** Average zone of inhibition of eight silver dressings and antimicrobial creams *Staphylococcus aureus*

susceptible to five silver-impregnated dressings at 72 hours: Acticoat® 7, Acticoat® Moisture Control, Acticoat® Absorbent, Contreet® F and Aquacel® Ag. As depicted in Table 1, *S. faecalis* was shown to be 100% susceptible to four silver-impregnated dressings at 72 hours: Urgotul® SSD, Acticoat® 7, Acticoat® Moisture Control and Acticoat® Absorbent. Table 1 also shows 100% susceptibility of *S. aureus* to two silver-impregnated dressings at 72 hours: Acticoat® Absorbent and Contreet® F. Finally, *P. aeruginosa* was 100% susceptible to two dressings at 72 hours: Acticoat® 7 and Acticoat® Absorbent. All four bacteria showed greatest susceptibility to the Acticoat® Absorbent dressing by quantitative analysis. Bacteria appear to show the least susceptibility to dressings with the lowest silver concentration (3). Topical antimicrobials, including silver sulfadiazine, Sulfamylon®, SilvaSorb® and gentamicin sulfate, showed superior bacterial inhibition and bactericidal properties in vitro (Table 1, Figures 1–4), demonstrating complete inhibition of growth in quantitative cultures at 24, 48 and 72 hours.

## DISCUSSION

Infection is a significant cause of delayed or prolonged wound healing, and high bacterial levels interferes with the progression of wound healing (12–14). Silver's antibacterial properties have made it an attractive and practical choice for creating silver-based topical creams and dressings to comprise a class of antimicrobial topical treatments that have been used for wound care (17,18). This study compares topical silver compounds, mafenide acetate, gentamicin sulfate cream and eight commercially available silver-impregnated dressings, with respect to their antimicrobial properties against *S. aureus*, *S. faecalis*, *P. aeruginosa* and *E. coli*. The results of this study show the differences and importance in choosing the appropriate dressing or cream for an infected wound.

### Key Points

- topical antimicrobials, including silver sulfadiazine, Sulfamylon®, SilvaSorb® and gentamicin sulfate, showed superior bacterial inhibition and bactericidal properties *in vitro*, demonstrating complete inhibition of growth in quantitative cultures at 24, 48 and 72 hours
- infection is a significant cause of delayed or prolonged wound healing, and high bacterial levels interferes with the progression of wound healing
- silver's antibacterial properties have made it an attractive and practical choice for creating silver-based topical creams and dressings to comprise a class of antimicrobial topical treatments that have been used for wound care
- the results of this study show the differences and importance in choosing the appropriate dressing or cream for an infected wound

## Key Points

- our study suggests that topical antimicrobial silver agents as well as non silver agents performed superiorly to the silver-impregnated dressings
- in our study, both tests suggested that in general, higher silver concentrations are parallel to higher bactericidal antibacterial properties

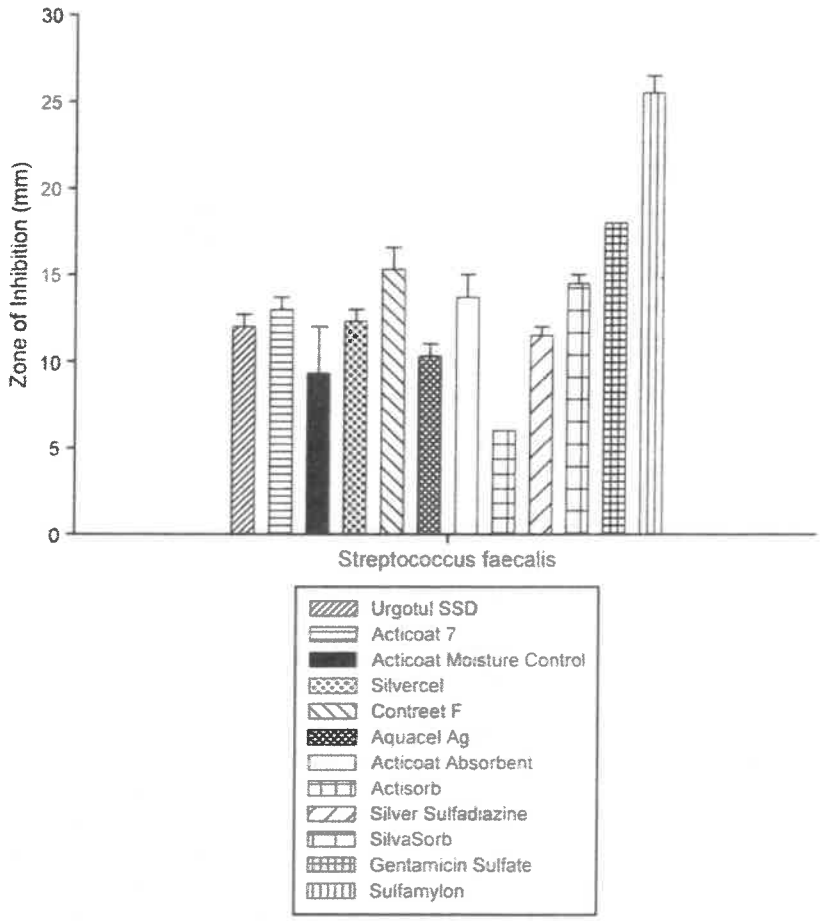


**Figure 4.** Average zone of inhibition of eight silver dressings and antimicrobial creams *Streptococcus faecalis*.

The quantitative analysis of the antimicrobial activities concluded that of the silver-impregnated dressings, Acticoat® dressings and its derivatives, specifically Acticoat® Absorbent, showed greater antimicrobial activity. Of the silver-impregnated dressings, Acticoat® Absorbent showed superior effects to gram-positive organisms, with Acticoat® 7 and Acticoat® Moisture Control close behind in susceptibility. Acticoat® Absorbent also showed the greatest susceptibility of the silver-impregnated dressings to gram-negative organisms. It has been shown in other studies that Acticoat® is an effective antimicrobial agent against various gram-negative and gram-positive organisms (1). Tredget *et al.* (11) showed a decrease in the frequency of the development of burn wound infection in the Acticoat®-treated wounds than in the silver nitrate-treated control sites. Our study suggests that topical antimicrobial silver agents as well as non-silver agents performed superiorly to the silver-impregnated dressings, demonstrating superior gram-positive and gram-negative bacterial susceptibility, making thema more logical choice for wounds containing bacterial loads of $>1 \times 10^5$ CFU, to rapidly reduce bacterial counts, based on this in vitro data.

The reason for reporting both zones of inhibition and quantitative analyses over time was because both tests may have some disadvantages when comparing both dressings and creams or gels (19). Gallant-Behm *et al.* suggested that the results from the two tests did not correlate at all. However, in our study, both tests suggested that in general, higher silver concentrations correlate to higher bactericidal antibacterial properties. This corroborates what was reported by Lansdown (3). However, Parsons *et al.* (15) showed that a greater amount of silver released by a dressing does not lead to a greater rate or degree of antimicrobial activity. It is suggested by some that the active form of silver released from a commercially available dressing is different than the active form of silver released by silver

**Table 1** Comparison of quantitative culture results

| | *Staphylococcus aureus* | | | *Streptococcus faecalis* | | | *Escherichia coli* | | | *Psuedomonas aeruginosa* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 24 hours | 48 hours | 72 hours | 24 hours | 48 hours | 72 hours | 24 hours | 48 hours | 72 hours | 24 hours | 48 hours | 72 hours |
| Control | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ |
| Acticoat Absorbent | NG | NG | NG | NG | NG | NG | NG | NG | NG | NG | NG | NG |
| Acticoat Moisture Control | $7.0 \times 10^4$ | $4.0 \times 10^3$ | $1.1 \times 10^4$ | NG | NG | NG | NG | NG | NG | NG | $5.6 \times 10^4$ | $>1 \times 10^5$ |
| Acticoat 7 | $3.5 \times 10^4$ | $1.9 \times 10^4$ | $4.0 \times 10^3$ | NG | NG | NG | $1 \times 10^5$ | NG | NG | $>1 \times 10^5$ | $1.0 \times 10^5$ | NG |
| Contreet F | $>1 \times 10^5$ | $>1 \times 10^5$ | NG | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | NG | NG | $>1 \times 10^5$ | $>1 \times 10^5$ | $3.0 \times 10^3$ |
| Urgotul SSD | $>1 \times 10^5$ | $>1 \times 10^5$ | $3.0 \times 10^3$ | $>1 \times 10^5$ | $2.0 \times 10^3$ | NG | $6.9 \times 10^4$ | $>1 \times 10^5$ | $2.6 \times 10^4$ | NG | $>1 \times 10^5$ | $>1 \times 10^5$ |
| Aquacel Ag | $1 \times 10^5$ | $>1 \times 10^5$ | $2.0 \times 10^4$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $4.8 \times 10^3$ | $2.4 \times 10^4$ | NG | NG | $6.2 \times 10^4$ | $>1 \times 10^5$ | $>1 \times 10^5$ |
| Silvercel | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ |
| Actisorb | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $5.0 \times 10^3$ | $4.0 \times 10^3$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ | $>1 \times 10^5$ |
| Silver Sulfadiazine | NG | NG | NG | NG | NG | NG | NG | NG | NG | NG | NG | NG |
| Sulfamylon | NG | NG | NG | NG | NG | NG | NG | NG | NG | NG | NG | NG |
| SilvaSorb | NG | NG | NG | NG | NG | NG | NG | NG | NG | NG | NG | NG |
| Gentamicin Sulfate | NG | NG | NG | NG | NG | NG | NG | NG | NG | NG | NG | NG |

NG = No growth

**Key Points**

- the relative cellular toxicities of the dressings, creams and gel reported here have not been addressed in this study
- further investigation is necessary to determine the relative safety of these products on the healing wound

nitrate or silver sulfadiazine (11). Whether the active form of silver differs between the dressings and whether the concentration is independent of effectiveness are unknown, and would be interesting aspects for further investigation.

Overall, silver-containing cream or gel compounds as well as non-silver antimicrobials Sulfamylon® and gentamicin sulfate show superior bactericidal properties than commercially used silver-containing dressings. The other issue regarding topical antimicrobial agents and dressings is their potential for cytotoxicity. Fleming (20) has stated that anything that is bactericidal may well be tissue cidal. The relative cellular toxicities of the dressings, creams and gel reported here have not been addressed in this study. Further investigation is necessary to determine the relative safety of these products on the healing wound. Once that is done, the relative value of the products can be determined by balancing their antimicrobial and cytoxicity characteristics.

## ACKNOWLEDGMENTS

Dr Payne has received research funding from Johnson and Johnson Wound Management for past projects (however, not for this project).

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CASE REPORT

# The use of Silvercel® to dress excision wounds following burns surgery

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Extensive skin necrosis in patients who have been severely burnt exposes them to a high risk of septicaemia with possible severe consequences (Dioguardi et al, 1994; Di Lonardo, 2005). When treating such patients there are two main aims: to remove the necrotic tissue as quickly as possible through surgical excision and then to protect the excised areas until enough autologous skin is available to perform reconstruction.

One way of protecting the excised sites is by taking allogeneic skin from a living or dead donor. The fresh or cryofrozen skin can temporarily take root on escharectomised areas before being unavoidably rejected. However, by removing the epidermal layer of the allograft, it is possible to avoid dermal layer rejection. It will therefore stay on the wound bed, creating a substratum that autologous keratinocytes harvested in vitro can take root in (Cuono's technique) (Cuono et al, 1986).

If there is no allogeneic skin available, however, an alternative covering is required that is temporarily capable of carrying out the skin's main functions. Such a dressing should have:

- Good mechanical resistance that allows it to remain in place for long periods without having to be frequently changed. There are clinical and economical advantages when the number of dressing changes are reduced. The patient experiences less stress, bleeding in the damaged area is reduced, materials are saved and there is a reduced involvement of medical staff
- The ability to conform closely to the wound bed providing an effective barrier against micro-organism infection
- The ability to absorb and retain the abundant exudates usually produced by such wounds, providing a moist wound healing environment that favours wound closure
- Efficient antiseptic properties against pathogens commonly responsible for infections
- Haemostatic action that is able to limit the degree of haemorrhage in the excised areas.

## Silvercel

Silvercel® (Johnson & Johnson Wound Management, Ascot) is indicated for use in the management of all moderate to heavily exuding partial and full-thickness chronic wounds. The dressing consists of a sterile, non-woven pad composed of hydroalginate and silver-coated fibres. Silvercel conforms well to the wound bed and quickly forms a resistant barrier against bacteria.

Hydroalginate is a highly-absorbent material that maintains an optimal moist wound healing environment in exuding wounds. Its unique composition is a mixture of high G calcium alginate and carboxymethylcellulose. The hydroalginate material increases its tensile strength when in contact with wound exudate, facilitating easy dressing removal from exuding wounds.

Carboxymethylcellulose is very absorbent which makes it appropriate for treating patients with severe burns who have undergone surgical excision of eschar tissue, because they produce abundant exudate (Vloemans et al, 2001). Calcium alginate increases the absorbency of the dressing and exerts a haemostatic action at the same time. Finally, the presence of silver results in a local antimicrobial action for 5–7 days without remarkable histotoxic effects (Dioguardi et al, 2004).

With all these characteristics, Silvercel is a useful alternative to the allogeneic skin used during surgical repair of severely burnt skin. In the following case, the clinical effectiveness of Silvercel was compared with Aquacel® Ag (ConvaTec, Ickenham). Aquacel Ag is composed of sodium carboxymethylcellulose and 1.2% ionic silver, and is frequently used to dress wounds arising from the surgical excision of eschar tissue.

## Materials and methods

A 28-day evaluation was carried out in June 2005 in the Division of Burns Surgery, Azienda Policlinico, in Bari. The patient was a 13-year-old male who had deep burns over more than 50% of his body following an explosion. Early surgical excision of eschar tissue was carried out on the upper limbs after five days of hospitalisation. Accurate haemostasis was reached through diathermocoagulation and the administration of saline solutions and adrenaline packs with a concentration of 1:5mg/l. No allogeneic skin or other biological dressings were available to protect the excision sites. As an alternative, modern aseptic dressings in non-textile fibre were considered because of their absorptive properties and for their ability to exert an extended and efficient aseptic and non-histotoxic action.

Both wounds measured approximately 800 $cm^2$. The wound on the left arm was covered with four 10cmx20cm Silvercel dressings and the wound on the right arm was covered with two 20x30cm Aquacel Ag dressings (*Figures 1 and 2*).

A secondary dressing was made on both arms using sterilised cotton pads with a layer of cotton wool and

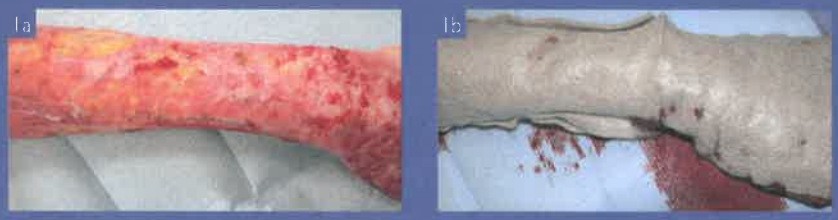


Figure 1. a Left Arm after an escharectomy (above) and, b. temporarily covered with Silvercel.

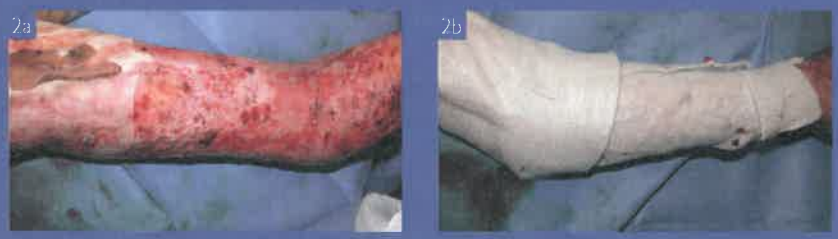


Figure 2. a. Right arm after escharectomy and, b. temporarily covered with Aquacel Ag.

an elastic three-layer compression bandage. Post-operative check-ups were performed every 48 hours to assess the status of the dressings and to look for clinical evidence of infection. Microbiological samples were taken from the wound exudates on the surface of the primary dressing using superficial pads every four days for 28 days. A final evaluation was performed analysing the following clinical parameters:

- Period of permanence
- Ability to absorb exudates
- Incidence of septic complications.

## Results

### Period of permanence

For almost three weeks, both Silvercel and Aquacel Ag conformed well to the wounds on both arms. Both primary dressings showed no structural alterations to necessitate immediate substitution. Indeed, only one application post-debridement was needed for both Silvercel and Aquacel Ag. Abundant irrigation with saline solution made the removal of the dressings very easy (*Figures 3,4,5 and 6*).

### Ability to absorb exudates

Both primary dressings were able to absorb and retain fluids, despite the hyperproduction of blood serum, with no maceration of surrounding healthy skin or structural deterioration occurring. Post-operative check-ups on the excised areas were quick and easy and secondary dressings were easily removed from the primary dressing, avoiding pain or contingent bleeding (*Figures 3,4,5 and 6*).

### Incidence of septic complications

Both dressings conformed closely to the wound bed, providing protection from infection. Every four days for 28 days, superficial pads applied to both arms showed colonisation with only *Pseudomonas aeruginosa* that was detected on day 8 post-surgery in both wounds. There was no clinical evidence of local infection on either of the arms during the whole period of the evaluation. Before surgical reconstruction, when the dressings were removed, the wound beds appeared to be well cleaned with a good amount of granulation tissue present. Both were well vascularised, confirming that there were no infective complications (*Figures 5 and 6*) and it was possible to perform a skin self-transplant on both excision sites that rooted completely.

Both Silvercel and Aquacel Ag were applied directly after surgical excision following accurate haemostasis through diathermocoagulation. The Silvercel dressings appeared to be helpful in supporting haemostasis (*Figures 6 and 7*), judging by the low amount of blood soaked by the dressing at the end of the wear time. This may be as a result of its calcium alginate component, however, this claim warrants further investigation.

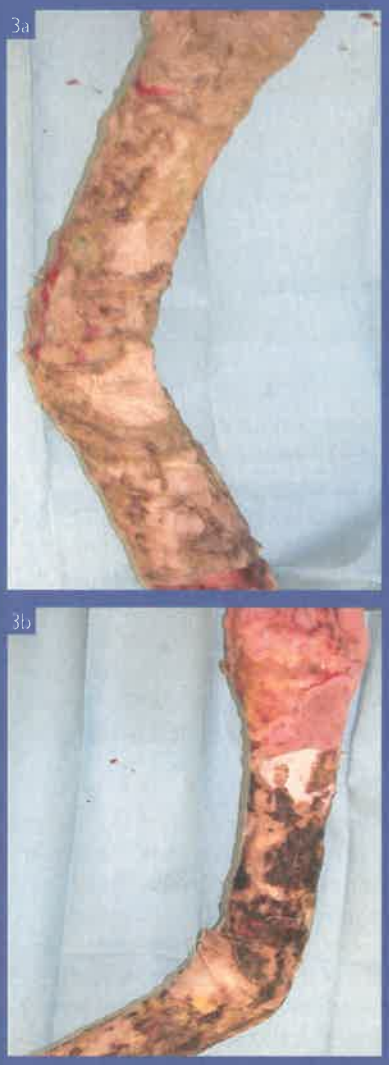


Figure 3. Review after two weeks treatment. a. left arm (Silvercel); b. right arm (Aquacel Ag).

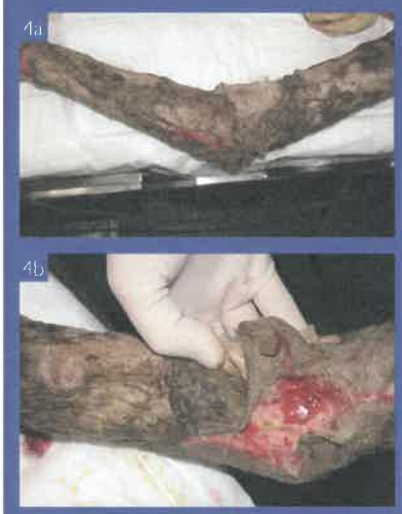


Figure 4. a,b.Check-up on the left arm after three weeks of treatment before removing Silvercel.

## Discussion and conclusions

Modern antiseptic and absorptive dressings can be extraordinarily effective when temporarily covering escharectomised areas. In a patient with severe burns, these kinds of lesions are difficult to manage, especially if no allogeneic skin is available. A large amount of blood serum is wasted (which has an obvious impact on dyscrasic and metabolic issues) with the resultant risk of dangerous complications and infections. Thus it is necessary to form a perfect barrier between the wound and the outside environment using materials that are able to resist the macerating effect of abundant exudate.

In this study, both primary dressings showed good results. They quickly transformed to produce a solid, compact membrane that sufficiently adhered to the bed of the wounds, thus limiting the loss of metabolites and constituting a valid barrier against bacterial aggression. Managing the wounds during the post-operative period was easy and limited pain for the patient. Both products were able to absorb and retain exudates of excessive blood serum, thus maintaining a moist wound environment conducive to healing. On removal of the dressings, a clean wound bed with granulation tissue could be seen and this, coupled with a lack of infective complications, ensured the patient could successfully receive skin autografts and continue along the road to recovery. WUK

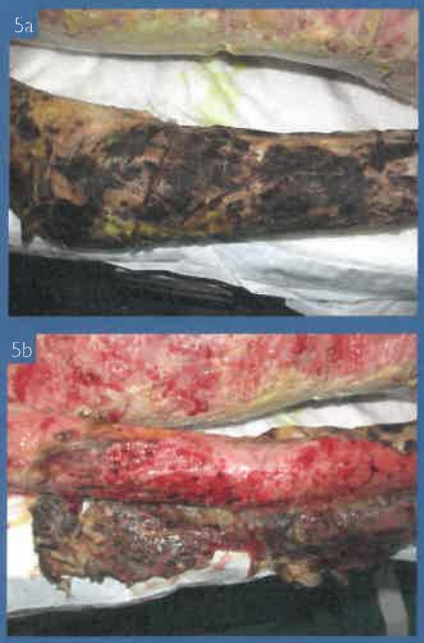



Figure 5. a. Right arm. b. Aquacel Ag removal after three weeks : no clinical evidence of local infection; good vascularisation of the wound bed.

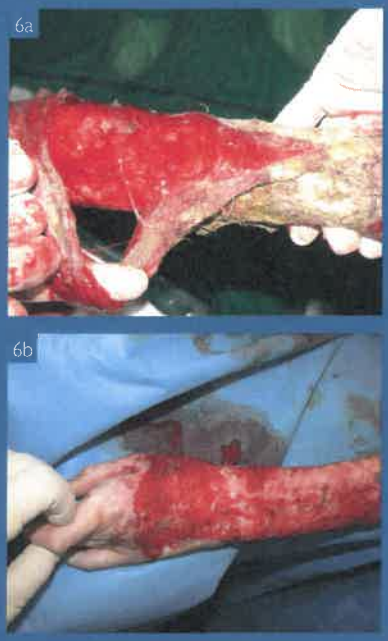
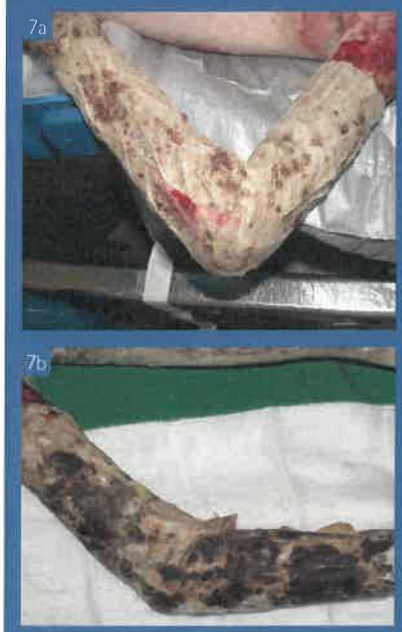



Figure 6. a. Left arm. b.Silvercel removal with no clinical evidence of local infection; good vascularisation of the wound bed.




Figures 7. Silvercel dressing (a) and Aquacel Ag (b). Less blood can be seen soaked through on the Silvercel dressing, which may be a result of its calcium-alginate component supporting haemostasis.

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# Comparative Evaluation of Silver-Containing Antimicrobial Dressings on In Vitro and In Vivo Processes of Wound Healing

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**Objectives:** To compare the in vitro and in vivo effects of silver products on wound healing. **Methods:** Eight silver products were compared to determine: fibroblast function using fibroblast-populated collagen lattices (FPCLs), fibroblast viability using the Trypan Blue exclusion test, and fibroblast mitochondrial activity using the MTT [yellow tetrazolium salt; 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay. In vivo effects of 9 silver products were evaluated utilizing a rat model of contaminated wounds. Serial quantitative bacteriology was performed on tissue biopsies over a 10-day period and serial wound areas were obtained over 12 days. **Results:** Fibroblast cytotoxicity occurred for all of the silver products evaluated. Remaining viable fibroblasts were insufficient to allow FPCL contraction. Mitochondrial activity of the fibroblasts allowed a separation of the various silver compounds. Actisorb Silver and Silvercel had the greatest viable fibroblast activity, but less than the control. Despite in vitro cytotoxicity, all of the silver products except Contreet Foam and Acticoat Moisture Control accelerated wound healing. **Conclusions:** Silver-containing dressings appeared to benefit healing of the wounds. Just as in vitro bacterial analyses do not fully predict the effect of an antimicrobial in the in vivo setting, in vitro cytotoxicity tests do not fully predict the effect of an agent on wound healing trajectories. Because of the varied antimicrobial and wound healing responses among products, a careful consideration of the particular effects of individual silver-containing dressings or drugs is warranted.

Wound healing is the end result of a series of interrelated cellular processes initiated by humoral factors such as cytokine growth factors.[1] These cellular processes are inhibited by a large tissue bacterial bioburden.[2] The cytokines and growth factors are also degraded by bacteria.[3] The level of tissue bacterial bioburden that inhibits healing has been shown in multiple studies to be greater than $1 \times 10^5$ or at least $1 \times 10^6$ bacteria per gram of tissue.[4,5] Such high levels of tissue bacteria can be present without clinical signs of infection, and when present can deleteriously affect wound healing.[6]

Attempts at controlling the tissue bacterial bioburden have been difficult. Systemically administered antibiotics do not effectively decrease the level of bacteria in a chronic granulating wound.[7] Therefore, topical antimicrobials or temporary biologic dressings have been the methods of choice.[4,8] Topical use of antibiotics that are used effectively systemically for purposes other than wound infection is discouraged because of an increased risk for developing allergies or the potential for bacteria to develop resistance to the drug.[9]

Because of the deleterious effect of a high tissue bacterial burden on the processes of wound healing, an effectual antimicrobial agent becomes a therapeutic imperative. Such an agent should be effective as a topical preparation, yet not to be cytotoxic to the cells involved in the wound healing process.[10] The antibacterial properties of silver have made it an attractive and practical choice for creating silver-based topical creams and dressings to comprise a class of antimicrobial topical treatments that have been used in wound care.[11-13]

Topical silver creams and solutions have a broad spectrum of antimicrobial activity, low development of resistance, few adverse reactions, and a low risk of systemic toxicity, but require frequent application, are care-intensive to apply and remove, and are sometimes painful. In contrast, wound dressings containing silver have been introduced in various designs to control the release of silver to the wound allowing the dressings to be changed less frequently.[14] The authors previously reported on the comparative antibacterial properties of eight silver-containing dressings and 2 nondressing silver agents.[14]

The other issue regarding topical antimicrobial agents and dressings is their potential for cytotoxicity. Fleming has stated that anything that is bactericidal may well be tissuecidal.[10] Some silver-containing antimicrobials have been found to exert cytotoxic effects on wound tissue and to inhibit keratinocyte production.[15-16] There is also concern that using them on open wounds may be injurious to fibroblasts and inhibit wound healing.[17-19] The purpose of this study was to evaluate the effect on various in vitro and in vivo processes involved in the wound healing using the silver-containing dressings and agents previously reported for their antimicrobial effects.

## METHODS

### In vitro fibroblast function

Fibroblast function was assessed by 3 methods. The first and second methods were the fibroblast-populated collagen lattice (FPCL) and Trypan Blue exclusion assay to assess for functionality and viability. The third was a measure of mitochondrial activity in living fibroblasts using the MTT [yellow tetrazolium salt; 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay. The fibroblasts for both tests were prepared by explanation as previously described.[20] The collagen lattices were prepared from type I rat tail collagen (acetic acid extracted) as recommended by the manufacturer (Upstate Biotechnology, Lake Placid, New York).[20] Undiluted collagen (1 mL) was placed in 35-mm culture dishes (Falcon 1008) and evenly spread. The dishes were placed in an ammonia vapor chamber for 3 minutes to solidify. Sterile distilled water (5 mL) was added to the culture dishes, allowed to stand for 1 hour, and then aspirated. This was repeated 4 times to remove excess ammonia and the collagen lattices were then incubated for 24 hours at 4°C. Phosphate-buffered saline with 1.0% serum was added to replace the final aspirate. An

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18-gauge needle was used to detach the collagen gel lattices from the surface of the culture dishes so that they would be loose and suspended in saline. A total of 45 collagen lattices were prepared to allow triplicate measurement based on eight treatment groups, plus an untreated control. To form the FPCLs, all saline was aspirated from the 35-mm culture dishes containing the lattices. Two mL of $2 \times 10^5$ fibroblasts per milliliter were placed on the surface of each of the prefabricated collagen gel lattices.[20-23]

Fibroblast-populated collagen lattices were divided into 9 groups. One group was kept as a control with no treatment, and the other 8 groups received one of the 8 types of silver-containing dressings. The silver-containing dressings were laid over the collagen matrix. The 8 types of silver dressings were Acticoat 7 (Smith and Nephew, London, UK), Acticoat Absorbent (Smith and Nephew, London, UK), Acticoat Moisture Control (Smith and Nephew, London, UK), Actisorb (Systagenix, North Yorkshire, UK), Aquacel Ag (ConvaTec Inc, Skillman, New Jersey), Contreet Foam (Coloplast, Minneapolis, Minnesota), Silvercel (Systagenix, North Yorkshire, UK), and Urgotul SSD (silver sulfadiazine) (Laboratoire Urgo, Chenove, France).

The FPCLs were incubated at 37°C in a humidified atmosphere of 5% carbon dioxide. The amount of gel contraction was measured every 24 hours for 5 days.[20-23] Acetate overlays were used for tracing the area of the gels. Gels were performed in triplicate (3 gels) for the fibroblast line established and measurements were then calculated using digital planimetry and Sigma Scan software (Jandel Scientific, Corte Madera, California). Each collagen gel area measurement was converted to reflect percentage of gel contraction.[20]

A one-way analysis of variance was used to determine significant differences among groups. When a difference was identified, a Tukey's test (all pairwise multiple comparisons test) was used to delineate the differences. Sigma Stat statistical software (Jandel Scientific, Corte Madera, California) was used for data analysis.

In addition, the 24-hour FPCLs with silver-containing dressing overlays were examined microscopically and photographed.[24] One of the gels was evaluated for fibroblast viability at 48 hours utilizing the Trypan Blue exclusion assay. Cell numbers were evaluated spectrophotometrically as a function of mitochondrial activity in living fibroblasts using the MTT assay.[25] In brief, the MTT assay is as follows: after exposure of $5 \times 10^5$ fibroblasts to the test silver-containing dressings, a 48-hour suspension in Dulbecco's Modified Eagle Medium was reincubated for 2 hours and 4 hours and then exposed to MTT assay. Mitochondrial dehydrogenases from viable fibroblasts cleave the tetrazolium ring, yielding purple formazan crystals. These are dissolved in acidified isopropanol resulting in a purple solution, which can then be spectrophotometrically measured. An increase or decrease in cell numbers results in a concomitant change in the amount of formazan formed, indicating the degree of toxicity caused by the test material.

### In vivo comparative wound model

All procedures followed a protocol approved by the Bay Pines VA Healthcare System Institutional Animal Care and Use Committee. Male Sprague-Dawley rats weighing 275 to 325 g had general anesthesia introduced by intraperitoneal injection of pentobarbital (35 mg/kg). Following satisfactory anesthesia, the animals' backs were clipped of hair and depilated. Four square $1.5 \times 1.5$ cm$^2$ symmetrical wounds were created in the midline of the back.[26-29] A copper template was used to create a line of 4 square wounds through the

skin and panniculus carnosus muscle to the deep fascia of the back. The template was sited centrally in a position that did not allow animals to reach the wounds with their paws or mouths to prevent potential interference with healing from ingestion of the treating agent or from trauma.

The wounds were then treated according to the following protocol: Each of the wounds was inoculated with $5 \times 10^5$ colony forming units (CFUs) of *Escherichia coli* ATCC 25922 (American Type Culture Collection, Rockville, Maryland).[27,29] Each animal had the cephalic wound left untreated as a control and the caudad 3 wounds dressed with one of 9 silver-containing dressings.[26] There were 5 animals ($n = 5$) in each dressing comparison group (15 wounds). The silver dressings evaluated were Acticoat 7, Acticoat Absorbent, Acticoat Moisture Control, Actisorb, Aquacel Ag, Contreet Foam, Silvercel, Urgotul SSD and Silverlon (Cura Surgical, Geneva, Illinois). In addition, there were 2 control groups, an open control and a closed control treated with Tegaderm (3M, St Paul, Minnesota). Animals were housed in individual cages (following 10 days acclimatization to separate caging) and given food and water ad libitum.

Dressings were changed every 24 hours. Every second day, the animals were reanesthetized and wounds were traced on acetate sheets and biopsied for quantitative bacteriology. Quantitative bacteriology was performed according to the method of Heggers and Robson.[5] Prior to biopsy, surface swabs were obtained for surface bacterial analyses. The wound surface was then cleansed and biopsies taken with a disposable punch biopsy trephine, and the biopsy weighed aseptically. The specimen was then dipped in alcohol and flamed to remove surface contamination, and then homogenized, after a 1:10 dilution with thioglycollate broth. Serial 10-fold dilutions were prepared and backplated to arrive at an accurate bacterial count.[5] Animals were followed for 12 days and biopsies obtained on days 2, 4, 6, 8, and 10.

Bacterial results were analyzed by the Duncan's range test (multiple comparisons), the alpha error set at 0.05, and quantitative bacteriology was reported as CFUs per gram of tissue. Analog tracings were made on alternate days on acetate sheets of both the open wound areas and of the advancing full-thickness skin edges of all wounds. To eliminate site-related variability in healing dynamics, the cephalad most wound of each animal was excluded from wound healing data analysis.[30] Any dried exudate was atraumatically removed prior to any wound tracings or biopsies. Wound areas were measured by digital planimetry of the acetate tracings (Sigma Scan, Jandel Scientific, Corte Madera, California). As described by Hokanson et al,[31] data acquired from each wound, as well as cumulative data from each group, was plotted graphically. Wound areas were compared at each measurement point using a 1-way analysis of variance, an all pairwise multiple comparisons test (Tukey test), and Mann-Whitney rank sum test to determine significant differences.

## RESULTS

### In vitro fibroblast function

Contractions of the FPCLs were completely inhibited by all of the test silver-containing dressings compared with the control ($P < .05$) (Fig 1). At least $1 \times 10^5$ viable fibroblasts are required in this model to produce lattice contraction. As can be seen in Table 1,

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Trypan Blue viability data demonstrated that an insufficient amount of viable fibroblasts remained to produce lattice contraction. This was corroborated by microscopy, which showed destruction of the fibroblasts. The FPCLs treated with Contreet Foam, and Acticoat Absorbent absorbed all the media in the gels thus no data were available for these 2 dressings.

**Table 1.** *Fibroblast survival after 48 hours of exposure to silver-containing dressings*

| Dressing | pH | Fibroblast Survival Count With Trypan Blue Stain* |
|---|---|---|
| Control | 7.05 | 361.5 |
| Silvercel | 6.68 | 26.8 |
| Actisorb | 7.41 | 16.0 |
| Acticoat 7 | 6.80 | 3.4 |
| Aquacel Abs | 7.36 | 1.6 |
| Urgotul SSD | 6.90 | 1.2 |
| Actisorb | 6.85 | 0 |
| Acticoat MC | 6.93 | No cells identified due to absorbency |
| Contreet Foam | 7.09 | No cells identified due to absorbency |

*Average of 5 fields counted with a 10X microscopic lens.
Abs indicates absorbent; MC, moisture control; SSD, silver sulfadiazine.

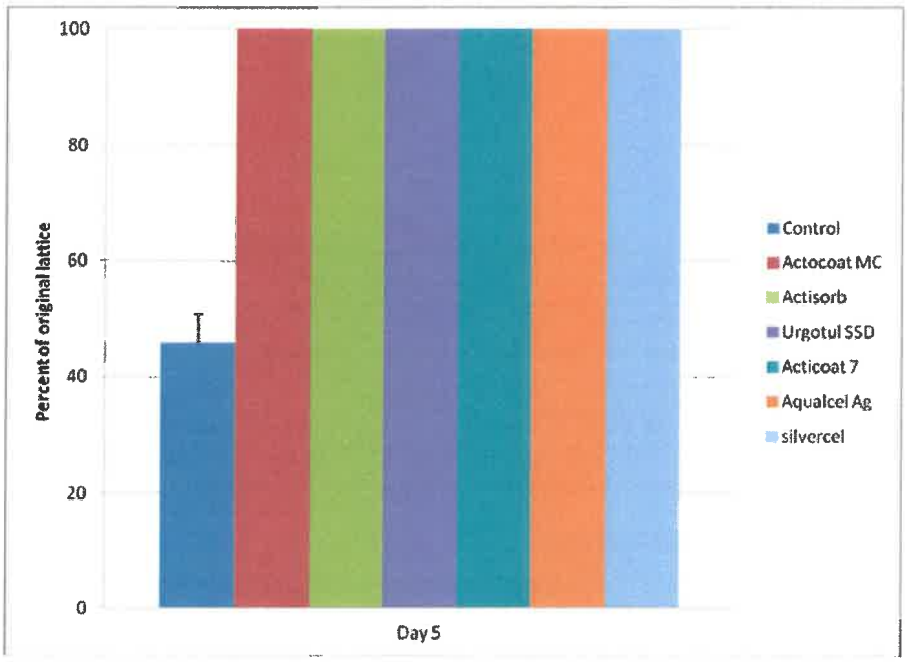
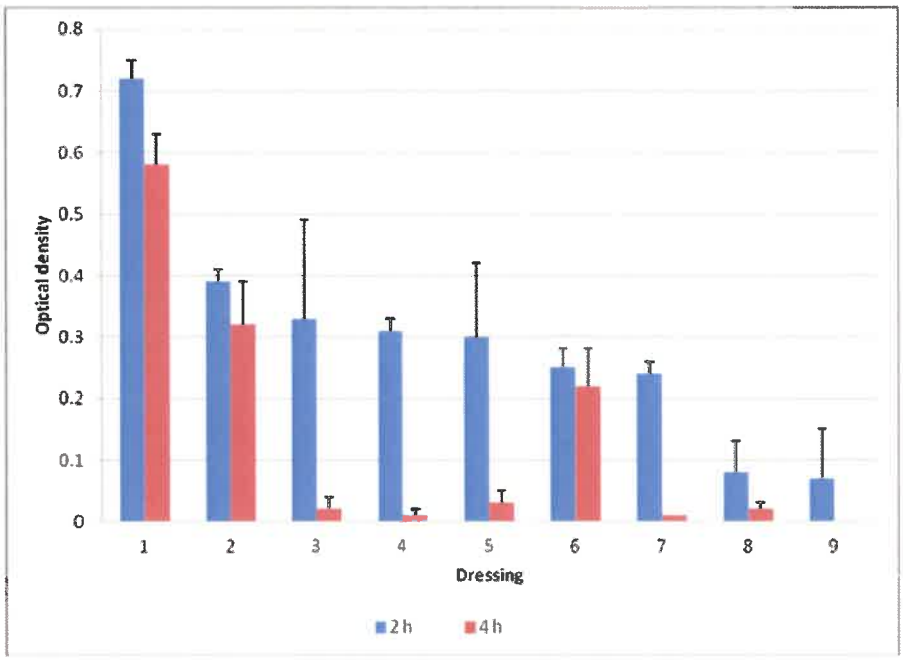



**Figure 1.** FPCLs did not contract because of lack of sufficient viable fibroblasts remaining after exposure to silver-containing dressings. Contreet Foam and Acticoat Absorbent absorbed all of the gel, thus preventing any data collection for those 2 dressings.



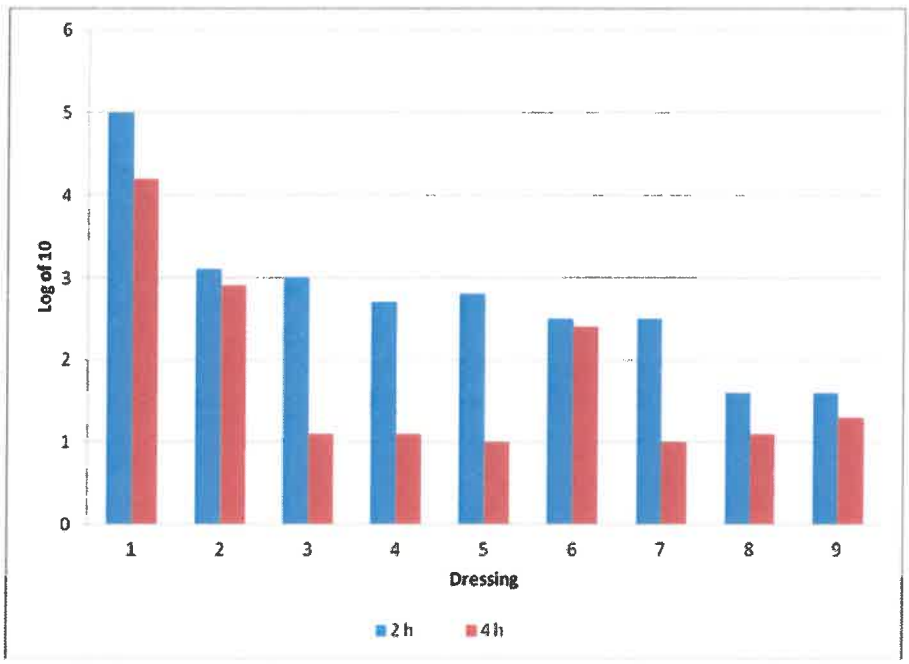

1- Control
2- Actisorb
3- Acticoat Moisture Control
4- Acticoat Absorbant
5- Concreet F
6- Silvercel
7- Acticoat 7
8- Aquacel Ag
9- Urgotul SSD

**Figure 2.** Results of the MTT Assay demonstrating markedly decreased mitochondrial activity in fibroblasts exposed to silver-containing dressings.

The mitochondrial testing allowed a true differentiation among the various dressings. Figure 2 demonstrates that Actisorb and Silvercel had significantly more mitochondrial activity at 4 hours compared with the other silver-containing dressings, but significantly less activity when compared with the control ($P < .05$). Figure 3 converts the optical density in Figure 2 to number of fibroblasts that expressed mitochondrial activity. Again, Actisorb and Silvercel were the least cytotoxic of the silver-containing dressings.

### In vivo comparative wound model

All of the silver-containing dressings decreased the tissue bacterial counts compared with the 2 control groups (Table 2). Contreet Foam did not eradicate all of the wound bacteria over the 10-day course of sampling, although it did decrease the CFUs per gram of tissue over 1000-fold. Five of the silver-containing dressings eradicated all wound bacteria within 48 hours (Table 2). The surface swabs identified the remaining bacteria in the wound as *E coli*.




1- Control
2- Actisorb
3- Acticoat Moisture Control
4- Acticoat Absorbent
5- Concreet F
6- Silvercel
7- Acticoat 7
8- Aquacel Ag
9- Urgotul SSD

**Figure 3.** Conversion of mitochondrial activity to numbers of functioning fibroblasts shows that fibroblasts are markedly decreased after exposure to silver-containing dressings.

There were marked differences among the dressings in their abilities to facilitate wound healing (Table 3). This model has historically required approximately 22 days to achieve complete wound closure. In the open control group (comparable to the historic control), 30% of the wound remained open at 12 days. Actisorb and Acticoat Absorbent Absorbent-treated wounds were essentially healed by day 12. All of the silver-containing dressings except Contreet Foam and Acticoat Moisture Control appeared to greatly accelerate healing of these contaminated wounds. Actisorb began to separate from the other dressings in its healing trajectory by day 8.

## DISCUSSION

Silver-containing solutions and compounds have enjoyed over a century of use as topical wound treatments.[13] Incorporating silver into wound dressings is a more recent use of silver's

antimicrobial properties. Silver is injurious to bacteria in several ways including damaging the bacterial cell wall and membrane permeability, blocking enzyme and transport systems, and preventing transcription and cell division.[17] Since agents which are bacteriostatic and/or bactericidal are often also injurious to cells in the wound healing scheme, difficulties arise when attempting to evaluate the various silver-containing dressings and drugs as far as a benefit:risk ratio. Part of the difficulty has been due to use of only in vitro data to evaluate the antimicrobial or cytotoxic effects of various antiseptics and antimicrobials including silver. For instance, silver-containing dressings are often compared in the language of bacteriology.[13] In vitro tests such as zones of inhibition, minimum inhibitory concentrations, minimum bactericidal concentrations, and bacterial log reductions are used to define an agent's antimicrobial effectiveness. This information is useful and allows comparisons of products. Similar in vitro tests are used to demonstrate potential cytotoxicity. Tests can demonstrate potential toxicity to keratinocytes, fibroblasts, and other cells in the wound healing scheme.[15,16,19]

**Table 2.** *Tissue bacterial count in CFUs/gram of tissue**

| Treatment | Day 2 | Day 4 | Day 6 | Day 8 | Day 10 |
|---|---|---|---|---|---|
| Open control | $2\times10^5$ | $3.2\times10^5$ | $4.6\times10^5$ | $3.2\times10^5$ | $3.2\times10^5$ |
| Closed control | $1\times10^5$ | $3.2\times10^5$ | $1.2\times10^5$ | $2\times10^5$ | $1.2\times10^5$ |
| Actisorb | NG | NG | NG | NG | NG |
| Acticoat MC | NG | NG | NG | NG | NG |
| Urgotul SSD | NG | NG | NG | NG | NG |
| Aquacel Ag | NG | NG | NG | NG | NG |
| Acticoat Abs | NG | NG | NG | NG | NG |
| Silverlon | $8\times10^2$ | NG | NG | NG | $4\times10^2$ |
| Silvercel | $2.5\times10^2$ | NG | NG | $4\times10^2$ | NG |
| Acticoat 7 | $4\times10^2$ | $3\times10^2$ | $1.4\times10^2$ | NG | NG |
| Contreet foam | $7\times10^2$ | $8\times10^2$ | $1\times10^2$ | $7\times10^2$ | $2\times10^2$ |

*All wounds inoculated with $5\times10^5$ CFUs on day 0.
Abs, indicates absorbent; CFU, colony forming unit; MC, moisture control; NG, no growth; SSD, silver sulfadiazine.

**Table 3.** *Healing of acute contaminated wound model: percent of original wound remaining open*

| Treatment | Day 2 | Day 4 | Day 6 | Day 8 | Day 10 | Day 12 |
|---|---|---|---|---|---|---|
| Open control | 95 | 83.5 | 77.5 | 65 | 47.5 | *30* |
| Closed control | 87.5 | 70 | 50 | 33.5 | 20 | 20 |
| Actisorb | 95 | 71.5 | 46.5 | 18.5* | 1.5* | 0* |
| Acticoat Abs | 85 | 61.5 | 40 | 20* | 10* | 1.5* |
| Urgotul SSD | 82.5 | 60 | 37.5 | 20* | 8.6* | 2.5* |
| Silverlon | 72.5 | 48.5 | 32.5* | 20* | 10* | 5* |
| Acticoat 7 | 75 | 53.5 | 32* | 20* | 11.5* | 5* |
| Silvercel | 72.5 | 51.5 | 35* | 22.5* | 15* | 6.5* |
| Aquacel Ag | 82.5 | 65 | 47.5 | 30 | 17.5 | 7.5* |
| Contreet Foam | 91.5 | 77.5 | 60 | 42.5 | 23.5 | 15 |
| Acticoat MC | 97.5 | 85 | 67.5 | 48 | 25 | 15 |

*$P < .05$ compared with the closed control.
Abs indicates absorbent; MC, moisture control; SSD, silver sulfadiazine.

The problem is that in vitro tests alone do not demonstrate the full efficacy, nor the potential harm of drug or dressing. In vivo tests often demonstrate a different picture. The combination of in vitro and in vivo test is useful in evaluating and comparing a benefit:risk ratio. The ultimate test may be the clinical trial, but for silver dressings the information is unclear. A 2010 Cochrane review of clinical trials on silver dressings concluded that there was insufficient evidence to determine the effectiveness of silver-containing dressings in promoting wound healing or preventing wound infection.[32]

Because the comparative antimicrobial effects of the various silver-containing dressings and drugs have been reported,[14] the present study was performed to evaluate the possible injurious effects of these agents on wound healing. Although there are definite cytotoxic effects on the fibroblasts, as shown by the FPCL assay, the MTT assay, and the Trypan Blue assay, those effects do not appear to be severe enough to impede the remaining fibroblasts from allowing wound contraction. In fact, healing was accelerated with the use of most of the silver-containing dressings. The findings of in vitro fibroblast toxicity are similar to those reported in the literature.[15,16,19] Not only has cytotoxicity been shown for normal fibroblasts, Zou et al reported cytotoxicity of silver dressings to human diabetic fibroblasts.[33] In addition to fibroblasts, cytotoxicity to keratinocytes has also been reported.[15,16,19] The effective killing of the tissue bacterial load seemed to be the best predictor of acceleration of healing. Actisorb, Acticoat Absorbent, and Urgotul SSD had the most rapid wound healing and all had effective in vivo antimicrobial results (Tables 2 and 3).

The lack of direct correlation of in vitro cytotoxicity and in vivo wound healing effects is not surprising. Kuhn et al[34] explained that the FPCL was an in vitro method to evaluate fibroblast function and the effect that the fibroblast had at contracting a collagen lattice, and that for chronic wounds such as pressure ulcers, diabetic foot ulcers, and venous stasis ulcers, the FPCLs do not predict healing. Although silver sulfadiazine has been shown to have in vitro toxicity to keratinocytes, Bishop et al[35] demonstrated that Silvadene (1% silver sulfadiazine, King Pharmaceuticals, Bristol, Tennessee) was more effective than the placebo in allowing epithelialization in a clinical trial of venous stasis ulcers. For that reason, a reproducible wound healing model is useful for evaluating wound healing effects. The contaminated wound model reported here demonstrated that silver-containing dressings appeared to benefit healing of the wounds. Similarly, Wright et al[36] using a contaminated wound porcine model showed that silver-coated dressings improved wound healing by reducing wound levels of matrix metalloproteinases and increasing the level of apoptosis. The authors postulated that these effects of the silver would alter or compress the inflammatory events in the wound. Paddock et al[37] also demonstrated an inhibitory effect on certain proinflammatory cytokines with the use of silver-containing dressings.

In conclusion, in vitro bacterial analyses do not fully predict the effect of an antimicrobial in the in vivo or clinical setting. The data presented demonstrate that in vitro cytotoxicity tests do not fully predict the effect of an agent on wound healing trajectories. Silver-containing dressings are not identical and affect both bacterial killing and wound healing with very different responses. Therefore, one must choose carefully when deciding on use of a specific silver-containing dressing or drug.

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# Evaluation of a silver-releasing hydroalginate dressing in chronic wounds with signs of local infection


• **Objective:** To evaluate the clinical impact of using a silver-releasing hydroalginate dressing to minimise the risk of local infection in colonised chronic wounds.

• **Method:** This was a randomised (stratification according to wound type) open-label multicentre comparative two-arm parallel-group study. Thirteen centres recruited 99 patients with either a venous leg ulcer or a pressure ulcer. None of the wounds required systemic antibiotics or were associated with lymphangitis and/or fever, but at least two of the following criteria had to be present: continuous pain; erythema; oedema; heat; and moderate to high levels of serous exudate. Patients were allocated to receive either a silver-releasing hydroalginate dressing (Silvercel, the test group) or a pure calcium alginate dressing (Algosteril, the control group). Wounds were assessed daily over 14 days to complete a modified ASEPSIS index to evaluate risk of infection, and then weekly for two additional weeks. A global wound severity score and area tracings were recorded weekly.

• **Results:** Fifty-one and 48 patients were randomised in the test and control groups respectively: 28 pressure ulcers and 71 venous leg ulcers. The total mASEPSIS score over 14 days did not differ significantly between groups: 95.4 ± 62.2 and 104.2 ± 72.8 in control and test groups respectively ($p=0.791$). Of the patients who completed the total four-week study duration, four out of 38 (10.5%) in the control group and none of the 40 in the test group were treated with systemic antibiotics at the final visit ($p=0.053$). According to the investigators, fewer wounds developed a clinical infection over the four-week follow-up in the test group (33% versus 46%; $p=0.223$). Overall, the four-week closure rate was statistically greater in the test group (0.32 ± 0.57cm$^2$/day versus 0.16 ± 0.40cm$^2$/day; $p=0.024$). Compared with baseline, the absolute decrease in wound severity score at week four was higher in the test group (-5.6 ± 3.2 versus -4.1 ± 4.3; $p=0.063$); this was also true of the percentage reduction (-32 ± 17% versus -23 ± 25%; $p=0.034$). Poor dressing acceptability and/or tolerability was noted in five out of 48 patients (10.4%) in the control group and in five out of 51 (9.8%) in the test group.

• **Conclusion:** This study suggests that the use of silver-releasing dressings in the management of wounds at high risk of infection may have a clinically favourable influence on wound prognosis; the dressings also appeared to be well tolerated. However, the evaluation of these advantages in controlled clinical trials is complex and requires potent studies and the development of more specific endpoints than those currently used.



• **Declaration of interest:** This study was funded by a grant from Johnson and Johnson Wound Management.

infection; critical colonisation; systemic antibiotics; silver


Chronic wound infection is a major cause of delayed healing and can lead to significant local and systemic complications. Precise prevalence and incidence rates are unknown, although studies suggest a range of 2–7%.[1,2]

The presence of bacteria alone does not indicate infection and is not a risk factor for impaired wound healing.[3-6] All chronic wounds are contaminated and the progression to local infection seems to occur in stages,[7] including colonisation (where bacterial proliferation reaches a certain load but without causing tissue damage) followed by critical colonisation.

While this concept is controversial and may be regarded as an intellectual construct, it is supported by clinical and bacteriological evidence. High bacterial levels in wound tissues and failure to heal is directly correlated:[8,9] wounds with >$10^5$ colony-forming units (CFU) per gram of tissue are associated with healing failure[10] and it has been suggested that healing is possible only when bacterial counts are maintained at $10^5$ CFU/g.[11]

It is therefore likely that reducing the bacterial load, particularly during 'critical colonisation', may prevent both infection and failure to heal. Debridement and cleansing minimise colonisation,


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**Box 1. Dressing properties**

**Algosteril**

A sterile, non-woven pad composed of 100% calcium alginate, indicated for the treatment of infected, bleeding or exuding wounds

**Silvercel**

A sterile, non-woven pad composed of a high-G (guluronic acid) alginate, carboxymethylcellulose (CMC) and silver-coated fibres. Its tensile strength increases when in contact with wound exudate, facilitating its removal from exuding wounds

but the effectiveness of prophylactic local antimicrobial agents in reducing bacterial load has not been demonstrated in controlled trials.[12,13] Indeed, as some of these agents have antibacterial and cytotoxic properties, they may inhibit healing.[14]

This article reports a controlled clinical trial that evaluated the clinical impact of an antibacterial agent in minimising the risk of local infection in colonised chronic wounds. The trial compared a simple alginate dressing (Algosteril, Brothier Laboratories SA, France) (control dressing) with a new silver hydroalginate dressing (Silvercel, Johnson & Johnson) (test dressing) (Box 1).

The study protocol and documents were submitted to and approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédiale of the Hôtel-Dieu University Hospital (Paris, France). All subjects received detailed information about the study and gave written consent.

## Design and procedures

This was a randomised open-label multicentre comparative two-arm parallel-group study. Two *a priori* randomisation lists were prepared and balanced by blocks of six: one list was for venous leg ulcers and one list for pressure ulcers (stratification). Each participating centre was provided with at least one block for each type of wound.

### Modified ASEPSIS Index Score

In the absence of other suitable tools, a modification of the ASEPSIS score was proposed for assessing the wounds and to determine the sample size (Table 1).

The ASEPSIS scoring system, a well-validated tool,[14–21] was developed to quantify postoperative wound infections and evaluate the effectiveness of antibiotic prophylaxis prior to cardiac surgery.[14]

The modified ASEPSIS index prolongs ASEPSIS use over 14 days without changing its scoring rate. This modification was proposed by the *European Multicentre Study Leukocyte Depletion of Autologous Whole Blood LDAWB 2001*.[22] The modification reflects the fact that chronic wounds take longer to heal than acute postoperative wounds.

Before the study, the suitability of the modified score (mASEPSIS) was examined at four of the 13 participating centres in 26 patients with chronic wounds (15 pressure ulcers, nine venous leg ulcers and two diabetic foot ulcers). In none of these cases was it necessary to isolate bacteria or perform debridement under general anaesthesia. Purulent exudate was drained in one patient under local anaesthetic.

While the average global score — 56.9 (SD) ±27.6 — did not differ between the groups, the values for the different items varied according to wound type. Scores for the items serous exudate and erythema were higher for patients with leg ulcers than for those with pressure ulcers. However, scores for the item 'duration of inpatient stay' were higher for pressure ulcers. Three items (serous exudate, erythema and separation of deep tissue) encompassed 83% of the global mASEPSIS score.

When the mean mASEPSIS subscale (the mean of the total daily wound scores) was plotted against time, there was a clear trend in favour of a decrease in scores, while the wound status improved. This suggests that the mASEPSIS can detect global wound evolution over a relatively short time period.

None of the team of investigators reported difficulties in using this coding scale.

### Sample size determination

Using the highest observed variance (256) for ASEPSIS in published studies of post-surgical wound management and hypothesising that it might be similar for mASEPSIS in chronic wounds, the required number of subjects per group was determined to be 50 (bilateral test, power 0.8, alpha risk 0.05) to detect a maximal between-group difference of 8 to 10 points on this index.

### Endpoints

The primary endpoint was the mASEPSIS index score obtained in the first two weeks of treatment.

### Study sample

A total of 101 subjects were enrolled by 13 centres between April 2003 and May 2004. One patient was incorrectly included (erroneous >0.7 ankle brachial pressure index [ABPI] value due to mediacalcinosis, with radiographic confirmation of the arterial origin of the leg ulcer and need for amputation). Another died suddenly (gastrointestinal haemorrhage) three days after randomisation and was not evaluated.

The intent-to-treat (ITT) population thus comprised 99 subjects: 51 in the test group (13 pressure ulcers and 38 leg ulcers) and 48 in the control group (15 pressure ulcers and 33 leg ulcers).

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**Table 1. Modified ASEPSIS scoring system**

| Parameter for daily inspection | Finding* | Points |
|---|---|---|
| Serous exudate | 0% | 0 |
| | 1–19% | 1 |
| | 20–39% | 2 |
| | 40–59% | 3 |
| | 60–79% | 4 |
| | ≥80% | 5 |
| Erythema | 0% | 0 |
| | 1–19% | 1 |
| | 20–39% | 2 |
| | 40–59% | 3 |
| | 60–79% | 4 |
| | ≥80% | 5 |
| Purulent exudate | 0% | 0 |
| | 1–19% | 2 |
| | 20–39% | 4 |
| | 40–59% | 6 |
| | 60-79% | 8 |
| | ≥80% | 10 |
| Separation of deep tissues | 0% | 0 |
| | 1–19% | 2 |
| | 20–39% | 4 |
| | 40–59% | 6 |
| | 60–79% | 8 |
| | ≥80% | 10 |

| Additional parameters assessed at end of 14 day assessment period | Finding | Points |
|---|---|---|
| Antibiotic therapy for wound infection (additional treatment) | Not given | 0 |
| | Given | 10 |
| Drainage of pus under local anaesthesia (additional treatment) | Not done | 0 |
| | Done | 10 |
| Debridement under general anaesthesia | Not done | 0 |
| | Done | 10 |
| Isolation of pathogenic bacteria | Not done | 0 |
| | Done | 10 |
| Prolonged hospital stay (>14 days) | Not prolonged | 0 |
| | Prolonged | 10 |

Global mASEPSIS score is the sum of points from 10 daily inspections plus points for additional parameters assessed at the end of the 14-day assessment period

*% of wound affected

### Inclusion criteria

The study sample comprised hospitalised adult patients or patients who could be seen every day for 14 days by the investigators and who had one of the following:

- A leg ulcer >2cm in one dimension but no larger than 20cm
- An ABPI >0.7 within the previous six months
- A grade III–IV (NPUAP system) pressure ulcer located on the ischium, sacrum, trochanter or heel
- In the investigators' opinion, there were no clear signs of infection requiring the use of systemic antibiotics or lymphangitis and/or fever. However, at least two of the following criteria had to be present: continuous pain; erythema; oedema; heat; moderate to high levels of serous exudate
- At least 50% of the wound covered with yellow slough, discoloured or friable granulation tissue, pocketing or undermining at the base of the wound, or foul odour.

### Exclusion criteria

- Patients who had received systemic antibiotics during the previous five days for any reason
- Patients with a very poor life expectancy or with a clinical condition that might interfere with wound healing such as active carcinoma, vasculitis, use of systemic corticosteroids, immunosuppressive agents, radiation therapy or chemotherapy within the past 30 days
- Patients who had received a topical chemical debriding agent within the previous seven days.

## Method

At the inclusion visit, patients' demographic details and medical and surgical history were recorded. A Norton score was calculated to verify that the risk level was balanced between the two treatment groups and the ABPI was measured where appropriate. The target wound was assessed and an acetate tracing of its perimeter was performed.

Patients were stratified according to wound type and randomly allocated to receive one of the two dressings. All venous leg ulcers were treated with class II–III (French classification) compression bandaging.

The target wound was assessed and its condition recorded daily (Monday to Friday) over 14 days beginning the day after enrolment in the study. The mASEPSIS was completed during these assessments. Patients were followed up whenever possible for an additional two weeks to evaluate wound surface


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**Table 2. Wound severity score system**

| | Strong | Moderate | Weak | None |
|---|---|---|---|---|
| % of wound area affected | >40% | 20–40% | <20% | 0% |
| Exudate | 4 | 3 | 2 | 1 |
| Odour | 4 | 3 | 2 | 1 |
| Necrotic tissue (black) | 4 | 3 | 2 | 1 |
| Fibrinous deposit (yellow) | 4 | 3 | 2 | 1 |
| Granulation tissue (red) | 1 | 2 | 3 | 4 |
| Epithelialised tissue (pink) | 1 | 2 | 3 | 4 |

Total severity score = sum of all items (minimum: 12; maximum: 18)

reduction and to continue monitoring dressing acceptability and tolerability.

Medical evaluations were performed each week during the four-week study period. At each visit the following were noted:

- Details of the wound appearance and closure (closed, improved, unchanged or worsening)
- Whether or not complete wound debridement had been performed (including by the dressing)
- The occurrence of all adverse events except those indicative of a topical reaction to the applied dressings
- Any changes to the subject's medication.

The target wound was then measured (planimetry) and photographed.

All subjects received at least one application of the allocated dressings and had at least one clinical evaluation (ITT population).

### Dressings and local care

Any necrotic plaques were removed on entry into the study by surgical or mechanical debridement. Thereafter, this was the only method of debridement used, and was given on an as-required basis. As all of these wounds were at high risk of developing frank local infection, it was expected that slough or necrotic tissue would reappear during the course of the study. Skin emollients and/or moisturisers were permitted provided they did not come into contact with the wound bed or edge.

Both the test and control dressings were alginate based, which enabled us to evaluate the clinical benefit of the addition of silver. In both groups sterile pads (Topper, Johnson & Johnson) were used as secondary dressings; these were secured with hypoallergenic adhesives. Wounds were cleansed with sterile saline (CDM, Lavoisier, France).

During the first two weeks of the study dressings were changed at each mASEPSIS index evaluation (at least five changes per week). Thereafter, changes were performed at least every two to three days as needed. The daily use of the mASEPSIS tool during the first 14 days necessitated this frequency of dressing change.

Wound cultures, either qualitative or quantitative, were taken at the investigators' discretion. These wounds were at very high risk of developing frank local infection. If the wound became infected and the investigator believed intervention was appropriate, systemic antibiotic therapy was permitted. It was decided to do this rather than exclude these patients from the trial in order to achieve the most accurate picture of wound evolution.

### Data processing and statistical analysis

Data analysis was conducted using SPSS 11.5 software. Comparability of groups was verified using univariate ANOVA for continuous variables and Chi-square test for categorical variables.

Group comparisons used an univariate general linear model (GLM) procedure (type III) with dressing (test or control) and wound (leg or pressure ulcers) as fixed factors. For variables evaluated at weekly intervals, a GLM procedure for repeated measures was performed. To deal with missing data, the last observed value was carried forward (LOVCF).

The main efficacy parameter was the two-week global mASEPSIS score calculated on the ITT population. A second analysis was conducted for the per-protocol (PP) population, defined as all randomised subjects without a major protocol violation who completed the 14 days of treatment (at least 10 daily evaluations of the mASEPSIS index).

The reduction of the use of systemic antibiotics was examined using the chi-square test (or Fisher's exact test), while the proportion of wounds that the investigators regarded as definitely infected at any time during the four-week study period were compared using the chi-square test. The proportion of totally debrided wounds at week 4 was compared using the chi-square test. Changes in wound surface area were calculated from wound tracings obtained at baseline and each week over the four weeks.

All tracings were assessed by two experienced clinicians using a validated method.[23,24] The percentage reduction in wound surface area compared with baseline was calculated for each week (Wn–Wo/Wo). Wound closure rate (the rate of reduction in the open area of the wound) was calculated per week as (Value Wn - Value Wn-1)/t, where t was the number of days between the two measurements. The results are expressed as $cm^2$/day. Log-transformed data were used for statistical analysis.

The proportion of closed/improved wounds at week 4 were compared using the chi-square test by regrouping the original 'closed' and 'improved' groups as 'improved' and 'worsening', and

**Table 3. Patients' baseline characteristics**

| | Test (n=51) | Control (n=48) | p |
|---|---|---|---|
| Sex (F/M) | 58.8%/41.2% | 68.8%/31.2% | 0.403 |
| Age (years) | 74.9 ± 9.0 | 77.6 ± 10.9 | 0.181 |
| Age >80 years | 21.6% | 52.1% | 0.005 |
| BMI (kg/m²) | 28.6 ± 8.7 | 25.9 ± 7.1 | 0.118 |
| BMI ≥30kg/m² | 36.4% | 23.8% | 0.229 |
| **Associated disease/history** | | | |
| Atopic history* | 11.8% | 14.6% | 0.770 |
| Diabetes (type 1 or 2) | 33.3% | 12.5% | 0.018 |
| Hypertension | 60.8% | 52.1% | 0.422 |
| Coronary disease | 19.6% | 16.7% | 0.797 |
| Lower limb arteriopathy | 9.8% | 2.1% | 0.206 |
| History of leg ulcer | 51.0% | 56.3% | 0.688 |
| History of pressure ulcer | 19.6% | 12.5% | 0.418 |
| Recent surgery | 7.8% | 10.5% | 0.675 |
| Other relevant history | 33.3% | 27.1% | 0.520 |

*Atopic disease such as eczema or asthma
Mean ±SD

'unchanged' as 'non-improved'. To evaluate the condition of the surrounding skin, the level of exudate, wound odour, the wound severity score and the percentage reduction at the last clinical evaluation as compared with baseline (ANOVA procedure) were all calculated. The system used to calculate wound severity score is given in Table 2.

## Results

### Baseline characteristics

There were no statistically significant differences in baseline demographics between the two groups; these data are given in Table 3.

Wound type (leg or pressure ulcer) was balanced between the groups, as was the total number of wounds per subject. There was a non-significant trend of wounds with a longer duration in the test group compared with the control (Tables 4). While global wound areas did not differ significantly between groups for each of the two wound types, the wound surface area of leg ulcers was on average larger in the test group (44.8 ± 46.3cm² versus 24.5 + 21.3cm² in the control group).

Mean wound severity scores at baseline were 16.9 ± 3.0 in the control group and 17.5 ± 2.5 in the test group (p=0.289). Similarly, there were no significant differences between the groups within the two wound-type strata.

There was a non-statistically significant trend for test wounds having more clinical signs of critical colonisation compared with control wounds (Table 5). With the exception of a higher percentage of maceration in the test group, no other difference was detected between groups for peri-wound aspect. A similar percentage of local adverse events in the weeks preceding enrolment was observed in both groups.

### Modified ASEPSIS index

Regardless of the population concerned (ITT or PP) or the calculation procedure (LOVCF or not), no significant between-group differences were detected (Table

**Table 4. Baseline characteristics of wounds**

| | Leg ulcers | | Pressure ulcers | | Total | | p |
|---|---|---|---|---|---|---|---|
| | Test | Control | Test | Control | Test | Control | |
| Duration (months) (median) | 42.5 ± 96.0 (12.0) | 25.0 ± 37.2 (7.0) | 4.4 ± 3.7 (2.0) | 3.7 ± 6.0 (2.0) | 32.6 ± 84.0 (10.0) | 18.3 ± 32.5 (6.0) | *0.165 |
| Area (cm²) (median) | 44.8 ± 46.3 (25.7) | 24.5 ± 21.3 (16.1) | 22.5 ± 21.5 (15.6) | 22.4 ± 25.5 (18.7) | 39.1 ± 42.3 (23.5) | 23.9 ± 22.5 (16.5) | 0.181 |
| Severity score (median) | 17.4 ± 2.4 (18.0) | 16.7 ± 2.7 (16.0) | 17.6 ± 3.0 (17.0) | 17.4 ± 3.7 (18.0) | 17.5 ± 2.5 (18.0) | 16.9 ± 3.0 (17.0) | 0.289 |

* Mann-Whitney U test
Results are presented as mean ±SD


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**Table 5. Wound type and signs of critical colonisation at baseline**

| | Test No. | % | Control No. | % | p |
|---|---|---|---|---|---|
| **Type and no. of wounds** | | | | | |
| Pressure ulcer | 13 | 25.5% | 15 | 31.3% | 0.656 |
| Venous ulcer | 38 | 74.5% | 33 | 68.8% | 0.656 |
| More than one wound present | 29 | 56.9% | 34 | 70,8% | 0.210 |
| Mean no. of wounds | 2.2±1.5 | | 2.2±1.4 | | 0.865 |
| **Events in the preceding week** | | | | | |
| Use of systemic antibiotics | 5 | 9.8% | 3 | 6.3% | |
| Debridement under general anaesthesia | 0 | 0.0% | 1 | 2.1% | |
| Isolation of a pathogen bacteria | 3 | 5.9% | 1 | 2.1% | |
| Prolonged hospital stay due to wound status | 1 | 2.0% | 4 | 8.3% | |
| **Signs of critical colonisation** | | | | | |
| Spontaneous pain | 23 | 45.1% | 18 | 37.5% | 0.541 |
| Increased local warmth | 22 | 43.1% | 19 | 39.6% | 0.839 |
| Erythema | 43 | 84.3% | 36 | 75.0% | 0.319 |
| Oedema | 25 | 49.0% | 19 | 39.6% | 0.420 |
| Moderate to strong serous exudate | 48 | 94.1% | 39 | 81.3% | 0.066 |
| Yellow deposit over 50% | 40 | 78.4% | 37 | 77.1% | 1.000 |
| Discolouration of granulation tissue | 17 | 33.3% | 18 | 37.5% | 0.680 |
| Friable granulation tissue | 14 | 27.5% | 11 | 22.9% | 0.649 |
| Dehiscence | 19 | 37.3% | 16 | 33.3% | 0.834 |
| Foul odour | 22 | 43.1% | 14 | 29.2% | 0.210 |
| Mean number of signs of critical colonisation | 5.4 ± 1.8 | | 4.7 ± 2.1 | | 0.117 |
| **Peri-wound skin aspect** | | | | | |
| Peri-wound erythema | 44 | 86.3% | 36 | 75.0% | 0.204 |
| Peri-wound oedema | 25 | 49.0% | 19 | 39.6% | 0.420 |
| Cellulitis | 1 | 2.0% | 0 | 0.0% | 1.000 |
| Eczema | 11 | 21.6% | 6 | 12.5% | 0.291 |
| Maceration | 18 | 35.3% | 7 | 14.6% | 0.021 |

6). For the ITT population, the mean mASEPSIS score was 95.4 ± 62.2 and 104.2 ± 72.8 in the control and test groups respectively (p=0.791). The mASEPSIS score was lower, on average, in the test group for pressure ulcers than in the control group. The reverse was the case for leg ulcers.

### Use of systemic antibiotics

Over the four-week study period, systemic antibiotics were administered to five subjects (10.4%) in the control group and four (7.8%) in the test group. This difference was not significant (p=0.736). However, evaluation of the subpopulation that completed the four weeks showed that four of the 38 subjects (10.5%) in control group and none of the 40 in the test group were treated with systemic antibiotics at that final visit (p=0.053).

According to the investigators, fewer wounds developed a clinical infection during the four-week follow-up in the test group than in the control group (33% versus 46%), but this difference was not statistically significant (p=0.223).

### Wound area

Compared with baseline, the absolute reduction in surface area (Table 6) was -8.9 ± 16.0cm² in the test group and -4.4 ± 11.3cm² in the control group (p=0.117). Expressed in terms of percentage wound-area regression over the four weeks, this was -23.7 ± 43.6% and -24.0 ± 41.6% in the test and control groups, respectively (p=0.923). While not statistically significant, mean wound areas differed substantially between the groups at inclusion.

To account for this difference, closure rate (CR) was calculated. At each week CR was greater in the test group (Table 7). Overall, the four-week closure rate was statistically greater in the test group (0.32 ± 0.57cm²/day versus 0.16 ± 0.40cm²/day; p=0.024 by ANOVA on log-transformed data).

### Evolution of wound severity score

Compared with baseline, the absolute decrease in wound severity score at week 4 was higher in the test group than in the control group (-5.6 ± 3.2 versus -4.1 ± 4.3; p=0.063) (Fig 1 and Table 6). In terms of percentage reduction, the score significantly decreased in the test group compared with the controls (-32 ± 17% versus -23 ± 25%; p=0.034).

According to the investigators, 47.1% of wounds were noted as totally debrided at the final evaluation in the test group compared with 35.4% in the control group (p=0.308).

### Global wound evaluation at the final visit

Over the four-week study period, no silver staining was detected in the test group. One wound in each group closed and 33 and 25 wounds in the test and control groups respectively were noted as improved.

**Table 6. mASEPSIS, wound area and severity score changes during study**

| | Leg ulcers Test | Leg ulcers Control | Pressure ulcers Test | Pressure ulcers Control | Total Test | Total Control | p |
|---|---|---|---|---|---|---|---|
| **mASEPSIS index** | | | | | | | |
| ITT population | 111.8 ± 79.1 (n=38) | 86.3 ± 51.0 (n=33) | 81.8 ± 45.1 (n=13) | 115.3 ± 80.2 (n=15) | 104.2 ±7 2.8 (n=51) | 95.4 ± 62.2 (n=48) | 0.791 |
| PP population | 102.7 ± 70.3 (n=29) | 77.4 ± 48.4 (n=27) | 87.3 ± 42.2 (n=12) | 111.3 ± 74.2 (n=12) | 98.2 ± 63.2 (n=41) | 87.8 ± 58.7 (n=39) | 0.963 |
| ITT population no LOVCF procedure | 118.3 ± 83.7 (n=38) | 69.7 ± 62.9 (n=33) | 83.6 ± 45.3 (n=13) | 142.9 ± 140.9 (n=15) | 109.5 ± 76.8 (n=51) | 111.1 ± 95.2 (n=48) | 0.325 |
| **Wound area evolution*** | | | | | | | |
| Absolute decrease at week 4 ($cm^2$) | -9.5 ± 17.9 | -6.0 ± 11.7 | -7.2 ± 9.0 | -0.8 ± 10.0 | -8.9 ± 16.0 | -4.4 ± 11.3 | 0.117 |
| % wound reduction at week 4 | -21.0 ± 45.4% | -28.5 ± 37.0% | -31.6 ± 38.1% | -13.9 ± 50.3% | -23.7 ± 43.6% | -24.0 ± 41.6% | 0.923 |
| Healing rate over 4 weeks ($cm^2$/day) | 0.34 ± 0.64 | 0.21 ± 0.42 | 0.26 ± 0.32 | 0.03± 0.36 | 0.32 ± 0.57 | 0.16 ± 0.40 | **0.024 |
| **Wound severity score*** | | | | | | | |
| Mean score at week 4 | 11.8 ± 3.4 | 12.3 ± 3.3 | 12.1 ± 3.9 | 13.8 ± 4.3 | 11.9 ± 3.5 | 12.8 ± 3.7 | 0.171 |
| Absolute decrease at week 4 | -5.7 ± 2.8 | -4.4 ± 4.3 | -5.5 ± 4.2 | -3.6 ± 5.0 | -5.6 ± 3.2 | -4.1 ± 4.3 | 0.063 |
| % decrease in score | -32.6 ± 15.4% | -25.0 ± 21.8% | -30.7 ± 23.0% | -17.5 ± 32.0% | -32.1 ± 17.4% | -22.6 ± 25.3% | 0.034 |

* ITT population with LOVCF over 4 weeks
** ANOVA on log-transformed data
ITT: intent to treat; PP: per-protocol; LOVCF: last value carried forward

**Fig 1. Wound area and severity score at week 4 (means and SEM)**

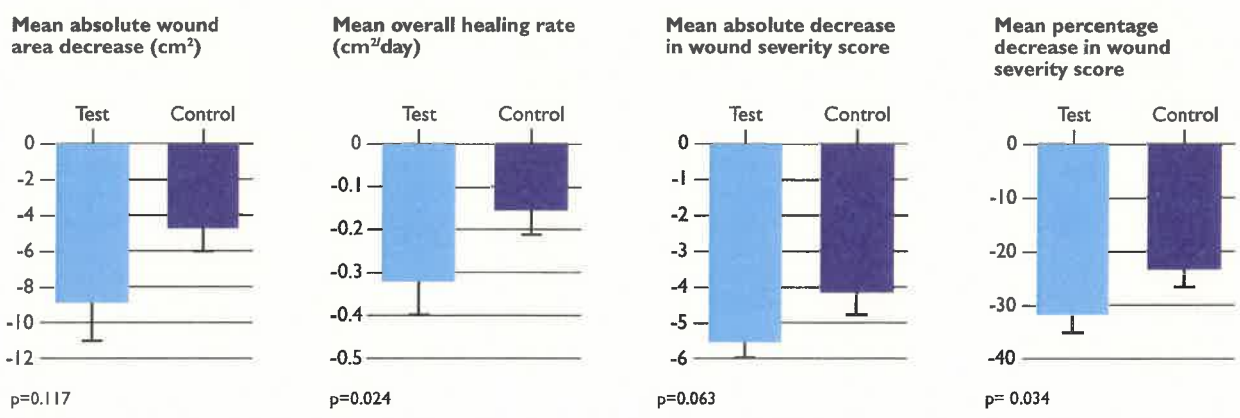

**Table 7. Closure rate (cm²/day)**

| | Test (n=51) | Control (n=48) |
|---|---|---|
| Week 1 | -0.79 ± 1.65 | -0.37 ± 0.90 |
| Week 2 | -0.55 ± 1.32 | -0.23 ± 0.86 |
| Week 3 | -0.14 ± 1.81 | +0.14 ± 0.86 |
| Week 4 | -0.52 ± 1.40 | -0.16 ± 0.57 |
| Weeks 0–4 | -0.32 ± 0.57 | -0.16 ± 0.40 |

**Table 8. Reasons for early discontinuation**

| Reason | Test | Control | Total |
|---|---|---|---|
| Alginate dressing no longer indicated (dry wound) | 1 | 1 | 2 |
| Consent withdrawal | 1 | 0 | 1 |
| Intercurrent event* | 4 | 1 | 5 |
| Wound grafting | 1 | 1 | 2 |
| Wound infection | 1 | 2 | 3 |
| Wound aggravation | 2 | 4 | 6 |
| **Total** | **10** | **9** | **19** |

* Cardiac arrest (1)
Car accident (1)
Patient transferred to another hospital (2)
Patient went on holidays (1)

The percentage of improved/closed wounds was higher, but not significantly so, in the test group (67% versus 54%; p=0.425).

### Adverse events

Nineteen (19.2%) out of the 99 subjects (10 and nine patients in the test and control groups respectively) did not complete the four-week study for reasons other than their wound (Table 8).

Poor local acceptability and/or tolerability (Table 9) was noted in five out of 48 patients (10.4%) in the control group (all leg ulcers) and five out of 51 patients (9.8%) in the test group (four leg ulcers and one pressure ulcer). In four patients (three in the test group and one in the control), the investigator was 'certain' there was a relationship between the applied dressing and the adverse event. The allocated dressing was discontinued, and a foam dressing was used instead.

## Discussion

This randomised trial was designed to evaluate the clinical impact of using a new silver-releasing dressing in the management of critically colonised chronic wounds. The principal objective was to verify if the silver dressing was able to prevent the occurrence of frank clinically recognised local infection.

Critical colonisation is not a well-defined concept. Indeed, classic signs of infection may not be present in chronic wounds despite high bioburdens. Conversely, continued tissue injury can trigger inflammatory responses that mimic these signs of infection in the absence high bioburden, causing false positive diagnoses of chronic wound infection. Cutting and Harding[25,26] suggested using symptoms of secondary wound infection, such as serous drainage with concurrent inflammation, delayed healing, discoloured granulation tissue, pocketing at the wound base, foul odour and wound breakdown, as diagnostic signs of infection.

However, it has been suggested that critical colonisation may be identified where bacterially induced host injuries are not yet apparent.[27-31] Integration of this concept into clinical practice may help clinicians to decide when to aggressively reduce bacterial load to prevent infection. Nevertheless, identification of critical colonisation is not easy and there is as yet no consensus on the subject. In this study, we used a pragmatic approach to define critical colonisation by combining two criteria:

- The presence of at least two local signs that are indicative of local infection
- The clinical decision of the physician not to prescribe systemic antibiotics.

Thus, while some selected wounds might have been regarded as locally infected, in all instances signs were of insufficient severity to induce systemic antibiotic treatment. A posteriori, study results support the relevance of selecting wounds on such simple clinical criteria. Indeed, the various assessments of the enrolled wounds clearly suggest a high risk of developing infection, with 79.8% presenting erythema, 87.9% moderate or strong exudate, and 77.8% having yellow slough covering more than 50% of their area. Furthermore, 41.4% of the patients experienced spontaneous pain, 35.4% increased local warmth and 36.4% discolouration of granulation tissue with foul odour.

On average, per wound, more than four local signs compatible with critical colonisation were observed. However, due to their local status, the selected wounds were relatively heterogeneous and, despite stratified randomisation, the distribution of risk to developing infection was not optimally balanced.

In the test group the wound area was greater and of a longer duration, with more local signs of colonisation, and maceration was more frequently

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**27** Sibbald, R.G., Orsted, H., Schultz, G.S. et al. Preparing the wound bed 2003: focus on infection and inflammation. Ostomy Wound Manage 2003; 49: 11, 23-51.
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**29** Wall, I.B., Davies, C.E., Hill, K.E. et al. Potential role of anaerobic cocci in impaired human wound healing. Wound Repair Regen 2002; 10: 6, 346-353.
**30** Edwards, R., Harding, K.G. Bacteria and wound healing. Curr Opin Infect Dis 2004; 17: 2, 91-96.
**31** Ovington, L. The truth about silver. Ostomy Wound Manage 2004; 50: 9A suppl., 1S-10S.
**32** Gardner, S.E., Frantz, R.A., Doebbeling, B.N. The validity of the clinical signs and symptoms used to identify localized chronic wound infection. Wound Repair Regen 2001; 9: 3, 178-186.

observed on inclusion compared with the control group. While not statistically significant (with the exception of maceration), the magnitude of these differences might be regarded as clinically relevant as an influence on wound outcome.

We compared a simple alginate dressing (Algosteryl) with a new silver-releasing hydroalginate (Silvercel). As these wounds were not aggressively debrided at inclusion, the selection of an alginate dressing is largely regarded as appropriate.[7] While the two dressings are not similar, the chemical structures of these calcium salt alginate polymers are not too disparate, with a guluronic:manuronic ratio greater than one in both cases. The silver-releasing properties of Silvercel have been extensively evaluated *in vitro* and validated as sufficient to reduce bacterial load.[31]

Our main study endpoint was the modified ASEPSIS index. An advantage is that it is based on clinical evaluation, requiring only daily local inspection of wounds. Furthermore, each of the evaluated items is directly related to local signs of colonisation, and its evolution might be expected to correlate with bacterial load changes. Therefore, it was appropriate for the study, and neither the investigators nor the nurses encountered major difficulties in using the index.

Overall, this study did not detect any between-group differences in the mASEPSIS index over two weeks. Given that the relationship between bacterial burden and wound closure is fairly well established, there are two potential explanations for the failure of the mASEPSIS index to demonstrate differences:

- Silver is an ineffective antimicrobial agent
- This index is not sufficiently sensitive to measure changes in chronic wounds.

As it is well known that silver is an effective antimicrobial agent,[32] it seems more reasonable that the tool itself is inadequate. First, the variance of the mASEPSIS index score in this study of chronic wounds is considerably greater than that observed in postoperative wound studies.[14,16,18,21] This may be related to the more heterogeneous aspects of chronic wounds, resulting in the tool having a low sensitivity to changes in bacterial load in these settings.

Second, despite wounds in the test group having a worse baseline evaluation, the four-week closure rate was significantly better in this group. Furthermore, compared with baseline, there was a significantly greater decrease in the wound severity score in the test group, and fewer test subjects required antibiotic therapy during the study. In addition, while not statistically significant, more test wounds were totally debrided at the study endpoint, and more were noted as improved or closed.

Overall, the contradiction between differences in wound outcome over four weeks and the lack of difference in the two-week mASEPSIS score demonstrates that this index cannot adequately capture the global chronic wound evolution, even if this is related to infection risk. In addition, a single parameter may not be sufficient to document the interest of a bacterial load-decreasing agent when treating chronic wounds, and only composite outcomes including healing rate, severity scores based on wound aspects and need for antibiotics may be relevant from a methodological point of view for future clinical trials.

Microbiological evaluation was not used as the correlation between microbiological results and the risk of infection has not been extensively evaluated due to technical difficulties.

**Table 9. Local adverse events**

| Local event | Intensity | Dressing discontinued? |
|---|---|---|
| **Control group** | | |
| Pain during dressing change | Strong | Yes |
| Peri-wound eczema | Moderate | No |
| Intermittent burning sensation immediately after dressing application | Strong | No |
| Increase wound size, pain, patient refusal to continue | Moderate | No |
| Erythema, pain | Strong | Yes |
| **Test group** | | |
| Peri-wound eczema | Moderate | Yes |
| Peri-wound irritation due to maceration | Strong | No |
| Extension of slough; dry wound | Strong | Yes |
| Pruritus; pain | Strong | No |
| Pain during dressing change; peri-wound erythema and pruritus | Strong | No |

## Conclusion

This study suggests that the use of silver-releasing dressings in the management of wounds at high risk of infection may have a clinically favourable influence on wound prognosis and are well tolerated. Silver-releasing dressings may help to promote cleansing, control bacterial load and improve healing rate while preventing use of systemic antibiotics. However, the evaluation of these advantages in controlled clinical trials is complex and requires potent studies and the development of more specific endpoints. ■

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# The management of wounds using Silvercel hydroalginate

**Many factors result in delayed wound healing, one of which is infection. A variety of wound dressings with antimicrobial properties are now available. Practitioners need to select an antimicrobial dressing most appropriate for the wound being treated, while considering factors such as exudate management and maintenance of a moist wound healing environment. Silvercel, a new hydroalginate dressing with silver (Johnson & Johnson Wound Management, Ascot) appears to offer enhanced moisture management through hydroalginate technology along with the antibacterial potency of silver. This article looks at the role of silver and Silvercel in wound management.**

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**KEY WORDS**
Silvercel
Elemental silver
Antimicrobial
Moist wound healing
Exudate management

Normal wound healing in adults follows an ordered progression of events, which ultimately results in wound closure. In some cases, however, wound closure may not occur. There are many reasons why a wound will fail to heal, including both local (e.g. the presence of a foreign body or infection) and systemic (e.g. malnutrition or diabetes) factors. In a slow-healing or non-healing wound, it is important for the practitioner to consider all underlying pathologies and to treat them appropriately. While it is recognised (Kingsley, 2002) that no single dressing can provide all the answers to the problems and requirements of a wound throughout its life, effective treatments can be prescribed for wounds that become infected or critically colonised with micro-organisms.

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Micro-organisms are very likely to be present in all wounds but will vary in both type and quantity. Non-healing chronic wounds, e.g. leg ulcers and pressure ulcers are usually colonised with a number of species, many of which can be potential pathogens (Scanlon and Dowsett, 2002). When the microflora of the wound become imbalanced, the normal wound healing process is interrupted, resulting in a non-healing and deteriorating wound, which can ultimately lead to systemic infection if left untreated. Unfortunately, with increasing resistance, the treatment of infected wounds with antibiotics is becoming more and more problematic. It is possible, however, to reduce the wound bioburden to avoid systemic infection by the use of topical antibacterial agents such as silver and iodine (White et al, 2001).

## Background to the medicinal use of silver

Silver is a broad-spectrum antimicrobial for controlling a wide range of bacterial, fungal, and viral pathogens (White, 2001) and has a long history of use. In a historical overview, White (2001) noted how it has been used medicinally since the 19th century for conditions such as eye infections, burns and postoperative sepsis, but how interest in it declined with the advent of antibiotics, penicillin and sulphonamides. Interest in the antibacterial properties of silver was renewed in the 1960s, and today, it is being used again, mainly in the management of burns. Silver is also being increasingly used as an antimicrobial in medical devices such as wound dressings, catheters, stents, and external fixation pins.

The first wound dressing containing silver, available since 1989 in the UK and across Europe, was Actisorb Plus (now known as Actisorb Silver 220; Johnson & Johnson Wound Management, Ascot), an activated charcoal cloth with silver.

Since that time there have been numerous new silver dressings launched on the market of Europe and North America. These vary in their structure and composition, and, in the chemical nature of the silver source; elemental (metallic) or compound (silver salt). This article will concentrate on the very newest of these dressings — Silvercel (Johnson & Johnson Wound Management, Ascot).

## Silver in wound management

Two forms of silver are used in topical wound dressings: compound (silver salts) and elemental (metallic). Both forms of silver release silver ions into the wound, and this is what provides the antimicrobial effect.

The mechanism by which this is acheived differs for each form. Silver compound, on exposure to water (as found in wound fluid), rapidly dissociates giving rise to silver ions ▸▸

Figure 1. Silvercel hydroalginate dressing with silver.

**Table 1.**
**Silvercel hydroalginate with silver: size availability**

| Size | Number of dressings per box |
|---|---|
| 5x5cm | 10 |
| 11x11cm | 10 |
| 10x20cm | 5 |
| 2.5x30.5 cm | 5 |

($Ag^+$). Elemental silver, on the other hand, is virtually insoluble, and needs to form an intermediate stage. This is usually silver oxide (AgO) that is formed on exposure to air or water (as present in the wound fluid). It is the silver oxide that then dissociates into silver ions.

White (2001) in a review of the use of silver in wound management noted that for silver-containing dressings to be effective it is important that the solubility of silver is low (i.e. that it does not solubilize into the wound quickly but does so slowly over a period of days thereby providing sustained release and prolonged antimicrobial activity). He suggested that this slow release ensures there is no bolus dosing that could give rise to transient high silver levels in tissue, blood or urine, which could increase the risk of systemic toxicity.

Healthcare practitioners are rightly concerned about using products that are linked with a risk of toxicity, however, the toxicity attributed to silver is usually associated with the silver carrier (used to deliver or stabilise the silver) rather than the silver ions, e.g. nitrate from silver nitrate or sulphadiazine from the silver sulphadiazine creams (Demling and DeSanti, 2001). These effects are therefore not regarded as being applicable to modern wound dressings (Cutting, 2001).

The recent development of a number of wound dressings that contain metallic silver and provide a sustained release of low but effective levels of ionic silver can be seen as a way of reducing the risk of silver toxicity. Cutting (2001) also observed that most negative reports on elemental silver were published before 1940 and suggested that the bad press associated with the use of silver relates to the use of silver nitrate solution which may cause staining and a burning sensation on the skin.

The systemic absorption of deposits of silver which can result in a cosmetic problem of skin discolouration (which can be permanent), is known as argyria. It arises due to the deposition of minute granules of silver or silver sulphide in the dermis around the basement membrane and sweat ducts (at least 10g of silver needs to be absorbed to observe argyria). It is usually associated with prolonged non-medical environmental exposure to silver metal. There is no current evidence that modern silver wound dressings result in detectable systemic absorption of silver through chronic wounds. One case of argyria has been reported in a patient treated with a modern nanocrystalline silver dressing for 30% TBSA burns of the legs and abdomen (Lansdown and Williams, 2004). There have been no reports of argyria or other toxic responses with silver hydroalginate in clinical use.

As for the development of silver resistance, it is recognised (Lansdown, 2002) that most, if not all, of the sustained silver ion release products are effective against methicillin and vancomycin resistant strains and that no resistant strains have been encountered. While the potential for development of resistance to silver exists, it has been suggested that this is low. Bacteria have been exposed to silver for four billion years with no widespread resistance to date, whereas widespread resistance to antibiotics has developed within the last 60 years (Percival and Bowler, 2005).

## Proposed mechanism of action of silver

The antimicrobial effects of silver ions have been attributed to four different mechanisms (Thurman and Gerba, 1989):

- Interference with bacterial electron transfer
- Binding to bacterial DNA and spores thus increasing the stability of the double helix and impairing cell replication
- Binding to the bacterial cell membrane causing structural and receptor function damage

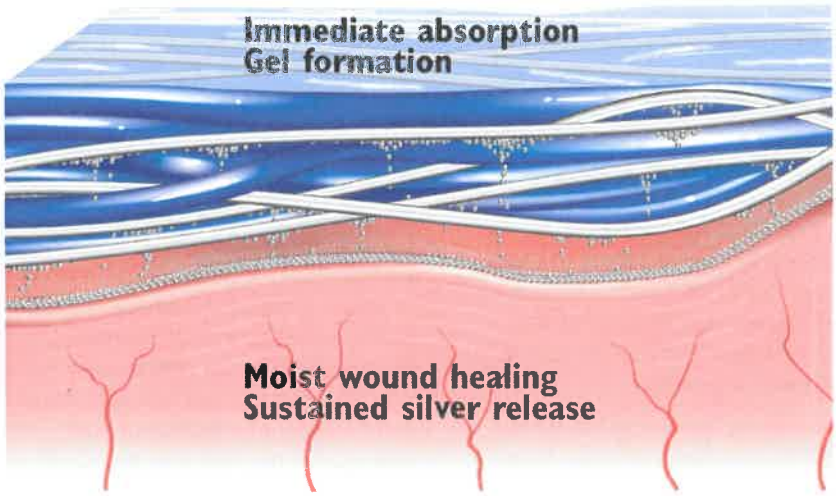


Figure 2. The mode of action of Silvercel.

- Formation of insoluble, metabolically ineffective compounds with bacterial anions, sulphydryl groups as in methionine and thiolated nucleotides, histidine and enzymes.

### Silvercel

Silvercel hydroalginate with silver is a new product from Johnson and Johnson Wound Management, Ascot. It is indicated for use in the management of all moderate to heavily exuding partial- and full-thickness chronic wounds. The dressing consists of a sterile, non-woven pad composed of high G (guluronic acid) calcium alginate, carboxymethylcellulose (CMC), and silver-coated fibres (*Figure 1*). It combines the moisture management properties of the alginate and CMC with the broad-spectrum antimicrobial action of silver ions. Silvercel is available in both pad and rope format in a variety of sizes (*Table 1*) and is available for use in both hospital and community settings in the UK, as well as in other European countries and the US.

### Hydroalginate technology

Hydroalginate is a highly-absorbent material that maintains an optimal moist wound healing environment in exuding wounds. Its unique composition is a mixture of high G calcium alginate and CMC. The hydroalginate material increases its tensile strength when in contact with wound exudate, facilitating dressing removal from exuding wounds.

### Mode of action

The absorbency of Silvercel is attributed to the hydroalginate component of the dressing, which also maintains a moist wound healing environment.

**Table 2. Absorbency of dressings: SMTL method TM101 based on BP1993 monograph for alginate dressings**

| Dressing | Absorbency g of fluid/100cm² |
|---|---|
| Hydroalginate | 22.9 |
| Hydrofibre | 16.3 |
| Alginate | 22.7 |

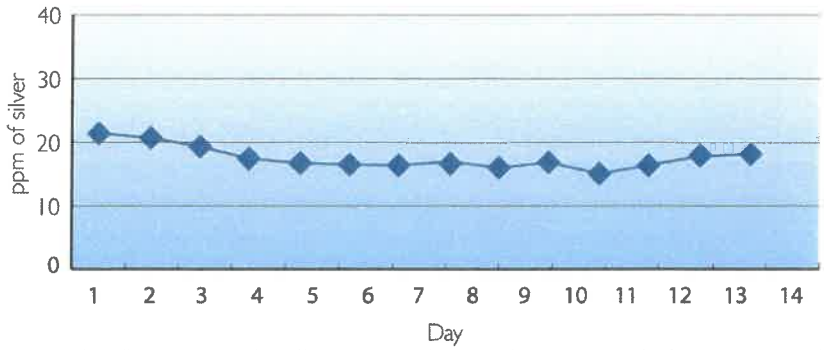


**Figure 3. In-vitro silver release profile of Silvercel hydroalginate dressing over 14 days in simulated wound fluid.**

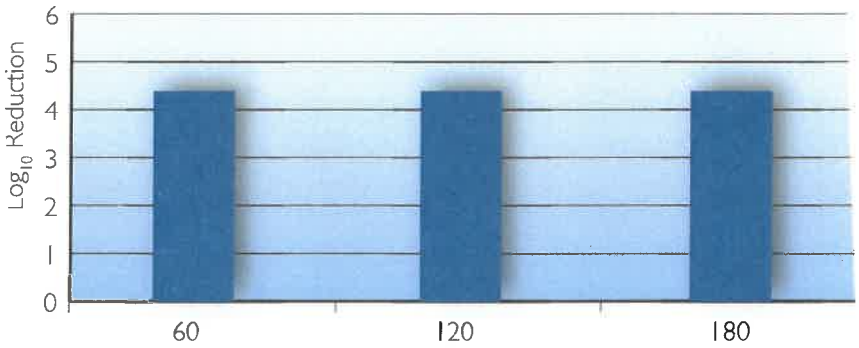


**Figure 4. Silvercel dressing $Log_{10}$ reduction *Pseudomonas aerugenosa* post-14 day challenge in simulated wound bed.**

The silver fibres kill a broad spectrum of microorganisms associated with bacterial colonisation and infection of wounds. Silvercel uses elemental silver, which releases ions in a sustained and controlled manner, allowing access to all wound areas, including into cavities (*Figure 2*).

### Absorption and gelling properties

Alginates have found their use in a wide variety of acute and chronic wounds (especially wet), since their introduction into wound care practice.

Alginic acid is a hydrophilic, high molecular weight polymeric acid that is derived from seaweed and is readily formed into fibres. Alginate is a polymer composed of a mixture of two monomer units in varying proportions. These are:

- Alpha-L-guluronic acid (G type)
- Beta-D-mannuronic acid (M type).

Alginate that consists largely of G-type monomer units is referred to as high G alginate. Silvercel dressing utilises high G calcium alginate (JJWM, 2003).

High G fibres are not as absorbent as high M, and do not form a gel, but they retain their structure more and do not break down and gel in the presence of sodium ions. When in contact with wound fluid, there is an exchange of sodium ions from the wound fluid with calcium ions on the high-G calcium alginate. In order to increase the exudate handling properties of Silvercel, CMC has been incorporated which gives the dressing increased absorbency, similar to a high M alginate (JJWM, 2003). The absorbency properties of the hydroalginate have been tested in-vitro and have been shown to be superior to a hydrofibre dressing (*Table 2*) (SMTL[Surgical Materials Testing Laboratory]/JJWM, 2003).

The alginate and CMC combination also provide a certain level of gelling of the hydroalginate fibres, designed to maximise the conformability of the dressing to the wound contours and to ease dressing removal.

Silvercel is indicated for use on all moderate to heavily exuding

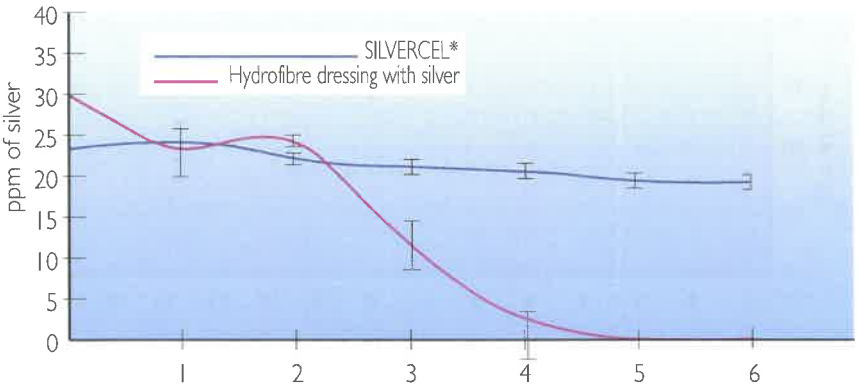


**Figure 5. In vitro silver release in simulated wound fluid.**

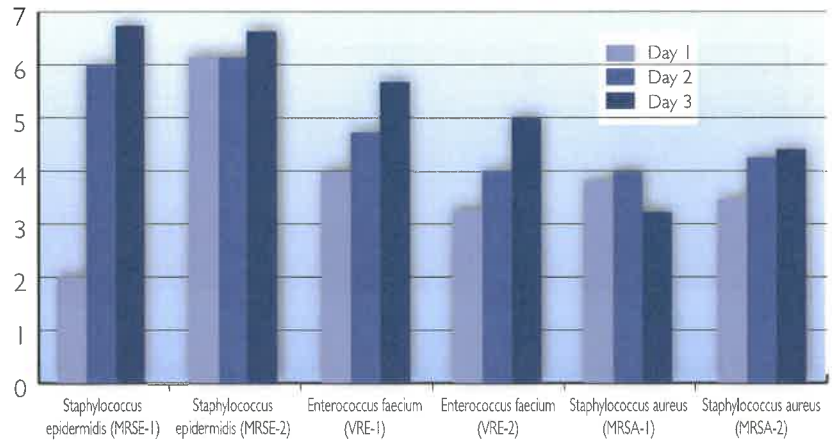


**Figure 6. Average zone of inhibition around Silvercel hydroalginate dressing, in mm.**

chronic wounds. As wound conditions improve and exudate levels decrease, it may be preferable to switch to a more appropriate dressing.

## Silver release profile

The release of silver ions from the Silvercel hydroalginate dressing is a dynamic process that is triggered by application to an exuding wound with micro-organisms present. An in-vitro comparison of two elemental silver dressings in simulated wound fluid at 37°C demonstrated that silver release stopped when saturation was reached (15–25 ppm) (Addison et al, 2004). Maintaining this level of saturation is a constant process. The silver ions are taken up and used within the wound fluid, promoting further release of silver ions from the dressing to achieve saturation again. It is therefore suggested, that it is the wound environment that controls the release of the silver ions from Silvercel, keeping the release controlled and balanced. There is no depositing of high doses of silver ions from dressings impregnated with elemental silver, such as Silvercel. The silver-coated fibres within the dressing provide a reservoir of silver ions and data (*Figure 3*) confirms that these are released at effective antimicrobial levels, in-vitro, for at least 14 days in simulated wound fluid, with the simulated wound fluid being changed daily (Addison et al, 2004).

At the end of the 14-day study period in this in-vitro test, the samples were tested for their antimicrobial activity against *Pseudomonas aeruginosa* in a $Log_{10}$ reduction test over three hours. The data showed that even after 14 days of silver release in simulated wound fluid (which was changed every 24 hours), the dressing samples demonstrated a 5 Log reduction, i.e. essentially no viable bacteria remained (Addison et al, 2004).

It is suggested that slow-release products are ideal at both decreasing bacterial burden as well as diminishing or eliminating excess exudate (Falanga, 2001) and that silver-impregnated fabrics that continuously release silver ions into the wound have the greatest antibacterial effect (Lansdown, 2002). A further in-vitro study compared the silver release in simulated wound fluid of a silver compound dressing with an elemental silver dressing, Silvercel hydroalginate. Samples of dressings were placed in fresh simulated wound fluid each day over seven days and the silver release was determined by atomic absorption (*Figure 5*) (Addison et al, 2005).

The elemental silver product, Silvercel hydroalginate, provided a continuous sustained in-vitro release of silver ions over the entire test period. The silver compound product, a hydrofibre dressing, showed diminished silver ion release between days 3–4. The elemental silver provides a reservoir of silver ions which is likely to be far greater than the potential wear time of the dressing. For dressings containing silver compounds, the longevity of silver ion release may be more difficult to predict. In vitro with wound fluid changed only once every 24 hours, the silver compound product's silver ion release fell to residual levels before the end of the test period. In a wetter/heavily exuding environment there may be potential for the release to stop even sooner.

Elemental silver dressings typically have much higher levels of silver within the product (8–20%) than dressings containing silver compounds (0.02–1.5%). The actual parts per million (ppm) of silver released from both types of dressings is approximately the same (15–25 ppm) in simulated wound fluid during the first few hours. However, the two products differ in the length of time that they can sustain silver release. As elemental products have a higher percentage of silver within the dressing, not necessarily linked to a higher concentration of silver ions released, the time that they can sustain silver ion release appears to be greatly extended. The silver that is not utilised for silver ion release is removed with the dressing.

### Antimicrobial activity

It is generally regarded that silver is a broad spectrum anitmicrobial. In-vitro data on the antimicrobial activity of Silvercel has confirmed this effect against a wide range of microorganisms (>150 human clinical isolates tested), including *Pseudomonas aeruginosa, Escherichia coli, Streptococcus pyogenes, Staphylococcus aureus, Staphylococcus epidermidis, Klebsiella pneumoniae* and *Candida albicans* (Addison et al, 2005). Testing was conducted using the zone of inhibition test, where a 2.5cm x 2.5cm sample of the dressing is placed on an agar plate pre-inoculated with the microorganism under test. The zones were read after 24 hours incubation, then again at 48 and 72 hours, with the dressing sample being transferred to a new-freshly prepared pre-inoculated agar plate at each timepoint. The zone of inhibition was measured in mm.

These in-vitro tests included assessing the repeat challenge zone of inhibition over a three-day period for antibiotic resistant strains including *Staphylococcus epidermidis* (MRSE), *Staphylococcus aureus* (MRSA), *Enterococcus faecium* (VRE) and *Enterococcus faecalis* (VRE) where Silvercel was shown to have a bactericidal effect on these organisms over a three-day period following repeat challenge (*Figure 6*)(Addison et al, 2005).

### Wet tensile strength

It has been demonstrated (SMTL / JJWM, 2003) that Silvercel hydroalginate dressing has a very high wet tensile strength not usually associated with alginates or hydrofibres. The data shows that the wet tensile strength of Silvercel increases by over 50%, permitting the dressing to be removed easily from the wound (*Figure 7*).

### Clinical evidence

A randomised, multi-centre, clinical trial is in progress to assess the impact of Silvercel in the management of chronic wounds with signs of local infection and it is expected that the results will be available during 2005. Initial evidence of the effectiveness of Silvercel in managing critically colonised wounds comes from case reports. Several have been documented to date (JJWM, data on file, Case Studies) and two are described here to provide an insight into its use on a chronic venous leg ulcer and a pressure ulcer over a 28-day period.

### Case report 1

A 93-year-old woman with a right venous leg ulcer and also suffering from malnutrition and coronary insufficiency, had Silvercel applied to her leg ulcer over a period of 28 days. She had a previous history of leg ulceration and had also undergone recent orthopaedic surgery after which the current leg ulcer developed. On assessment, the wound measured 4.5 cm x 2.6 cm, was heavily exuding with signs of inflammation and maceration of the surrounding skin. The wound was cleansed with saline solution and redressed using Silvercel 11cm x 11cm dressing under compression bandaging (*Figure 8a*).

By Day 7, a clinical improvement was seen with a decrease in the amount of exudate and commencement of epithelialisation. Wound size had reduced by 42.5% and the dressings were well-tolerated and accepted by the patient. Only seven days later the wound size had reduced by 70% to 3.1cm x 1.1cm, the amount of exudate continued to reduce and epithelialisation to increase. There were signs of inflammation of the wound and surrounding tissue at this timepoint (Day 14), which had all disappeared by Day 28. There was a further reduction in exudate levels. By the end of the evaluation, the wound size had reduced by 83.1% to 2cm x 1cm (*Figure 8b*).

### Case report 2

A 93-year old man, with a history of coronary insufficiency and Parkinson's disease, presented with a deep sacral pressure ulcer. The ulcer was Grade 3 and had been present for two months. On assessment, the wound measured 5.5 cm long x 2 cm wide, was necrotic with extensive fibrin deposits, exuding, malodourous and painful. There was erythema, eczema and trophic changes of the surrounding skin (*Figure 9a*). Previous treatment was with a sterile hydrocellular dressing. After initial assessment, the wound was cleansed with saline solution and a Silvercel 11cm x 11cm dressing applied. Hydrating gel and cream were applied to the surrounding skin.

By day 7, there was a significant decrease in exudate, odour and necrosis, with the appearance of some granulation tissue (*Figure 9b*). After a further 14 days (day 21), there was no longer any odour. The necrotic tissue and fibrin deposits had also disappeared, with significant ▸▸

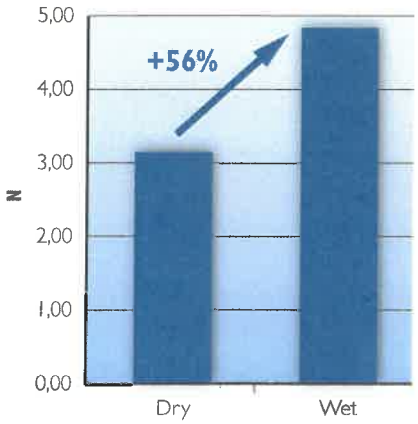


**Figure 7. The tensile strength of Silvercel hydroalginate dressing.**

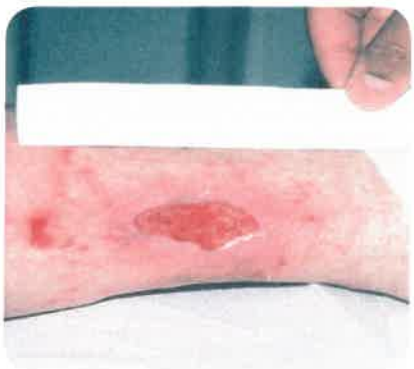

**Figure 8a. Venous leg ulcer at presentation.**

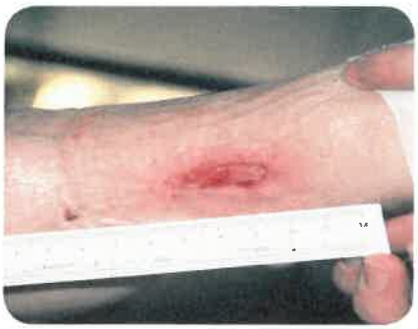

**Figure 8b. Venous leg ulcer at day 28 of dressing with Silvercel.**

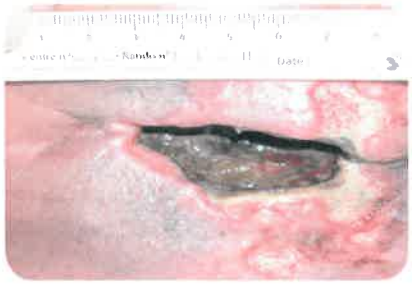

**Figure 9a. Grade 3 pressure ulcer at presentation.**

**Figure 9b. Grade 3 pressure ulcer at day 7 of dressing with Silvercel.**

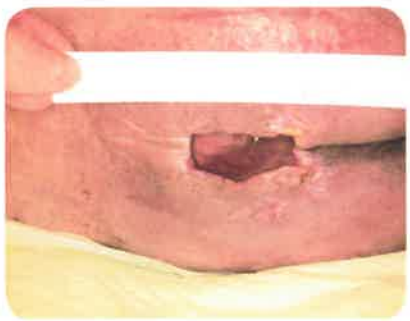

**Figure 9c. Grade 3 pressure ulcer at day 28 of dressing with Silvercel.**

amounts of new tissue growth and consequent reduction in wound area and depth. The amount of exudate was also regarded as having decreased significantly. By the end of the evaluation (day 28), the wound was assessed as being healthy, with no further signs of infection. Inflammation had decreased and the wound had reduced in size by 52% to measure 4.1cm x 1.3cm (*Figure 9c*). It was noted that the dressing was well-tolerated by the patient and easy to remove and apply.

## Conclusions

Increasing resistance to antibiotics has meant that the treatment of infected wounds is becoming more and more problematic. The recent introduction of a number of dressings containing silver into the wound care market is a reflection of the interest in topical antimicrobial agents in reducing wound bioburden, in order to avoid systemic infection. When choosing an antimicrobial dressing, practitioners need to take into consideration other factors such as ability to handle exudate and maintenance of moist wound healing. Clinical evaluation of the hydroalginate silver-releasing dressing is underway in a randomised, multi-centre clinical study. Initial case reports have shown that the hydroalginate technology of Silvercel is beneficial in managing exudate and encouraging moist wound healing and that it may help to promote wound cleansing. Silvercel may become a useful addition to the range of wound care products available. WUK

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### Key Points

- Silvercel combines silver and alginate with carboxymethylcellulose to provide the benefits of both exudate handling to encourage moist wound healing and a broad spectrum antimicrobial.
- The wound environment controls the release of the silver ions from Silvercel, keeping the sustained release controlled and balanced at effective levels.
- Silvercel Hydroalginate is effective against a wide range of microorganisms (>150 human clinical isolates tested).
- The tensile strength of Silvercel increases by more than 50% when wet, making it easy to remove from the wound
- Silvercel is intended for use in the management of all moderate to heavily exuding partial- and full-thickness chronic wounds.


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