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ORIGINAL ARTICLE

A randomized controlled evaluation of absorption of silver with the use of silver alginate (Algidex) patches in very low birth weight (VLBW) infants with central lines

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Objective: To measure systemic silver absorption when using silver-impregnated alginate central catheter dressings in very low birth weight (VLBW) neonates and to monitor blood stream infection.

Study Design: Fifty infants were enrolled in a prospective, randomized controlled trial lasting 28 days. Each patient was assigned to standard dressing or silver alginate (Algidex) group. Serum silver concentrations were obtained on day 1, 7, and 28.

Result: Significant differences in mean serum silver concentrations for the treatment versus standard dressing group were observed using student's *t*-test analysis. The silver alginate group had a 45.8% reduction in infection/1000 line days, although too few patients were enrolled to draw meaningful efficacy conclusions about prevention of blood stream infection.

Conclusion: Mean serum silver concentrations in the treatment group were significantly higher than controls although below levels anticipated to result in toxicity. A large study evaluating reduced blood stream infections in VLBW infants is warranted.
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Keywords: blood stream infections; topical silver dressings; silver toxicity

Introduction

Hospital-acquired bacteremia is currently a significant problem in hospitals in much of the United States. The risk to immunocompromised adults and the very low birth weight (VLBW) neonatal population can be frequent and life threatening.

In the United States, approximately 850 000 infections are attributed to catheters annually, occurring primarily in intensive care unit patients.[1] The National Institute of Child Health and Human Development estimates that 20% of infants who weigh less than 1500 g will have at least one positive blood culture, prolonging their stay in the Neonatal Intensive Care Unit. These infections contribute to increases in medical expenditure for the patients as well as the healthcare systems. Indwelling catheters can be a significant contributor to the occurrence of positive cultures. Rapid technological advancement in the development of catheters has lead to an increase in their use as standard patient care for fluid and intravenous nutrition administration over varying periods of time. Unfortunately, prolonged intravenous catheter utilization remains one of the major causes of bacteremias and candidemias in intensive care unit patients.

Significant reduction in the incidence of hospital-acquired infections has been shown in adults when using silver-impregnated plastic catheters and biofilms.[2] Another successful approach to reducing the incidence of such infections has been to use the antimicrobial properties of silver by incorporating silver alginate as a protective dressing. Silver alginate has been shown to be safe and effective in preventing catheter-related infections in adults.[3–5]

Currently, there is no information on the use of silver alginate dressings in the VLBW neonatal population. There is limited information regarding the impact of silver absorption and toxicity potential in neonates even though silver compounds such as silver nitrate for eye prophylaxis and silver sulfadiazine (Silvadene) for i.v. infiltrate dressing have been used topically for many years. Based on adult dosing and absorption information as well as animal toxicology studies with multiple silver compounds, we hypothesized that using a silver alginate dressing in neonates would be safe without significant absorption of silver into the neonatal circulation. This pilot study was conducted to evaluate the absorption of silver when using silver alginate dressings in VLBW infants.

Objectives

The primary objective of this study was to assess the absorption of silver from a topically applied silver alginate dressing in VLBW infants when used as a dressing for central intravascular catheters. Safety was subjectively hypothesized in comparison to published data in animals and concentrations of exposure and toxicity in adults.

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The secondary objective was to compare the infection rates between the control and the study groups as well as to observe for any side effects. This preliminary trial was undertaken to determine if transdermal silver absorption was low enough that a multicenter trial regarding efficacy in decreasing blood stream infections could be safely conducted.

Methods

A prospective, randomized controlled pilot study was conducted to determine the safety of silver alginate dressing in Neonatal Intensive Care Unit infants compared with traditional catheter care and maintenance. The Baylor Research Institute Institutional Review Board approved the study. Parental informed consent was obtained from the mother or both parents of each participant. The study consisted of fifty infants who were randomized to receive silver alginate or standard of care dressing. Both standard of care (control) and silver alginate dressings were secured with clear occlusive dressing (Tegaderm or Opsite). Infants with birth weights between 500 to 1500 g admitted to Baylor University Medical Center Neonatal Intensive Care Unit with any of the following lines were eligible for inclusion into this study: umbilical arterial line, umbilical venous line, peripheral arterial line, peripheral long line, and central venous line. Participants were enrolled within 72 h of birth.

Serum silver concentrations were obtained from control and treatment groups on study days 1, 7, and 28 to assess absorption. Study day one was defined as the 24-h period in which participants enrolled in the study (up to 72 h after birth). We obtained concentrations on day one for baseline data after placement of the Algidex patch or standard dressing in the control group, day 7 to evaluate acute exposure, and day 28 to evaluate the possibility of cumulative absorption. We observed all patients for adverse reactions, including skin staining, alteration of hepatic or renal function, or changes in central nervous system status. All silver samples were analyzed using a dual inductively coupled plasma–mass spectrometry methodology (ICP–MS).[6] For this study accepted reference values for non-exposure silver concentrations are defined as $<15\,ng\,ml^{-1}$ (or <15 p.p.b.) with standard Mayo Clinic reference lab technique.

Blood cultures were used to assess infection rates between the two groups. All patients were followed until discharged from the hospital. Infection was defined as recovery of a bacterial pathogen or fungus from any single blood culture.

Study patients did not receive any medications or nutritional supplements that contained silver that could potentially alter serum silver concentrations.

The data collected for analysis included: gestational age, birth weight, gender, race, initial date of line placement, type of line(s) placed, number of line days, number of hospital days, date of positive blood culture(s) and source of blood sample, and whether the patient received respiratory support such as mechanical ventilation, continuous positive airway pressure (CPAP), or nasal cannula, chest tube placement, or tracheostomy. In addition, data regarding antibiotic therapy, description of infection site, and adverse effects showed by the babies in association with dressing placement was recorded. Results were analyzed using an intention to treat presumption.

Review of all patient charts to obtain biochemical and hematological laboratory data as well as neuroimaging studies were accomplished while the study was ongoing and retrospectively.

Materials and procedure

Algidex is a sterile patch of polyurethane foam coated with silver alginate and maltodextrin matrix. The patch is impregnated with 141 mg of ionic silver per 100 cm^2. At the interface of the surface of the patch and the skin, silver ions are released at a constant rate of approximately 1.5 $\mu g/0.062\,cm^2$ per day to achieve antibacterial effect for about 10 days. The concentration is maintained at a fairly constant level by replacement of silver ions as they are depleted using chemical equilibrium with calcium alginate, which also prevents excessive release of ionic silver at the gel surface. Silver alginate dressing, Algidex, was donated by DeRoyal, however, the manufacturer was not involved in study design, analysis of data, or preparation of the article.

Upon obtaining informed consent, neonates were enrolled in the study within 72 h postpartum following placement of one or more of the predefined catheters. Blocked randomization method was used. Randomization cards, marked either treatment or control, were placed in opaque envelopes with the study number noted on envelopes. The participants were then assigned to either the treatment or control group based on the randomization card. Study design included intent-to-treat for data collection and intention to stop if signs of toxicities or adverse effects were noted.

Control and study groups

Sterile technique was used per hospital policy for line placement and insertion sites were subsequently cleansed again with 70% isopropyl alcohol for both groups. Although adult data indicates a constant rate of silver delivery to the gel surface for up to 10 days, we were uncertain as to whether transdermal absorption in VLBW infants could result in faster depletion of the silver supply in the gel matrix and we desired to maintain a stable and constant delivery during the study period, therefore we elected to change dressings every 7 days during the trial period.

Infants in the control group received line-dressing changes according to standing hospital protocols specific for the type of line inserted. Insertion sites were covered with an occlusive dressing (Tegaderm or Opsite) after the sterile technique was performed. Infants in the study group received the silver alginate (Algidex Extra Small Patches) during routine line-dressing changes. After the insertion sites were cleansed, the silver alginate patch was

Table 1 Patient demographics

	Control n = 25	*Treatment* n = 25
Race		
Caucasian	15	3
African American	6	13
Hispanic	4	7
Asian	0	1
Other	0	1
Birth weight in grams		
Mean (s.d.)	913 (± 209)	955 (± 250)
Median	880	945
Range	625–1345	570–1424
Average line days	19 (± 9.9)	17.95 (± 8.8)
Gestational age (weeks)		
Mean (s.d.)	27.2 (± 1.85)	27.3 (± 2.03)
Median	26.6	27.3

placed on top of the line insertion sites and covered with an occlusive dressing (Tegaderm, Opsite). The study groups were similar in composition (Table 1).

Statistical analysis

Comparison of the mean silver concentrations between the two groups was analyzed using two-tailed Student's *t*-test to calculate probability of differences of means. Adverse events were none and infection rates between the control and study groups had insufficient numbers to do a meaningful statistical analysis.

Results

We enrolled our intended target of 50 patients (25 cases and 25 controls).

Infants enrolled in the treatment group had a mean gestational age (GA) ± s.d. of 27.3 (± 2.03) weeks and mean birth weight of 955 g (± 250) whereas the control group had a mean GA of 27.2 (± 1.92) weeks and birth weight of 913 g (± 209). Serum silver sample numbers differ due to deaths of patients during the study period. (Table 2)

We also did a subset analysis of ELBW infants, <750 g, and found no serum silver concentration difference when compared with higher birth weight infants. A wide s.d. for day 1 samples was due to one patient who had a level of 103 ng ml^{-1}. This variance was probably due to multiple patch placements in attempts to get the patch to stick to the skin. The patient died after the first level was drawn.

Table 2 Serum Silver concentrations

Study day	*Control*		*Treatment*		P-*value*
	Mean (ng ml^{-1}) ± s.d.	n	*Mean (ng ml^{-1}) ± s.d.*	n	
Day 1	0.22 (± 0.09)	24	7.6 (± 20.93)	25	<0.001[a]
Day 7	0.23 (± 0.14)	24	4.79 (± 4.37)	24	<0.001
Day 28	0.21 (± 0.07)	24	3.19 (± 3.23)	23	<0.001
Serum Silver concentrations for infants <750 g					
Day 1	0.2 (± 0)	5	22.5 (± 40.4)	6	<0.001[a]
Day 7	0.2 (± 0)	4	4.18 (± 2.9)	5	<0.001
Day 28	0.2 (± 0)	4	2.05 (± 1.29)	5	<0.001

[a]Comparisons of these means was not significant at $P>0.5$.

Although serum silver concentrations are significantly different between control and treatment groups, the concentrations obtained were well below what is felt to cause toxicity in humans (see Discussion section) and there was no evidence of serum accumulation over the study period. No adverse skin reactions were noted during the study period. No changes in hepatic or renal function were noted. (Appendix 1, see online version) BUN was not different between groups, implying no interference with protein metabolism or nitrogen fixation. The investigators or other care providers noted no clinical change in central nervous system function.

Outcome

Six total deaths occurred in the study population. (Table 2) The mortality percentages are consistent with our non-study population when compared with 100-g birth weight cohorts. Four deaths occurred in the control group, three after the trial time was concluded and one before trial entry. Thus, two deaths occurred in the treatment group during the trial period. Etiology of death and day of death after trial entry are reported in Table 3.

Discussion

The curative properties of silver have been recognized as early as the middle ages and the bacteriostatic properties were known in modern medicine during the 19th century.[7] Until the mid 1980s recommended prophylactic therapy for neonatal gonococcal ophthalmitis was topical silver nitrate solution; however, due to broader antimicrobial coverage and less frequent eye irritation, erythromycin prophylaxis for neonatal ophthalmia has become more popular. Silver sulfadiazine has been used as a protective antimicrobial covering for wounds and i.v. infiltrates in intensive care nurseries for many years.

Table 3 Deaths in study subjects

Control (subject no.)	*BW*	*EGA*	*SEX*	*Race*	*Comments/etiology*
4	635	26.3	F	Caucasian	Randomized to control, expired before trial entry from pulmonary hypoplasia and pulmonary hypertension: support withdrawn
14	840	26.6	M	Hispanic	Died 19 days after trial completion from surgical NEC and shock
20	690	25.3	F	Caucasian	Died 4 days after trial completion from NEC, peritonitis and shock
47	805	26.5	M	Caucasian	Died 26 days after trial completion from inoperable NEC and shock
Treatment (subject no.)					
29	660	25.4	F	African American	Died 16 days before trial completion after ileal perforation and post-operative shock
43	595	23.3	F	Hispanic	Died 21 days before trial completion from severe RDS, and pulmonary hemorrhage

Abbreviations: BW, birth weight in grams; EGA, Estimated gestational age at birth in weeks; NEC, necrotizing enterocolitis; RDS, Respiratory distress syndrome.

Silver alginate has demonstrated *in vitro* bactericidal activity against *Staphylococcus aureus*, methicillin-resistant *S. aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Candida albicans*.[4] The antimicrobial activity is believed to be due to a disturbance of the electron transport chain and disruption of protein metabolism at sulphydryl or histidyl protein sites. A silver alginate dressing combines the desired antimicrobial attributes of ionic silver and the favorable absorptive properties due to the chemical balance with calcium alginate potentially providing a safe and effective antimicrobial dressing in a VLBW patient population. However, since the action of silver probably occurs from the inhibition of protein metabolism, the amount of silver absorbed must be minimal to avoid potential effects in a rapidly growing VLBW neonate.

Toxicity

There is almost no available literature regarding silver toxicity and systemic absorption in premature VLBW infants. Rustogi *et al*.[8] reported silver concentrations ranging from <0.05 to $1\,\mu mol\,l^{-1}$ (or <5.393 to $107.868\,ng\,ml^{-1}$) following the application of Acticoat to eight VLBW infants suffering from burn wounds. Acticoat is a gauze dressing that is coated with nanocrystalline silver within a high-density polyethylene mesh. They reported no occurrence of silver toxicity in their participants.

Systemic absorption of silver can result in Argyria, a syndrome of silver deposition in tissues that can result in graying of the skin, growth retardation, disturbed hemopoiesis, as well as cardiac, hepatic and renal dysfunction. Silver concentrations greater than $1000\,ng\,ml^{-1}$ are indicative of significant acute silver exposure. Argyria occurs when silver concentrations are greater than $2000\,ng\,ml^{-1}$. No clinical symptoms of moderately elevated concentrations of silver ($<1000\,ng\,ml^{-1}$) have been reported in adult humans however toxicity may occur at lower levels in infants as noted below in the case report.[6,9]

A case report of silver toxicity in a 12-month-old female infant who was also iron, vitamin B12, thiamine and copper deficient due to vegan dietary restrictions and supplemental oral colloidal silver showed a silver concentration of $3.4\,\mu mol\,l^{-1}$ (normal $<0.02\,\mu mol\,l^{-1}$)[10] or approximately $323\,ng\,ml^{-1}$ (normals in non-exposed humans $<2.15\,ng\,ml^{-1}$). This conversion was ours and performed for data comparison. The reported normal value in the case report of toxicity is seven times lower than the Mayo Clinic standard reference used in our study. The highest silver level observed was $103\,ng\,ml^{-1}$. Conversions of the silver levels used in the discussion are available in Appendix 2 (see online version).

Human toxicity and animal toxicity information after exposure to environmental or ingested silver from OHSA and the CDC states that the LD_{50} (dosage that results in 50% mortality for exposed animals) data for ingested silver acetate is 23.7 mg silver/kg body weight in mice and 67 mg silver/kg body of colloidal silver weight in rats and LD of $29.5\,mg\,kg^{-1}$ over 30 min of ingested silver for humans. For silver chloride lethal oral doses of greater than $10\,g\,kg^{-1}$ in mice and greater than $5\,g\,kg^{-1}$ in guinea pigs have been reported. Chronic toxicity in rats was demonstrated with i.v. dose of $1.5\,mg\,kg^{-1}\,day^{-1}$ with no toxicity was observed at $0.31\,mg\,kg^{-1}\,day^{-1}$ for 30 days of total exposure. Adult human toxicity appears to require approximately $13.3\,mg\,kg^{-1}$ of silver to develop acute toxicity.[7,11–13] The transdermal exposure in burned or denuded rats yields up to a 20% extraction rate of the exposed concentration.[12]

A human study by Robkin *et al*.[14] investigated the possibility of a relationship between the concentration of silver in the tissue of fetuses and the occurrence of developmental abnormalities. These authors reported that the concentration of silver in the fetal liver of 12 anencephalic human fetuses was higher ($0.75 \pm 0.15\,mg\,kg^{-1}$) than the values from 12 fetuses obtained either through therapeutic abortions ($0.23 \pm 0.05\,mg\,kg^{-1}$), or in 14 spontaneously aborted fetuses ($0.21 \pm 0.05\,mg\,kg^{-1}$). The concentration in nine premature

Table 4 Blood stream infections per line days in the study group

	Control	*Treatment*
Total line days	486	448
Total infections	6	3
Infection per 1000 line days	12.34	6.69

infants was $0.68 \pm 0.22\,mg\,kg^{-1}$. Serum silver concentrations were not reported.[12]

One percent Silver sulfadiazine was evaluated in human burn patients as well as in animals with abraded skin[15] but cannot be logically compared with silver ion absorption because the sulfadiazine is pharmacologically active and can be toxic in and of itself. Acticoat appears to release de-ionized silver at 50 to 100 p.p.m. in de-ionized, sterile water. Silvasorb is a methacrylate gel sheet impregnated with silver chloride and generally delivers silver in the 1 to 2 p.p.m. range.[16] Silver chloride dressing and silver nitrate liquid have been used for wound and burn healing mostly in adults but absorption was not assessed and the concentration required for antimicrobial activity and improved wound healing that has been reported varies from 1 to 120 p.p.m.[17–19]

We calculated that the potential daily skin exposure from Algidex was less than $62\,\mu g\,day^{-1}$ for one patch and less than $124\,\mu g\,day^{-1}$ when up to two extra small patches were applied to the skin (6 to 12 p.p.m., see Table 4). Thus the potential transdermal dosage was 100 times less than the parenteral dosages causing toxicity in animals and enteral dosages that are reported to cause chronic toxicity in adult humans. If the CDC estimate of 20% maximum dermal absorption of available ion is correct, the resulting potential silver exposure would be almost 1000 times lower than reported doses expected to result in toxicity. The relatively stable means of silver levels in the treatment group supports our hypothesis that the silver and calcium alginate matrix provides silver that is absorbed at a fairly constant rate.

Decrease in blood stream infections

We noted a 45.8% reduction in blood stream infection/1000 line days in the treatment group (Table 4); however, the groups were not large enough to have significant power for a meaningful analysis and could have been skewed by a longer surgical central venous line time in the control group and very small numbers in that specific subgroup. (Appendix 3, see online version) The occurrence of any late infection in the same population in our nursery during the study period was between 10 and 50% in 100-g birth weight cohorts. The use of a silver alginate dressing has been effective in reducing wound infections by up to 25% in adults.[4] There have also been reports of up to a 60% decrease in blood stream infections in adults with central catheters when using silver-impregnated dressings.[20]

Limitations

A noted limitation of this study was that autopsy specimens were not obtained to test for specific tissue concentrations for silver. We only included central lines or arterial lines in this study. The addition of peripheral i.v. dressings might increase silver absorption and/or change the incidence of blood stream infections in this population of patients.

Conclusion

Our data suggests that silver exposure resulting from transdermal absorption of ionic silver from a sterile patch dressing of polyurethane foam coated with ionic silver alginate and maltodextrin matrix results in measurable increases in serum silver concentrations in VLBW infants when used up to 28 days at central line sites without evidence of toxicity. These concentrations are statistically different but do not appear to be significant based on silver toxicity reports in animals and human adults as well as published CDC information regarding exposure.[12]

The noted silver concentration from Algidex should provide antimicrobial activity at >1 p.p.m. which supports Mean Inhibitory Concentrations for approximately 85% of organisms reported.[17,18,21,22] We noted no trend towards increased serum silver concentrations over the 28 days of trial.

This study was a preliminary evaluation to determine if a larger multicenter efficacy study could be safely conducted. Our limited infection data from this trial showed a reduction in blood stream infections, although was insufficiently powered to make a specific conclusion. We speculate that a silver-impregnated polyurethane foam coated with silver alginate and maltodextrin matrix dressing has the potential for reducing acquired blood stream infections in VLBW neonates, similar to the effect reported in adult humans. However, further data is needed to prove clinical efficacy of this product in VLBW infants as well as continued monitoring of safety. We are currently involved in such a study.

Conflict of interest

The authors declare no conflict of interest.

References

1 Elliott TSJ. Role of antimicrobial central venous catheters for prevention of associated infections. *J Antimicrobl Chemother* 1999; **43**: 441–446.

2 Roe D, Karaandikar B, Bonn-Savage N, Gibbons B, Roullet J. Antimicrobial surface functionalization of plastic catheters by silver nanoparticles. *J Anitimicrob Chemother* 2008; **61**: 869–876.

3 Madeo M, Martin CR, Turner C, Kirkby V, Thompson DR. A randomized trial comparing Arglaes (a transparent polyurethane dressing) toTegaderm (a transparent polyurethane dressing) for dressing peripheral arterial catheters and central venous catheters. *Intensive Crit Care Nurs* 1998; **14**: 187–191.

4 Meaume S, Vallet D, Morere MN, Teot L. Evaluation of a silver-releasing hydroalginate dressing in chronic wounds with signs of local infection. *J Wound Care* 2005; **14**: 411–419.
5 Algidex (package insert). Powell: DeRoyal 2005.
6 Mayo Clinic Reference laboratory 2005, http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+interpretive/8607 Imbedded references:
a. Seller HG, Sigel A, Sigel H. Handbook on Metals in Clinical and Analytical Chemistry. Marcel Dekkter, Inc: New York 1994
b. Coombs, CJ, Wan AT, Masterson JP *et al.* 'Do burn Patients have a silver lining?' Burns 199218: 179–184.
7 Fung M, Bowen D. Silver products for medical indications: risk benefit assessment. *Clin Toxicol* 1996; **34**: 119–126.
8 Rustogi R, Mill J, Fraser JF, Kimble RM. The Use of Acticoat in Neonatal Burns. *Burns* 2005; **31**: 878–882.
9 Williams N, Gardner I. Absence of symptoms in silver refiners with raised blood silver concentrations. *Occup Med* 1995; **45**: 205–208.
10 McIntyre E, Wilcox J, McGill J, Lewindon PJ. Silver Toxicity in an Infant of Strict Vegan Parents. *J Ped Gastroent and Nut* 2001; **33**: 501–502.
11 Rungy J, Danscher G. 'Hypoactivity in sliver exposed mice'. *Acta Pharmacol Toxicol* 1984; **55**: 398–401.
12 CDC. (accessed 10/28/2008) *Toxilogic Profile for Silver*. http://www.atsdr.cdc.gov/toxprofiles/tp146.pdf.
13 OHSA. http://www.cdc.gov/niosh/idlh/7440224.html(accessed 10/28/2008).
14 Robkin MA, Swanson DR, Shepard TH. Trace metal concentrations in human fetal livers. *Trans Am Nucl Sot* 1973; **17**: 97.
15 American Society of Health-System Pharmacists. *AHFS Drug information*. American Society of Health-System Pharmacists: Bethesda, MD, 1998. pp 2918–2919.
16 Guggenbichler JP, Boswald M, Lugauer S *et al.* A new technology of microdispersed silver in polyurethane induces antimicrobial activity in central venous catheters. *Infection* 1999; **22**: S16–S17.
17 Yin HQ, Lanford R, Burrell RE. Comparative evaluation of the antimicrobial activity of Acticoat® antimicrobial barrier dressing. *J Burn Care Rehabil* 1990; **20**: 195–200.
18 Poon KM, Burd A. *In vitro* toxicity of silver: implication for clinical wound care. *Burns* 2004; **30**: 140–147.
19 Ovington LG. The truth about silver. *Ostomy Wound Management* 2004; **50**(9A suppl): 1s–10s.
20 Brooks KL, Dauenhauer SA, Evans JT Decreased incidence of Central Line Related Bloodstream infections Associated with Use of Silver-Impregnated Dressing at Central Venous Catheter Sites Presented 4 h Decennial Conf on Nosocomial and Healthcare Associated Infections Atlanta 2000 (accessed November 2008) http://www.medline.com/woundcare/products/arglaes/PDFs/Case%20Study%20-%20Arglaes-Decreased%20Incidence.pdf.
21 Vanscheidtr W, Lazareth I, Routkovsky-Norval C. Safety evaluation of a new ionic silver dressing in the management of chronic ulcers. *Wounds* 2003; **15**: 371–378.
22 Ricketts CR, Lowbury EJ, Lawrence JC, Hall M, Wilkens MD. Mechanism of prophylaxis by silver compounds against infection of burns. *Br Med J* 1970; **2**: 444–446.

Supplementary Information accompanies the paper on the Journal of Perinatology website (http://www.nature.com/jp)