Please note: These studies may involve findings that exceed the claims currently cleared by the FDA for the product. Bravida Medical is not intending to make performance claims about its product. The intent is to disseminate the scientific literature on these products. We encourage you to read these studies to understand the strengths and limitations of the data. For some claims, Bravida is seeking to broaden the indications with the FDA in the future using data, such as these studies, to provide the substantiation.

BURNS 405 (2014) S30-S39



Silver-based dressings for the reduction of surgical site infection: Review of current experience and recommendation for future studies



Elia Charbel Abboud^{a,*}, Judson C. Settle^a, Timothy B. Legare^a, Jorge E. Marcet^a, Dave J. Barillo^b, Jaime E. Sanchez^a

^a University of South Florida, Department of Surgery, Morsani College of Medicine, Tampa, FL, USA ^b Disaster Response/Critical Care Consultants, LLC, Mount Pleasant, SC, USA

ARTICLE INFO

Keywords: Silver Silver dressing Surgical site infection Reduced infection rate Literature review

ABSTRACT

Surgical site infections (SSIs) are the most common hospital acquired infection in surgical patients, occurring in approximately 300,000–500,000 patients a year. SSIs occur across all surgical specialties, but have increased importance in abdominal, colorectal, obstetrical, gynecological, cardiac, vascular, neurological, transplant, and orthopedic procedures where either the inherent risk is elevated or the consequence of an infection would be severe. Current prevention guidelines reduce, but do not completely eliminate, the occurrence of SSIs. We have found the use of silver-nylon wound dressings to significantly reduce the risk SSI associated with colorectal surgery. In this review, we examine the incidence of SSI in high-risk groups, and identify procedures where silver dressings, and other silver products, have been evaluated for the prevention of SSI.

Silver-nylon dressings are a useful adjunct in the prevention of SSI in colorectal surgery, neurological surgery, spinal surgery, and certain cardiovascular and orthopedic procedures. Gynecologic, obstetric, breast, transplant, neck, and bariatric procedures, and surgery in obese and diabetic patients, represent other areas where patients are at increased risk of SSI, but in which silver dressings have not been adequately evaluated yet. Recommendation is made for large prospective studies of silver dressings in these populations.

© 2014 Elsevier Ltd and ISBI. All rights reserved.

1. Introduction

A surgical site infection (SSI) is defined as an infection occurring within 30 days of an operation, or within a year of surgery if an implant is left in place and the infection appears related to the implant [1]. SSIs may be classified as superficial incisional, deep incisional, or organ/space infections based on criteria developed by the United States (US) Department of

* Corresponding author. Tel.: +1 813 9926400.

Health and Human Services' Centers for Disease Control and Prevention (CDC) [1]. Collectively, deep incisional and organ/ space infections are termed 'complex' SSIs and comprise approximately 50% of all SSIs [2].

SSIs are associated with considerable cost, morbidity and mortality. For all hospitalized patients, these infections are the third most commonly reported nosocomial infection. Among surgical patients, SSIs are the most common hospital acquired infection, representing 38% of nosocomial infections in this

E-mail address: eabboud@health.usf.edu (E.C. Abboud). http://dx.doi.org/10.1016/j.burns.2014.09.011

^{0305-4179/} \odot 2014 Elsevier Ltd and ISBI. All rights reserved.

group [1]. Approximately 300,000–500,000 SSIs occur annually in the US, comprising 2–5% of all patients undergoing inpatient surgery [3–6]. A SSI is typically associated with an additional 7– 10 days of postoperative inpatient care, and an additional cost of \$3000-\$29,000 per patient, mounting to a total cost of \$10 billion dollars to the US healthcare system every year [1,5,7,8]. A SSI increases the risk of death by two to seven times, and 77% of deaths in patients with these infections are directly attributed to the infection [1,5]. A patient with a SSI is 60% more likely to require admission to the intensive care unit (ICU), and five times more likely to be readmitted within 30 days of discharge [8].

Certain populations and certain surgical procedures are at higher risk of SSI. The risk of developing such an infection involves a complex multifactorial relationship between the characteristics of the patient, procedure, and microbes involved [5]. The Surgical Infection Prevention Collaborative of the Centers for Medicare and Medicaid Services focuses on seven procedures: colorectal surgery, abdominal hysterectomy, vaginal hysterectomy, cardiac surgery, vascular surgery, hip arthroplasty, and knee arthroplasty [5]. These procedures are significant either because the risk of SSI is high (as is the case in surgery involving bacteria-containing viscera), or because the occurrence of a SSI would be remarkably consequential, for example requiring removal of a vascular or orthopedic implant.

Consensus guidelines for the prevention of SSI have been published in the US and Europe. The most recent US guidelines from the Hospitals Infections Program, division of the National Center for Infectious Diseases of the CDC, were published in 1999 [1,5]. These guidelines did not address postoperative dressings, other than to recommend the protection of primary-closure incisions with a sterile dressing for 24-48 h postoperatively [1]. In Great Britain, the National Collaborating Centre for Women's and Children's Health published similar guidelines in 2008 on behalf of the National Institute for Health and Clinical Excellence [9]. Their main recommendation for postoperative dressings was the use of an aseptic no-touch technique for changing or removing surgical wound dressings on primary-closure incisions. They did not advocate routine use of topical antibiotics, based on review of one underpowered study using topical chloramphenicol over hip fracture incisions [9].

Gram-positive cocci, predominantly Staphylococcus species, are thought to be the major pathogen involved in SSI. However, this view is being challenged. Wolcott and associates used bacterial tag-encoded FLX amplicon pyrosequencing followed by quantitative polymerase chain reaction to study bacterial populations in debridement samples from 23 SSIs [10]. All were infections of at least one month duration and were becoming chronic wounds. On average, six bacterial genera were found in any given SSI, with 60% being anaerobic bacilli. The primary genera encountered in the samples included Bacteroides (45.4%), Corynebacterium (41.5%), Pseudomonas (31.6%), and Staphylococci (29.9%) [10]. This suggests that perioperative topical or systemic antibiotic choice must include coverage for Gram-positive and Gram-negative bacteria, both aerobic and anaerobic.

Silver has strong antimicrobial properties, and has been used for centuries for hygiene, water purification, and its

wound healing effects. Storing water in silver vessels was practiced as early as 4000 BC and medical writings from the Roman civilization documented silver nitrate as a therapeutic agent [11,12]. Today, silver is widely used for the treatment of burns, surgical and traumatic wounds, chronic ulcers, and ophthalmic conditions, and as a coating for medical devices such as intravascular catheters, orthopedic devices, and vascular prostheses [11-13]. Silver is also commercially employed for water sterilization. The extensive coverage that silver provides against bacteria, fungi and viruses, including the notorious nosocomial pathogens methicillinresistant Staphylococcus aureus (MRSA) and vancomycinresistant Enterococci (VRE) [14], make it a valuable adjunct in the prevention and treatment of infection. Silver has both bactericidal effects via oxidation of the cell membrane, and bacteriostatic effects by inhibiting bacterial replication through damage to DNA [15-18]. Fortunately, toxicity of silver to human cells is considerably less than to bacteria [12]. Unlike antibiotics, resistance to silver is very rare; instead of targeting a specific cellular process, silver ions directly interact with proteins and other organic molecules, and disrupt electrolyte balances. Silver's affinity to multiple microbial molecules and structures further decreases the risks of resistance [17,19].

Colorectal surgery has a known high incidence of SSI. In our university-based colorectal surgery practice, we were able to demonstrate a decreased incidence of SSI by the use of silvernylon dressings placed over primary-closure abdominal incisions [14]. This prompted an interest in a literature review of the uses of silver dressings in other procedures that are considered high-risk for SSI, or in which the occurrence of a SSI would be especially detrimental to patient outcome.

In this review, we present the current evidence supporting primarily the use of silver-based dressings for the prevention of SSI. This is done both to document current practice, and to identify higher-risk populations and procedures where silver dressings have not yet been properly evaluated, and recommend large prospective studies.

2. Methods

A review of the current literature was performed using PubMed primarily. The search terms included "surgical site infection," "silver in surgery," "surgical site infection prevention," "silver surgical site infection," "silver dressing infection," "silver dressing surgery," "silver colorectal surgery," "silver colon surgery," "silver rectum," "silver abdominal surgery," "silver obstetrics," "silver gynecology," "silver cardiac surgery," "silver vascular surgery," "silver neurosurgery," "silver spine," "silver liver," "silver transplant," "silver orthopedic surgery," and "silver negative pressure." The atomic symbol of silver, Ag, was then used in place of the word "silver" to re-search all of the terms mentioned above. Google scholar was used to supplement the search. Results were narrowed to studies that included the use of silver dressings for surgical procedures, and to manuscripts discussing SSI and infection rates in various surgical procedures. Silver-coated vascular grafts and silver-impregnated ventriculoperitoneal shunts were also included.

3. Results

The literature search revealed certain procedures and populations to be at higher risk of SSI. Below is a description of risk factors of SSI, and of some of the surgical procedures that are at higher risk for SSI or in which the occurrence of a SSI would be especially detrimental to patient outcome. A description is given of studies investigating the use of silver dressings, as well as silver-coated vascular grafts and ventriculoperitoneal shunts, to decrease surgical infection rates in these various procedures.

The pooled means for infection rates are given for inpatient procedures per 100 operations (%), as published in the latest report (2009) of the National Healthcare Safety Network (NHSN) of the CDC [20]. The NHSN stratifies the SSI rates by procedure type and by National Nosocomial Infections Surveillance (NNIS) risk index categories [20]. The infection rates vary per procedure according to risk index category, and we therefore report them as percentage ranges.

3.1. Risk factors

Obesity, diabetes mellitus, and continued use of tobacco products are established risk factors and independent predictors of SSI. Obesity, being at near epidemic levels in the US, is an especially important risk factor. When defined by percent body fat rather than body mass index (BMI), the overall incidence of SSI in the obese rises from 11.6% to 15.2% [21]. Diabetes mellitus is more common in obese patients [8], and surgical procedures often take longer in this patient population. Perioperative antibiotics may be less effective, because tissue antibiotic levels are inversely proportional to level of obesity [22]. Clearly, this is especially important in bariatric patients. It was found that doubling the dose of perioperative cefazolin in obese women undergoing gastric bypass surgery decreases the SSI rate from 16.5% to 5.6% [22,23].

The duration of surgical procedure is a factor well-known to correlate with SSI risk [8,24]. Longer procedures carry a greater risk of infection. Today, minimally invasive surgery is well-known to decrease operative times, as well as infection rates. For example, the use of laparoscopy lowers SSI risk in cholecystectomy and colon procedures. However, this has less of an effect in appendectomy or gastric procedures [24]. In abdominal surgery, multiple additional comorbidities such as hypothermia and hyperglycemia are thought to increase the incidence of SSI as well [14,25].

3.2. Abdominal and colorectal surgery

Abdominal operations have many unique risks in the domain of surgery. This field commonly involves exposure to the contents of the gastrointestinal tract, and most procedures are therefore classified as either clean-contaminated or contaminated. The risk of infection is increased in emergency procedures, and 15% of SSIs occur in the emergency setting [26]. However, even elective colorectal surgery carries a risk for SSI as high as 30% [25]. The NHSN reports higher infection rates for the following inpatient procedures: rectal surgery (3.47–26.67%); bile duct, liver or pancreatic surgery (8.07–13.65%); colon surgery (3.99–9.47%); small bowel surgery (3.44–6.75%); herniorrhaphy (0.74–5.25%); gastric surgery (1.72–4.23%); appendix surgery (1.15–3.47%); and exploratory abdominal surgery (1.67–2.82%) [20]. The management of surgical abdominal wounds has been given considerable attention in recent decades, as surgeons strive to decrease overall infection rates. Pre-operative skin antisepsis has long been established to reduce these rates. Various dressings and wound management regimens are actively studied and developed to minimize the incidence of infection.

A randomized controlled trial (RCT) performed by our group in 2011 investigated the efficacy of a silver plated nylon dressing compared to standard gauze dressings for use in elective colorectal surgery with an abdominal incision at least 3 cm. We found that the use of silver-nylon dressings in 110 patients significantly reduced the rate of SSIs from 30% to 13% (p = 0.011) [14]. Another study published in 2012 found that the use of silver hydrofiber dressings in 112 laparotomic colorectal surgical patients decreased the infection rate from 20.4% to 15.5% [3]. However, this difference failed to reach statistical significance (p = 0.451). Both these studies followed patients for 30 days postoperatively, and included superficial, deep, and organ/space infections.

A prospective study by Siah and Yatim on colorectal surgery patients compared 81 patients receiving an ionic silver dressing to 79 patients treated without dressing [27]. Surface cultures were taken at the time of wound closure and on postoperative days five to seven. An equal percentage of wounds in the two groups had negative cultures at the time of surgery. At postoperative days five to seven, the number of wounds showing negative cultures were significantly less in the silver group (p < 0.001). There was only one SSI in the silver group, compared to eight infections in the control group, but statistical significance was not reached [27]. None of the patients with negative cultures at postoperative days five to seven developed an infection within 30 postoperative days, revealing a statistically significant relationship between bacterial colonization and SSI rate (*p* < 0.001) [27].

The ability of silver dressings to prevent SSI remains to be studied in rectal procedures, as well as in the higher-risk abdominal procedures mentioned above (liver, pancreas, biliary, small bowel, hernia, gastric, appendix, and exploratory surgery).

3.3. Obstetrics and gynecology

The rate of SSI in common obstetrics and gynecology procedures varies from 0.13% to 10.48% [7]. Cesarean section infection rates vary depending on population demographics, with BMI being a significant determinant [28]. Corcoran et al. reported a rate of 16.1% in a baseline study of 710 women [28]. The NHSN reports higher infection rates for the following inpatient procedures: abdominal hysterectomy (1.10–4.05%); cesarean section (1.46–3.82%); ovarian surgery (0.43–1.39%); and vaginal hysterectomy (0.73–1.16%) [20].

Connery and colleagues retrospectively compared the infection rates in Cesarean section patients receiving silverimpregnated dressings to wounds dressed with standard gauze [29]. The study found no significant difference between the two groups. However, it was noted that the women receiving the silver dressings had significantly more comorbidities than the control group, and the silver dressings were removed earlier than the standard one-week period. Both these factors could have impaired healing. A RCT with standardized wound care will better control for such confounding factors [29].

To the best of our knowledge, there are no studies investigating the use of silver dressings for SSI prevention in hysterectomies and ovarian procedures.

3.4. Cardiac surgery

The lowest risk for SSI in cardiac surgery is seen in patients undergoing two or three vessel coronary artery bypass graft (CABG) procedures (1.13–3.50%), and the highest risk is seen in open tricuspid valvuloplasty (4.32%) [7,30]. Left heart catheterization, although less invasive than procedures involving a sternotomy, has an infection rate of 3.74%. Infections following CABG are equally divided between superficial and deep, and typically occur around postoperative day 21 [30]. Most are monomicrobial, with *S. aureus* being the most common pathogen [30]. The NHSN reports the SSI rate in CABG to reach as high as 8.49% in patients with a risk index category of 3 [20].

Mediastinal infection is a major complication of open-heart surgery. The reported incidence varies from 0.04% to 5% [31]. A mediastinal infection has a significant associated mortality of 10–20% [31]. It typically increases length of stay by 12.2 days [31]. Huckfeldt et al. prospectively studied silver-nylon dressings in a cohort of 365 patients undergoing CABG or open valve replacement, and compared them to 1235 historical control patients receiving a dry gauze dressing [31]. There were 13 mediastinal infections in the control group compared to no infections in the silver-nylon group (p < 0.05).

Left ventricular assist devices (LVAD) are increasingly used either as a bridge to cardiac transplant or recovery, or as destination therapy for patients with intractable heart failure [32]. Placement of an LVAD requires a percutaneous driveline, which connects the implanted device to an external power supply. Infection is the second most common cause of death in LVAD patients [32]. Infections in this patient population are usually either driveline or pump pocket infections, and deviceassociated infections often occur after discharge from the hospital [32]. Selekoff and associates studied the use of silvernylon dressings on cutaneous entry points of LVAD drivelines in 43 patients over a 15-month period. There were no infections reported, compared to a 13% infection rate in 39 historical controls from the same institution treated identically (except for the silver dressing) [33].

3.5. Vascular surgery

Vascular device and graft infections represent a major challenge for vascular surgeons and their patients. Graft infection is a serious limb-threatening and lethal complication [34]. Reported infection rates vary from 1% to 6% [35]. Abdominal aortic aneurysm repair is another high-risk procedure in vascular surgery, with infection rates reaching as high as 6.46% [20].

The incorporation of silver in prosthetic vascular grafts has been shown in a postmarket surveillance registry of 230 patients to prevent SSI and improve wound healing [36]. Ten of these 230 patients had baseline graft infections, and the remaining 220 patients were all high-risk for SSI development. Only one re-infection occurred in the 10 patients with baseline infections, and 211 of the 220 in the high-risk group (95.9%) developed no infection [36]. Furthermore, a retrospective study of 913 patients treated for arterial occlusive disease showed silver-coated polyester grafts to reduce infection rates from 4.1% (with standard prostheses) to 1.1% in aortofemoral operations [37]. However, this difference was not statistically significant (p = 0.17). The study did not achieve reduced infection rates with the use of silver in femoropopliteal grafting [37]. A recent review of several studies investigating the use of silver vascular grafts found a trend toward success, but concluded that there is a lack of high level evidence for the effectiveness of silver grafts and other antimicrobial vascular prostheses [34].

Silver-coated grafts have been used for repair of aortoenteric fistulas as well. Aortoenteric fistula repair, with potential exposure to bowel microbes, represents an especially highrisk group of vascular surgery patients. Despite the efficacy of silver-coated grafts in preventing infection, mortality in complicated procedures such as secondary aortoenteric fistula repair is still quite high [38].

Canaud and colleagues reported the replacement of an infected thoracic stent graft (which caused severe mediastinitis) with a silver-coated tube graft in a re-operation for an aortobronchial fistula [39]. The replacement of infected traditional vascular prostheses with a wide range of silvercoated grafts is seeing increased use, but further studies are needed to compare the rates of SSI recurrence [34].

Surgical wounds from lower limb revascularization are prone to dehiscence and infection. Childress and associates studied the impact of a silver-eluting dressing system on wound complications for this procedure [40]. They found that the wound complication rate fell from 14% in the control group (17/118), to 5% in the group receiving the silver dressings (7/ 130) (p = 0.016) [40].

The use of silver in vascular grafts is promising. No studies were found looking specifically at the use of silver dressings in vascular surgery.

3.6. Neurological & spine surgery

Intracranial pressure is traditionally relieved by surgical placement of an external ventricular drain to remove excess cerebrospinal fluid (CSF). These devices and the CSF they are intended to drain commonly get infected, with reported infection rates reaching 22% [41]. A RCT of 278 patients requiring the placement of an external ventricular drain compared a standard catheter to a silver-impregnated catheter. The infection rates for the two groups were 21.4% (30/140) and 12.3% (17/138), respectively (p = 0.043) [41].

Surgical insertion of a ventriculoperitoneal shunt (VPS) carries a SSI rate of 4.04–5.93% [20]. Hydrocephalus, one of the most common birth defects, is treated using this procedure. In the United Kingdom (UK), the infection rate of primary VPS insertion for hydrocephalus is approximately 8% [42]. A RCT of

a projected 1200 patients is currently ongoing in the UK and Ireland to compare silver and antibiotic-impregnated shunts to standard silicone shunts [42].

Laminectomy is reported by the NHSN to carry a SSI rate as high as 2.30% [20]. Epstein examined the effects of postoperative dressings on SSIs in patients undergoing lumbar laminectomies with instrumented fusion [43]. A group of 128 patients receiving routine dressings (iodine or alcohol swabs under dry gauze) were compared to 106 patients managed with silver-nylon dressings. There were 11 superficial and three deep SSIs in the routine dressing group, and no infections in the silver-nylon group. Detailed statistical analysis was not performed and the author recommended further large-scale prospective trials [43].

Propionibacterium acnes is recognized increasingly as a SSIcausing organism, particularly in infections happening after spinal procedures and joint replacements [44,45]. An in vitro study found a silver-containing wound dressing to be active against this microorganism over seven days, and suggests that this dressing may help minimize the risk of SSI in patients undergoing such procedures [44].

Surgical infection rates in spine fusions and refusions reach 4.15% and 8.73%, respectively [20]. A 10 year review of posterior cervical spine surgery at a major referral center found infection rates to reach as high as 18% [46]. Craniotomies carry SSI rates reaching 4.66% [20]. No studies were found investigating the use of silver dressings in these procedures.

3.7. Transplant surgery

The incidence of SSI in adult, first time kidney-only transplant patients is 18.5% [47]. The NHSN reports a rate reaching 6.57% [20]. In addition to high-dose postoperative immunosuppression therapy, many kidney transplant patients are also diabetic and/or obese. In one study of 869 patients transplanted in a university setting, diabetics comprised 32.7% of the non-infected group and 46.6% of the SSI group (p < 0.001) [47]. The percentage of obese patients (BMI > 30) was 35.5% of the uninfected group and 59.6% of the SSI group (p < 0.001). Hospital costs associated with a SSI in this group averaged \$24,454.

Liver transplant surgery infection rates vary from 11.61% to 20.10%, and the infection rate for heart transplant is reported as 3.28% [20]. The use of silver dressings to prevent or treat SSI in transplant surgery is anecdotal, or in the form of unpublished or single case reports [48].

3.8. Orthopedic surgery

The NHSN reports an infection rate reaching 3.36% for open reduction of fractures, and 3.04% for limb amputations [20]. Infections happen less frequently with hip and knee prosthetics, with rates reported to reach 2.40% and 1.60%, respectively [20].

Nanocrystalline silver dressings have been retrospectively found to be effective for the debridement of open Gustilo/ Anderson type II and III fractures [49]. This study examined 17 patients and found only one to become infected (5.9%) [49]. The authors warranted prospective randomized clinical study. A prospective study of 59 patients investigated silver hydrogel dressings on postsurgical incisions in foot and ankle surgery [50]. The silver group was found to have just one (3.45%) superficial infection, while the control group had three (10%) superficial infections and one (3.33%) deep infection. However, this was not statistically significant (p = 0.37). The study did find that the standard petroleum-based dressing group had a statistically significant greater incidence of incisional complications in comparison to the silver dressing group (8 versus (vs.) 1 patient, p = 0.03) [50].

Pin-site infection is one of the most worrisome complications of external fixation. A study looking at pin sites for a variety of external fixation procedures prospectively compared a chlorhexidine dressing alone to a dressing combining chlorhexidine to silver sulfadiazine [51]. There were 38 patients on study, with 170 pin sites receiving silver dressings, and 164 pin sites in the control group. Three patients (7.9%) had pin tract infections in the study group, while nine patients (23.7%) developed infections in the control group (p = 0.03) [51].

There were no studies found examining the use of silver dressings in limb amputations or in hip and knee prosthetics.

3.9. Other findings: negative pressure wound therapy and silver dressings

Negative pressure wound therapy (NPWT) is used for the management of wounds in multiple settings. Our search of the surgical literature revealed evidence for the combination of silver dressings with NPWT in certain higher-risk procedures. Silver foam dressings easily cover open wounds, and adhere to various wound patterns. These dressings have been found to cause minimal discomfort, and combining silver foam dressings with NPWT is preferred in patients with significant comorbidities and chronic infections [52]. The addition of silver to NPWT has been shown to improve healing outcomes, decrease nursing time expenditure, and decrease cost [53].

In high-risk abdominal surgery patients, such as obese patients and those with grossly contaminated surgical sites, it is not always possible or desirable to perform exclusively a primary wound closure. In such situations, NPWT is often applied. A study in 2013 showed that the use of NPWT in open colorectal surgery significantly reduces the SSI rate from 29.3% to 12.5% (p < 0.05) [54].

NPWT is commonly used in the treatment of large wound and open fractures. Today, negative pressure is often combined with antimicrobial agents. A study on contaminated open fracture models found that addition of the silver dressing to NPWT caused a greater reduction in bacterial load compared to NPWT alone, especially Gram-positive *Staphylo*cocci [55].

Vacuum-assisted wound closure has been used for several years in the treatment of soft tissue loss in the pelvis, which may be due to infection, tumors, or trauma [56]. Pelvic trauma is a complex and debilitating problem that often requires repeated surgical debridement and frequent dressing changes. Silver plated nylon, due to its porous nature and flexible design, can be used in conjunction with vacuum-assisted wound closure. Siegel et al. showed that combining silver to the vacuum on massive pelvic or extremity soft tissue loss decreases the average number of surgical debridements needed from 7.9 in the vacuum-only group, to 4.1 in the combined group (p < 0.001) [56]. The frequency of wound dressing changes was also reduced, as well as the length of hospital stay (19 vs. 7.5 days, p < 0.041). Silver is also reported to have helped eliminate the foul odor often associated with vacuum treatment. Silver in combination with vacuum has thus become the routine treatment used for these patients [56].

Enterocutaneous fistulas present another high risk for infection, and the use of NPWT in such cases is controversial. Patients with high output fistulas often require NPWT to drain bowel effluent, and skin grafts may be used to complete wound healing [57]. However, NPWT cannot always be used in such cases, and silver-based dressings have recently been reported to effectively prevent infection and improve healing [57,58].

4. Discussion

SSIs are both predictable and potentially preventable. Standardized practices and infection control bundles are effective in reducing but not eliminating the risk of SSI [1,9]. These bundles extensively address the preoperative and intraoperative aspects of infection control, but have little to say regarding postoperative care of the surgical wound. In the US, CDC guidelines recommend nothing further than the protection of primary-closure incisions with a sterile dressing for 24-48 h postoperatively [1]. British guidelines recommend covering all surgical incisions post-procedure and advocate use of low-adherent transparent polyurethane film dressings where practical [9]. British guidelines also cite several studies of interventions that make no difference in infection rate: dry gauze vs. vaseline ointment for five days in head and neck cancer procedures; hydrocolloid dressings vs. dry absorbent dressings for median sternotomy and elective vascular surgery; hydroactive dressings vs. absorbent designs for sternotomy or orthopedic surgery; hydroactive vs. hydrocolloid dressings for cardiac surgery; polyurethane membrane compared with absorbent dressings or hydroactive dressings in orthopedic surgery; and use or non-use of topical chloramphenicol for femoral neck surgery [9].

Silver dressings placed at the time of incision closure may represent the next step in the bundle approach to SSI prevention. Further study in the form of large prospective trials is needed to establish the widespread use of silver dressings across the surgical specialties for infection prevention. Specifically, we have found a lack of data to support the use of silver dressings for the following higher-risk procedures: rectal, liver, pancreatic, biliary, small bowel, hernia, gastric, appendix, and exploratory abdominal surgery; hysterectomies and ovarian procedures; vascular procedures, such as abdominal aortic aneurysm repair; spine fusions, spine refusions, posterior cervical spine surgery, and craniotomies; kidney, liver, and heart transplantation; and amputations, open reduction of fractures, and orthopedic prosthetics. Breast surgery, with a SSI rate of 0.95–6.36%, and neck surgery, with rates reaching 11.40% [20], also deserve to be studied. We were also unable to locate any clinical study evaluating the use of postoperative silver-based dressings in the widespread and high-risk obese and bariatric population. Recommendation is therefore made for future studies of silver dressings in these patients.

One of the most important factors influencing postsurgical outcomes is healing of the incision site. With early healing, the risk of SSI is reduced. Healing is a complex process, involving a myriad of molecular pathways, and influenced by many factors. The presence of bacteria in a wound is one such important factor that can negatively impact healing. Bacterial endotoxins have been found to induce tumor necrosis factoralpha (TNF-alpha), which inhibits epithelial growth factors, leading to a decrease in collagen production and impaired wound healing [59,60]. Silver, with its antimicrobial properties, reduces the bioburden and associated endotoxins in wounds. It also has the ability to directly sequester endotoxins with a net effect of promoting re-epithelialization and improving healing [61]. Excess levels of matrix metalloproteinases are also associated with delayed healing, and cause increased inflammation. Nanocrystalline silver has been shown to reduce the levels of these proteolytic enzymes, promoting wound healing and decreasing inflammation [62,63]. This form of silver selectively promotes apoptosis of cutaneous inflammatory cells and decreases proinflammatory cytokines [63]

Alimov and colleagues prospectively investigated the use of a silver hydrofiber dressing vs. iodoform dressings to pack abscess cavity after incision and drainage in the emergency department. Logistic regression showed that the silvercontaining dressing was associated with a greater than 30% reduction in surface area of the abscess at first follow-up; in other words, faster healing [64]. Shirani and associates found that skin donor sites dressed with silver-nylon healed faster than sites dressed with fine mesh gauze (9.3 vs. 12.4 days, p < 0.05) [65]. Albrecht et al. later found donor site wounds to heal faster with silver-nylon dressings vs. an occlusive petrolatum dressing (10.2 vs. 11.4 days, p < 0.05) [66]. Silverimpregnated carboxymethylcellulose dressings have also been found to provide faster healing compared to transforming methacrylate (TMD) dressings in skin graft donor sites [67]. Silver dressings have also been described to promote healing of diabetic foot ulcers, and to prevent re-infection of skin ulcers after debridement [68,69]. Two case studies were found illustrating the successful wound healing achieved when NPWT is combined to silver dressings; one post-debridement for necrotizing fasciitis, and the other after radical excision of a difficult breast abscess [70,71]. The exact mechanisms by which silver promotes healing are not fully understood, and research shows mixed results. However, some silver products can increase healing time. For example, while silver sulfadiazine effectively prevents infection, it can inhibit proliferation of keratinocytes and fibroblasts [72]. Silver nitrate treatments have been shown to promote apoptosis of these cell types, and studies have suggested that silver promotes the chronic activation of neutrophils [73,74].

Pain is another important factor influencing the overall outcome of surgical patients. Recent evidence suggests that silver may reduce pain associated with surgical incision sites, as well as burns and other types of wounds [64,75–82]. Postoperative pain can lead to increased use of opioid analgesics with reduced respiratory effort and delayed

Table 1 – Commonly used forms of silver [19,83].			
	Types	Silver release	Common use/properties
Silver salts	Silver nitrate, silver lactate	Fast release	Topical treatment and cauterization
	Silver sulfadiazine	Fast release	Topical treatment, prevention of infection
Silver dressings	Silver nanocrystalline	Sustained release	Surgical incision and burn covering
	Silver foam	Sustained release	Open wounds and ulcers
	Silver hydrofiber	Sustained release	Lower concentration of silver
	Silver plated nylon	Sustained release	High concentration of silver

ambulation, leading to overall greater patient morbidity and mortality, increased hospital length of stay, and increased healthcare costs.

P. acnes can cause a wide range of SSIs other than the spinal and joint infections mentioned in the results section. These include brain, bone, and mouth infections, as well as devicerelated infections, such as shunts and prosthetic heart valves [45]. Implementation of silver dressings can therefore potentially reduce infections related to this microorganism in a wide array of surgical procedures.

Silver is used medicinally in various forms (Table 1). Salts, such as silver sulfadiazine (SSD) topical creams (Flamazine[®], Silvadene[®]), and silver sustained release products, such as silver plated nylon (Silverlon[®]) and silver nanocrystalline (Acticoat[®]) dressings, are examples of commonly used silver products. Silver nitrate, a water soluble silver salt, is often used to chemically cauterize. Various dressings for second and third degree burns are soaked with 0.5% silver nitrate [19]. Ammoniacal silver nitrate acts as a dental protective agent. Silver proteins are used as antiseptic solutions for gynecological procedures, irrigation, suppositories, and eye drops [19]. Silver has also been used for the sterilization of sutures.

Several studies in recent years have demonstrated the efficacy of silver in specific clinical situations. This paper focused on the uses of silver in postoperative dressings to reduce SSI rates. Other uses of silver include the management of traumatic wounds, ulcers, ophthalmic conditions, and, most commonly, the treatment of burns [11–13,61,76, 77,84–91].

5. Conclusion

Surgical site infections are common. The risk of developing a SSI depends on the operative procedure, and upon patient factors such as obesity and diabetes mellitus. Standardized bundle infection-control practices have reduced but not eliminated the risk of SSI. These infections are often polymicrobial, involving Gram-positive, Gram-negative, aerobic and anaerobic bacteria. Silver has a broad spectrum of antimicrobial activity. The placement of silver-nylon dressings over incision sites at the time of primary closure has been demonstrated to lower SSI rates in certain colorectal, neurological, spinal, cardiovascular, and orthopedic procedures. It is probable that similar reductions in SSI rates can be obtained by the use of silver dressings in gynecologic, obstetric, breast, transplant, neck, and bariatric procedures, and in obese and diabetic patients. However, these populations have not been adequately studied at present.

Silver dressings are inexpensive and well tolerated. Their widespread use in surgery is promising. Prospective clinical trials are needed to evaluate the utility of silver dressings in high-risk procedures and populations.

Conflict of interest statement

Elia Charbel Abboud: Cura Surgical research funding, 2013.

Jaime E. Sanchez: Cura Surgical research funding to the University of South Florida, 2011 (PMID: 21730792).

Jorge E. Marcet: Cura Surgical research funding to the University of South Florida, 2011 (PMID: 21730792). Cura Surgical stock ownership, 2012.

Dave Barillo: A paid consultant to Argentum Medical, LLC and serves as co-principal investigator of a research study run by Argentum and funded by the Biomedical Advanced Research Development Agency.

All the other authors have no potential conflict of interest.

REFERENCES

- Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999 Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1999;20(4):250–78. quiz 279–80.
- [2] Anderson DJ, Chen LF, Sexton DJ, Kaye KS. Complex surgical site infections and the devilish details of risk adjustment: important implications for public reporting. Infect Control Hosp Epidemiol 2008;29(10):941–6.
- [3] Biffi R, Fattori L, Bertani E, Radice D, Rotmensz N, Misitano P, et al. Surgical site infections following colorectal cancer surgery: a randomized prospective trial comparing common and advanced antimicrobial dressing containing ionic silver. World J Surg Oncol 2012;10:94.
- [4] Bratzler DW, Houck PM, Richards C, Steele L, Dellinger EP, Fry DE, et al. Use of antimicrobial prophylaxis for major surgery: baseline results from the National Surgical Infection Prevention Project. Arch Surg 2005;140(2):174–82.
- [5] Anderson DJ, Kaye KS, Classen D, Arias KM, Podgorny K, Burstin H, et al. Strategies to prevent surgical site infections in acute care hospitals. Infect Control Hosp Epidemiol 2008;29(Suppl. 1):S51–61.
- [6] Klevens RM, Edwards JR, Richards Jr CL, Horan TC, Gaynes RP, Pollock DA, et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. Public Health Rep 2007;122(2):160–6.
- [7] de Lissovoy G, Fraeman K, Hutchins V, Murphy D, Song D, Vaughn BB. Surgical site infection: incidence and impact on hospital utilization and treatment costs. Am J Infect Control 2009;37(5):387–97.

- [8] Pear SM. Patient risk factors and best practices for surgical site infection prevention. Manag Infect Control 2007;3: 56–64.
- [9] National Collaborating Centre for Women's Children's Health (UK). Surgical site infection: prevention and treatment of surgical site infection. RCOG Press, NICE Clinical Guidelines # 74; 2008.
- [10] Wolcott RD, Gontcharova V, Sun Y, Zischakau A, Dowd SE. Bacterial diversity in surgical site infections: not just aerobic cocci any more. J Wound Care 2009;18(8):317–23.
- [11] Silver S, Phung le T, Silver G. Silver as biocides in burn and wound dressings and bacterial resistance to silver compounds. J Ind Microbiol Biotechnol 2006;33(7):627–34.
- [12] Clement JL, Jarrett PS. Antibacterial silver. Met Based Drugs 1994;1(5–6):467–82.
- [13] Politano AD, Campbell KT, Rosenberger LH, Sawyer RG. Use of silver in the prevention and treatment of infections: silver review. Surg Infect (Larchmt) 2013;14(1):8–20.
- [14] Krieger BR, Davis DM, Sanchez JE, Mateka JJ, Nfonsam VN, Frattini JC, et al. The use of silver nylon in preventing surgical site infections following colon and rectal surgery. Dis Colon Rectum 2011;54(8):1014–9.
- [15] Lansdown AB, Silver I. Its antibacterial properties and mechanism of action. J Wound Care 2002;11(4):125–30.
- [16] Russell AD, Hugo WB. Antimicrobial activity and action of silver. Prog Med Chem 1994;31:351–70.
- [17] Bolton L. Are silver products safe and effective for chronic wound management? J Wound Ostomy Continence Nurs 2006;33(5):469–77.
- [18] Jørgensen B, Bech-Thomsen N, Grenov B, Gottrup F. Effect of a new silver dressing on chronic venous leg ulcers with signs of critical colonisation. J Wound Care 2006;15(3):97– 100.
- [19] Grier N. Silver and its compounds. In: Block SS, editor. Disinfection, sterilization and preservation. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 1983. p. 375–89.
- [20] Edwards JR, Peterson KD, Mu Y, Banerjee S, Allen-Bridson K, Morrell G, et al. National Healthcare Safety Network (NHSN) report: data summary for 2006 through 2008, issued December 2009. Am J Infect Control 2009;37(10):783–805.
- [21] Waisbren E, Rosen H, Bader AM, Lipsitz SR, Rogers Jr SO, Eriksson E. Percent body fat and prediction of surgical site infection. J Am Coll Surg 2010;210(4):381–9.
- [22] Walsh C, Scaife C, Hopf H. Prevention and management of surgical site infections in morbidly obese women. Obstet Gynecol 2009;113(2 Pt 1):411–5.
- [23] Anaya DA, Dellinger EP. The obese surgical patient: a susceptible host for infection. Surg Infect (Larchmt) 2006;7(5):473–80.
- [24] Gaynes RP, Culver DH, Horan TC, Edwards JR, Richards C, Tolson JS. Surgical site infection (SSI) rates in the United States, 1992–1998: the National Nosocomial Infections Surveillance System basic SSI risk index. Clin Infect Dis 2001;33(Suppl. 2):S69–77.
- [25] Smith RL, Bohl JK, McElearney ST, Friel CM, Barclay MM, Sawyer RG, et al. Wound infection after elective colorectal resection. Ann Surg 2004;239(5):599–605. discussion 605–7.
- [26] Neumayer L, Hosokawa P, Itani K, El-Tamer M, Henderson WG, Khuri SF. Multivariable predictors of postoperative surgical site infection after general and vascular surgery: results from the patient safety in surgery study. J Am Coll Surg 2007;204(6):1178–87.
- [27] Siah CJ, Yatim J. Efficacy of a total occlusive ionic silvercontaining dressing combination in decreasing risk of surgical site infection: an RCT. J Wound Care 2011;20(12):561–8.
- [28] Corcoran S, Jackson V, Coulter-Smith S, Loughrey J, McKenna P, Cafferkey M. Surgical site infection after

cesarean section: implementing 3 changes to improve the quality of patient care. Am J Infect Control 2013;41(12):1258–63.

- [29] Connery SA, Downes KL, Young C. A retrospective study evaluating silver-impregnated dressings on cesarean wound healing. Adv Skin Wound Care 2012;25(9):414–9.
- [30] Sharma M, Berriel-Cass D, Baran Jr J. Sternal surgical-site infection following coronary artery bypass graft: prevalence, microbiology, and complications during a 42month period. Infect Control Hosp Epidemiol 2004;25(6):468–71.
- [31] Huckfeldt R, Redmond C, Mikkelson D, Finley PJ, Lowe C, Robertson J. A clinical trial to investigate the effect of silver nylon dressings on mediastinitis rates in postoperative cardiac sternotomy incisions. Ostomy Wound Manage 2008;54(10):36–41.
- [32] Pratt AK, Shah NS, Boyce SW. Left ventricular assist device management in the ICU. Crit Care Med 2014;42(1):158–68.
- [33] Selekof JL, Lindsay M. Left ventricular assist devices: an innovative approach to decrease infections using a silver contact dressing. In: Poster session presented at: 41st annual wound, ostomy and continence nurses annual conference; 2009.
- [34] Ricco JB, Assadian O. Antimicrobial silver grafts for prevention and treatment of vascular graft infection. Semin Vasc Surg 2011;24(4):234–41.
- [35] Seeger JM. Management of patients with prosthetic vascular graft infection. Am Surg 2000;66(2):166–77.
- [36] Zegelman M, Guenther G, Waliszewski M, Pukacki F, Stanisic MG, Piquet P, et al. Results from the International Silver Graft Registry for high-risk patients treated with a metallic-silver impregnated vascular graft. Vascular 2013;21(3):137–47.
- [37] Larena-Avellaneda A, Russmann S, Fein M, Debus ES. Prophylactic use of the silver-acetate-coated graft in arterial occlusive disease: a retrospective, comparative study. J Vasc Surg 2009;50(4):790–8.
- [38] Delva JC, Deglise S, Berard X, Dubuisson V, Delva F, Stecken L, et al. In-situ revascularisation for secondary aortoenteric fistulae: the success of silver-coated Dacron is closely linked to a suitable bowel repair. Eur J Vasc Endovasc Surg 2012;44(4):417–24.
- [39] Canaud L, D'Annoville T, Ozdemir BA, Marty-Ané C, Alric P. Combined endovascular and surgical approach for aortobronchial fistula. J Thorac Cardiovasc Surg 2014. <u>http://dx.doi.org/10.1016/j.jtcvs.2014.01.018</u> [Epub ahead of print].
- [40] Childress BB, Berceli SA, Nelson PR, Lee WA, Ozaki CK. Impact of an absorbent silver-eluting dressing system on lower extremity revascularization wound complications. Ann Vasc Surg 2007;21(5):598–602.
- [41] Keong NC, Bulters DO, Richards HK, Farrington M, Sparrow OC, Pickard JD, et al. The SILVER (Silver Impregnated Line Versus EVD Randomized trial): a double-blind, prospective, randomized, controlled trial of an intervention to reduce the rate of external ventricular drain infection. Neurosurgery 2012;71(2):394–403. discussion 403–4.
- [42] Jenkinson MD, Gamble C, Hartley JC, Hickey H, Hughes D, Blundell M, et al. The British antibiotic and silverimpregnated catheters for ventriculoperitoneal shunts multi-centre randomised controlled trial (the BASICS trial): study protocol. Trials 2014;15:4.
- [43] Epstein NE. Do silver-impregnated dressings limit infections after lumbar laminectomy with instrumented fusion? Surg Neurol 2007;68(5):483–5. discussion 485.
- [44] Bowler PG, Welsby S, Hogarth A, Towers V. Topical antimicrobial protection of postoperative surgical sites at risk of infection with Propionibacterium acnes: an in-vitro study. J Hosp Infect 2013;83(3):232–7.

- [45] Perry A, Lambert P. Propionibacterium acnes: infection beyond the skin. Expert Rev Anti Infect Ther 2011;9(12):1149–56.
- [46] Barnes M, Liew S. The incidence of infection after posterior cervical spine surgery: a 10 year review. Global Spine J 2012;2(1):3–6.
- [47] Ho D, Lynch RJ, Ranney DN, Magar A, Kubus J, Englesbe MJ. Financial impact of surgical site infection after kidney transplantation: implications for quality improvement initiative design. J Am Coll Surg 2010;211(1):99–104.
- [48] Cottrill R. Guideline-directed wound care: a patient with a post kidney transplant surgical site infection. J Wound Care 2013;22(4):214–6.
- [49] Keen JS, Desai PP, Smith CS, Suk M. Efficacy of hydrosurgical debridement and nanocrystalline silver dressings for infection prevention in type II and III open injuries. Int Wound J 2012;9(1):7–13.
- [50] Galli MM, Protzman NM, Brigido SA. Utilization of silver hydrogel sheet dressing on postsurgical incisions: a pilot study in foot and ankle surgery. Foot Ankle Spec 2013;6(6):422–33.
- [51] Ogbemudia AO, Bafor A, Edomwonyi E, Enemudo R. Prevalence of pin tract infection: the role of combined silver sulphadiazine and chlorhexidine dressing. Niger J Clin Pract 2010;13(3):268–71.
- [52] Gabriel A, Heinrich C, Shores J, Baqai W, Rogers F, Gupta S. Reducing bacterial bioburden in infected wounds with vacuum assisted closure and a new silver dressing – a pilot study. Wounds 2006;18(9):245–55.
- [53] Karr JC, de Mola FL, Pham T, Tooke L. Wound healing and cost-saving benefits of combining negative-pressure wound therapy with silver. Adv Skin Wound Care 2013;26(12):562–5.
- [54] Bonds AM, Novick TK, Dietert JB, Araghizadeh FY, Olson CH. Incisional negative pressure wound therapy significantly reduces surgical site infection in open colorectal surgery. Dis Colon Rectum 2013;56(12):1403–8.
- [55] Stinner DJ, Waterman SM, Masini BD, Wenke JC. Silver dressings augment the ability of negative pressure wound therapy to reduce bacteria in a contaminated open fracture model. J Trauma 2011;71(1):S147–50.
- [56] Siegel HJ, Herrera DF, Gay J. Silver negative pressure dressing with vacuum-assisted closure of massive pelvic and extremity wounds. Clin Orthop Relat Res 2014;472(3):830–5.
- [57] Arhi C, El-Gaddal A. Use of a silver dressing for management of an open abdominal wound complicated by an enterocutaneous fistula-from hospital to community. J Wound Ostomy Continence Nurs 2013;40(1):101–3.
- [58] Warriner R, Burrell R. Infection and the chronic wound: a focus on silver. Adv Skin Wound Care 2005;18(Suppl. 1): 2–12.
- [59] Metzger Z, Nitzan D, Pitaru S, Brosh T, Teicher S. The effect of bacterial endotoxin on the early tensile strength of healing surgical wounds. J Endod 2002;28(1):30–3.
- [60] Kawaguchi H, Hizuta A, Tanaka N, Orita K. Role of endotoxin in wound healing impairment. Res Commun Mol Pathol Pharmacol 1995;89(3):317–27.
- [61] Cutting K, White R, Hoekstra H. Topical silver-impregnated dressings and the importance of the dressing technology. Int Wound J 2009;6(5):396–402.
- [62] Wright JB, Lam K, Buret AG, Olson ME, Burrell RE. Early healing events in a porcine model of contaminated wounds: effects of nanocrystalline silver on matrix metalloproteinases, cell apoptosis, and healing. Wound Repair Regen 2002;10(3):141–51.
- [63] Nadworny PL, Wang J, Tredget EE, Burrell RE. Antiinflammatory activity of nanocrystalline silver in a porcine contact dermatitis model. Nanomedicine 2008;4(3):241–51.

- [64] Alimov V, Lovecchio F, Sinha M, Foster KN, Drachman D. Use of a silver-containing hydrofiber dressing for filling abscess cavity following incision and drainage in the emergency department: a randomized controlled trial. Adv Skin Wound Care 2013;26(1):20–5.
- [65] Shirani KZ, McManus AT, Robertson F, Walton G, Barillo DJ, McManus WF, et al. Silver nylon dressings promote painless healing. Proc Am Burn Assoc 1993;25:66.
- [66] Albrecht MC, Renz E, Cancio LC, White CE, Blackbourne LH, Chung K, et al. Comparison of Silverlon[®] dressings to Xeroform[™] gauze in the treatment of skin graft donor site wounds. J Burn Care Res 2008;29(2):S134.
- [67] Assadian O, Arnoldo B, Purdue G, Burris A, Skrinjar E, Duschek N, et al. A prospective, randomised study of a novel transforming methacrylate dressing compared with a silver-containing sodium carboxymethylcellulose dressing on partial-thickness skin graft donor sites in burn patients. Int Wound J 2013. <u>http://dx.doi.org/10.1111/</u> <u>iwj.12136</u> [Epub ahead of print].
- [68] Lazaro-Martinez JL, Cecilia-Matilla A, Aragon-Sanchez J, Garcia-Morales E, Garcia-Alvarez Y, Alvaro-Afonso F. Treatment of infected diabetic foot ulcers clinical effectiveness of a dressing of alginate and hydrocolloid, with silver fiber analysis of results of a series of cases. Rev Enferm 2013;36(11):29–34.
- [69] Parmeggiani D, Apperti M, Goffredi L, Avenia N, Madonna I, Ambrosino P, et al. Verification of the effectiveness of silver dressings to prevent reinfection of skin ulcers after debridement. Ann Ital Chir 2013;84(3):295–7.
- [70] Pour SM. Use of negative pressure wound therapy with silver base dressing for necrotizing fasciitis. J Wound Ostomy Continence Nurs 2011;38(4):449–52.
- [71] Richards AJ, Hagelstein SM, Patel GK, Ivins NM, Sweetland HM, Harding KG. Early use of negative pressure therapy in combination with silver dressings in a difficult breast abscess. Int Wound J 2011;8(6):608–11.
- [72] Hollinger MA. Toxicological aspects of topical silver pharmaceuticals. Crit Rev Toxicol 1996;26(3):255–60.
- [73] Tautenhahn J, Meyer F, Buerger T, Schmidt U, Lippert H, Koenig W, et al. Interactions of neutrophils with silvercoated vascular polyester grafts. Langenbecks Arch Surg 2010;395(2):143–9.
- [74] Poon VK, Burd A. In vitro cytotoxity of silver: implication for clinical wound care. Burns 2004;30(2):140–7.
- [75] Craig GG, Knight GM, McIntyre JM. Clinical evaluation of diamine silver fluoride/potassium iodide as a dentine desensitizing agent. A pilot study. Aust Dent J 2012;57(3):308–11.
- [76] Mabrouk A, Boughdadi NS, Helal HA, Zaki BM, Maher A. Moist occlusive dressing (Aquacel([®]) Ag) versus moist open dressing (MEBO([®]) in the management of partial-thickness facial burns: a comparative study in Ain Shams University. Burns 2012;38(3):396–403.
- [77] Blome-Eberwein S, Johnson RM, Miller SF, Caruso DM, Jordan MH, Milner S, et al. Hydrofiber dressing with silver for the management of split-thickness donor sites: a randomized evaluation of two protocols of care. Burns 2010;36(5):665–72.
- [78] Chen C, Zhang Q, Xi ZJ, Li NC, Jin J, Zhang K. Nanometer silver dressing alleviates pain after circumcision. Zhonghua Nan Ke Xue 2011;17(3):261–3.
- [79] Castillo JL, Rivera S, Aparicio T, Lazo R, Aw TC, Mancl LL, et al. The short-term effects of diammine silver fluoride on tooth sensitivity: a randomized controlled trial. J Dent Res 2011;90(2):203–8.
- [80] Jørgensen B, Gottrup F, Karlsmark T, Bech-Thomsen N, Sibbald RG. Combined use of an ibuprofen-releasing foam dressing and silver dressing on infected leg ulcers. J Wound Care 2008;17(5):210–4.

- [81] Yang X, Zhou HF, Zhang SM, Wang YZ, Ye N, Wang Y, et al. Hydrofiber[™] dressing with silver in wound healing after surgery for anal fistula. Chin J Tissue Eng Res 2013;16(47):8835–41.
- [82] Demling RH. Burns: what are the pharmacological treatment options? Expert Opin Pharmacother 2008;9(11):1895–908.
- [83] Leaper DJ. Silver dressings: their role in wound management. Int Wound J 2006;3(4):282–94.
- [84] Shahzad MN, Ahmed N. Effectiveness of Aloe Vera gel compared with 1% silver sulphadiazine cream as burn wound dressing in second degree burns. J Pak Med Assoc 2013;63(2):225–30.
- [85] Yarboro DD. A comparative study of the dressings silver sulfadiazine and aquacel ag in the management of superficial partial-thickness burns. Adv Skin Wound Care 2013;26(6):259–62.
- [86] Boonkaew B, Kempf M, Kimble R, Supaphol P, Cuttle L. Antimicrobial efficacy of a novel silver hydrogel dressing compared to two common silver burn wound dressings: ActicoatTM and PolyMem Silver^(R). Burns 2014;40(1):89–96.

- [87] Grippaudo FR, Carini L, Baldini R. Procutase versus 1% silver sulphadiazine in the treatment of minor burns. Burns 2010;36(6):871–5.
- [88] Mostaque AK, Rahman KB. Comparisons of the effects of biological membrane (amnion) and silver sulfadiazine in the management of burn wounds in children. J Burn Care Res 2011;32(2):200–9.
- [89] Muangman P, Pundee C, Opasanon S, Muangman S. A prospective, randomized trial of silver containing hydrofiber dressing versus 1% silver sulfadiazine for the treatment of partial thickness burns. Int Wound J 2010;7(4):271–6.
- [90] Opasanon S, Muangman P, Namviriyachote N. Clinical effectiveness of alginate silver dressing in outpatient management of partial-thickness burns. Int Wound J 2010;7(6):467–71.
- [91] Vavassis P, Gelinas M, Chabot Tr J, Nguyen-Tan PF. Phase 2 study of silver leaf dressing for treatment of radiationinduced dermatitis in patients receiving radiotherapy to the head and neck. J Otolaryngol Head Neck Surg 2008;37(1):124–9.