ORIGINAL ARTICLE

Efficacy of a chlorhexidine-gluconate impregnated patch for prevention of catheter-related infections in pediatric patients: systematic review and meta-analysis

Rodolfo Rivas Ruiz,[1,2,3] Miguel Ángel Villasis Keever,[3] María Guadalupe Miranda Novales,[3] Daniel Castelán Martínez,[1] Nalleli Vivanco Muñoz,[1] Gabriela Chico Barba,[1] and Patricia Clark[1,2]

ABSTRACT

Background. Nosocomial infections are risk factors related to intrahospital mortality. Among other factors, these infections are strongly associated with invasive devices. In pediatric patients, the central venous catheter (CVC) is one of the most frequently related device-associated bloodstream infections. The aim of this study was to evaluate the efficacy and safety of a chlorhexidine-gluconate impregnated patch (CHGp) in reducing infections related to CVC in pediatric patients.
Methods. We conducted a systematic review and meta-analysis. An electronic search of the literature (Medline, EMBASE, Lilacs and the Cochrane Library Plus) from 1966 to December 2010 was carried out for clinical trials comparing the CHGp vs. standard case management for prevention of catheter tip colonization (CTC); bloodstream infections (BSI) were retrieved.
Results. Only two clinical trials were found with a total of 850 participants. Patients randomized to the CHGp group showed a lower incidence of CTC than the control group (14% vs. 25%), relative risk [RR]: 0.61, 95% confidence interval [CI 95% (0.45, 0.81)], $p = 0.001$), with a number needed to treat of 11. BSI showed a RR: 1.14, ([CI 95% (0.57, 2.28)], $p = 0.71$). Adverse events were found mainly in the CHGp group and were described as local skin reactions in 5.6% (RR 8.17 [95% CI: 1.19-56.14], $p = 0.04$). Local necrosis was present in only two infants of very low birth weight (0.48%).
Conclusions. This meta-analysis demonstrated that the chlorhexidine-gluconate impregnated patch is effective in reducing CVC-related infections in the pediatric population. Serious adverse events are rare.
Key words: central venous catheters, infections related to central venous catheters, meta-analysis, chlorhexidine-gluconate impregnated patch.

INTRODUCTION

Nosocomial infections are a risk factor related to intrahospital mortality. Among other factors, these infections are strongly associated with invasive devices. In pediatric patients the central venous catheter (CVC) is one of the most frequently related device-associated bloodstream infections.[1]

Intravascular catheters are needed for managing hospitalized patients, particularly those who require intensive care; however, such devices increase the risk of local and systemic infections. Catheter-related infections (CRI) are one of the most common complications.[2]

Different protection materials for the CVC insertion site such as gauze pads and adhesive wound tape have been used to prevent CRI.[3] Newer transparent dressings made of polyurethane thin film enable visual inspection of the insertion site. In addition, they provide an occlusive closure that helps to fix the catheter; however, there is some controversy regarding its use because of the related increase in bacteremia associated with CVC.[4] The increase in humidity produced beneath the transparent dressing due to lack of permeability or due to infrequent dressing changes has been mentioned as an infection mechanism.[5]

In Mexico, the current guidelines for care of CVCs recommend the use of a transparent dressing and sterile

1 Unidad de Epidemiología Clínica, Hospital Infantil de México Federico Gómez, Mexico, D.F., Mexico
2 Facultad de Medicina, Universidad Nacional Autónoma de México, Mexico, D.F., Mexico
3 Hospital de Pediatría, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, México D.F., México

Correspondence: Patricia Clark MD, PhD
E-mail: patriciaclarkmx@gmail.com

Received for publication: 7-8-11
Accepted for publication: 8-8-11

gauze at the catheter exit site. This protection should be removed in the presence of an infection or bleeding.

The main purpose of the chlorhexidine-gluconate impregnated patch (Biopatch, Ethicon, Johnson & Johnson Co.) is to reduce device-related infections. Chlorhexidine-gluconate is added to a hydrophilic absorptive foam that absorbs wound exudation caused by the use of medical devices such as CVC, arterial catheters (AC), dialysis catheters, cardiac catheterization, pleural seals, orthopedic fixations,[6,7] and epidural catheters.[8,9] In patients with CVC or AC, chlorhexidine-gluconate impregnated patch (CHGp) seems to be an alternative for the prevention of catheter tip colonization (CTC), bloodstream infections (BSI), and skin colonization with microorganisms related to BSI in patients with CVC or AC.[10]

In April 2011, the Centers for Disease Control and Infection (CDC) reviewed clinical data from patients treated with Biopatch Protective Disk with CHG as part of its update to the 2002 guidelines for reducing risk of intravascular catheter-associated infections in the United States. In the new guidelines, use of a CHGp dressing is designated as a category 1B recommendation. CHGp is the only CHG-impregnated sponge dressing clinically proven to reduce central line-associated bloodstream infections (CLABSI) and the only CHG-impregnated product with an FDA-cleared indication for this use.[11]

Despite this recommendation, there is still concern about the evidence that supports the use of CHGp because CVC-related infections are a significant problem in seriously ill or critically ill pediatric patients, and there is no consensus regarding which protection mechanism is the ideal or most effective for the prevention of CRI in pediatric and newborn patients.[12,13] In comparison to adult patients, children seem to be more susceptible to adverse events in skin due to their fragility and immature immune system. In spite of the facts mentioned above, we conducted a systematic review and meta-analysis of all randomized clinical trials published in order to determine the efficacy of the use of CHGp in the prevention of CRI in children.

MATERIALS AND METHODS

A systematic review addressing the efficacy of the use of CHGp in preventing CVC-related infections in children was conducted. In order to find relevant articles, we searched the main medical electronic databases (Medline, EMBASE, Lilacs and Cochrane Library Plus) followed by a manual search of articles selected for inclusion in the study.

Type of studies

Randomized and controlled clinical trials where invasive devices and Biopatch were used in children were included.

Type of participants

We included all pediatric patients (<18 years old) with any kind of CVC or any other intravenous device.

Type of interventions

Interventions included pediatric patients with CVC or any other intravenous device wounded with CHFp compared with any other type of catheter dressing.

Types of outcomes

The primary outcome measures were two: the rate of CTC and the rate of BSI. We also looked for adverse events for safety assessment such as with contact dermatitis, skin necrosis or any skin alteration. For diagnosis of contact dermatitis the International Contact Dermatitis Research Group System was used.[14]

General search mechanism

We electronically searched Medline (1966 to 2010), EMBASE and the Cochrane Library (1980–2010). For our search strategy, we used the following Medical Subject Headings (MeSH): ((“chlorhexidine”[MeSH Terms] OR Chlorhexidine[Text Word]) AND impregnated[All Fields]) AND (“bandages”[MeSH Terms] OR dressing[Text Word]). For the specific search of catheter-related infection (Catheter-Related Infections [MeSH Terms]) was added to the search. These same terms were used to search EMBASE and the Cochrane Library. For this last database a broad search was additionally done; therefore, an independent search mechanism was used for each question. All searches were limited to the pediatric population (0 to 18 years old). We also contacted the manufacturer of Biopatch to inquire about possible additional studies.

Data extraction

Using standardized data form, two authors (RR-R and PC) examined the title of all citations retrieved by the search.

We obtained the full text of those selected. Independently, both authors reviewed each article; all articles that fulfilled the inclusion criteria were included for data extraction phase. Differences between reviewers were resolved by consensus.

In case of discrepancy, a consensus was reached to decide which data would be included. Data obtained from each study were author, year of publication, patients' characteristics, compared device's intervention, rates of CTC and BSI, and adverse events.

Statistical analysis

Meta-analysis was conducted using RevMan v.5.0.20 in accordance with the recommendations of the guidelines of the *Cochrane Collaboration* and the *Quality of Reporting of Meta-analysis*.[15] Comparisons were made and the estimated effect was evaluated through determination of the relative risk (RR) for dichotomic variables, calculating 95% confidence intervals (95% CI). The RR shows the likelihood of an individual having a catheter-related infection when the Biopatch is used as compared to other patients with other types of catheter dressings. Heterogeneity was evaluated through χ^2, using a p value <0.05 to reject the null hypothesis. Heterogeneity related to effect size of included studies was evaluated using I^2. The RR was calculated using the fixed-effect model and Mantel-Haenszel method, if homogeneity was assumed. For detection of publication bias, funnel plots were constructed.[16]

In order to enhance the understanding of the effect size, the number needed to treat (NNT) and the 95% CI were calculated in all of the analyses that resulted statistically significant.

RESULTS

From the search strategy used, a total of 240 titles and abstracts were found; 231 were excluded (Figure 1). The final selection yielded eight clinical trials and one cohort study. From these eight randomized clinical trials (RCTs), only two were carried out in a pediatric population and included for the review, as well as one retrospective cohort. Kappa correlation among observers in the study selection was 0.78 (p = 0.005).

The two RCTs included 850 pediatric patients: Garland et al. in 2001 reported on newborns hospitalized in a

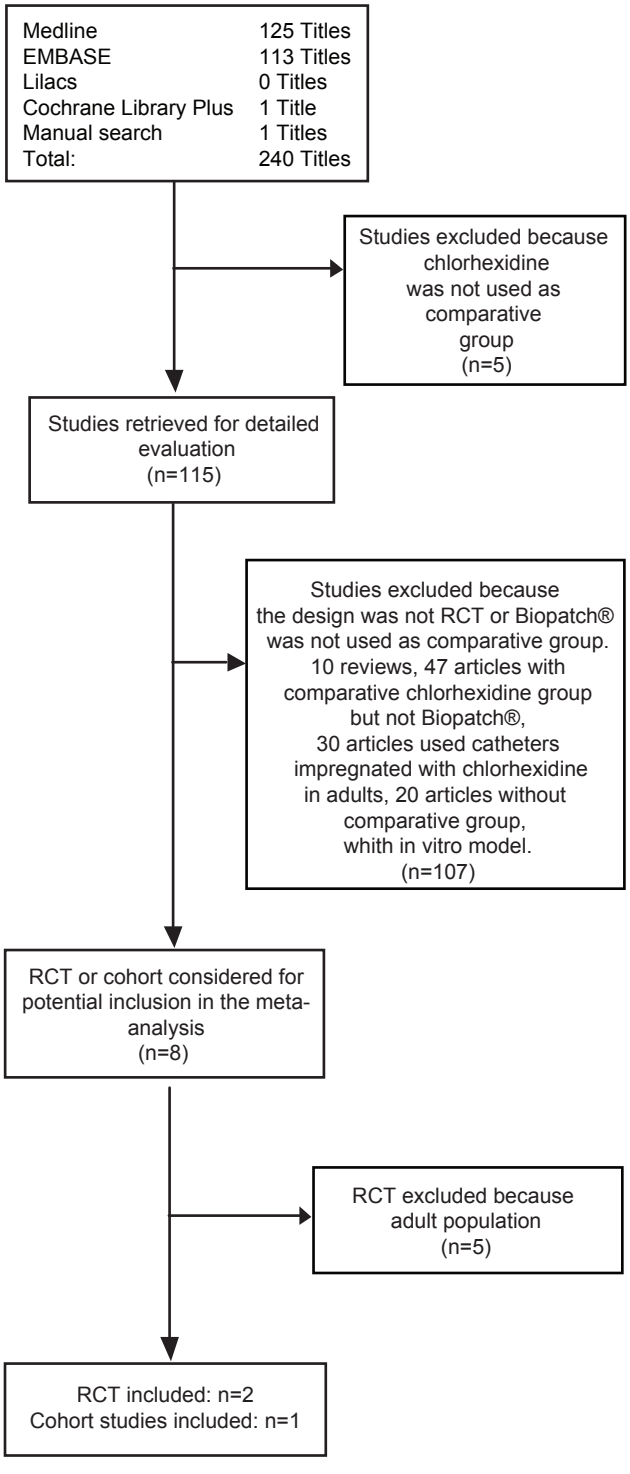

Figure 1. Trial flow depicting the selection process of studies included in the meta-analysis. RCT, randomized control trial.

neonatal intensive care unit.[17] The second RCT reported by Levi et al. in 2005 was performed in a sample of pediatric patients of different ages.[18] One historical cohort was found, performed by Onder et al. in 2009 with 40 children studied.[19] This study did not report adverse events (Table 1).

The two RCTs assessed the frequency of CTC in 850 pediatric patients; CHGp group showed a lower incidence of CTC (14%; 58 infections in 409 cases) compared with standard dressing (25%, 103 infections in 441 cases) with a RR of 0.60 (95% CI 0.45, 0.81; $p = 0.0007$), and a NNT of 11 (Figure 2). According to the results of the funnel plot, there was no publication bias (Figure 3).

No differences in the incidence of bloodstream infection with the use of CHGp were found (RR 1.14 95% CI 0.57, 2.28; $p = 0.71$) compared with the standard dressing (Figure 4).

Regarding the safety of using CHGp, adverse events were found in both studies, mainly in the Biopatch group. These were described as local skin reactions in 5.6% (RR 8.17, 95% CI: 1.19-56.14; $p = 0.04$) (Table 2). Local necrosis was present in two (0.48%) very low birth weight preterm newborns. Systemic adverse reactions to CHGp were not reported in any of the pooled studies.

DISCUSSION

This meta-analysis demonstrated that CHGp is effective in reducing CTC. Its use is clearly associated with a trend towards reduction in BSI related to CVC use. Local cutaneous reactions due to Biopatch are very uncommon and occur mainly in neonates. These results endorse the 2011 CDC recommendations of CVC care.[11]

Chlorhexidine is an antiseptic broadly studied; its microbiological and clinical efficacy has been proven. For example, its use reduced ~50% the risk of CTC.[13] Mimoz et al. showed that catheters assigned to the chlorhexidine group were less frequently colonized than those assigned to the povidone-iodine group (28/242 [11.6%] vs. 53 of 239 [22.2%], $p = 0.002$; incidence density of 9.7 vs. 18.3/1,000 catheter-days).[20] These results are consistent with other studies.[20-22] Based upon these data, a chlorhexidine solution-based device called Biopatch was designed.[21]

The positive impact of CHGp was successfully demonstrated in a large RCT for temporary catheters in adults. Biopatch group reduced significantly the risk of catheter colonization (RR 0.62, 95% CI 0.49–0.78) in comparison to standard dressings.[22] A later cost-benefit analysis

Table 1. Evidence of the efficacy as infection prevention and adverse events of Biopatch in a pediatric population

Author/ Year	*Patients*	*Method*	*Comparison group*	*Results*		*Adverse events*	
				Bio-patch	*Control*	*Biopatch*	*Control*
Onder 2009	Children in hemodialysis program	Historical cohort (retrospective)	Standard transparent dressing	*n* = 40 CRI: 3	*n* = 38 CRI: 9	0	Not reported
Levy 2005	Pediatric patients with CVC for cardiac surgery	RCT	Standard dressing	*n* = 74 CTC 26.8% 11/74 BSI 4/74	*n* = 71 CTC 30% 21/71 BSI 3/71	CD 5.6% 4/71	CD 1.3% 1/74
Garland 2001	Newborns with CVC	RCT	Dressing with povidone-iodine	n=335 CTC 15% 47/335 BSI 3.5% 12/335	n=370 CTC 24% 82/370 BSI 3.2% 12/370	n=118 CD 5.6% 19/335 Necrosis 1.7% 2/118	None

CVC, central venous catheter; RCT, randomized control trial; CTC, catheter-tip colonization; CRI, catheter-related infections, BSI, bloodstream infection; CD, contact dermatitis (International Contact Dermatitis Research Group System).

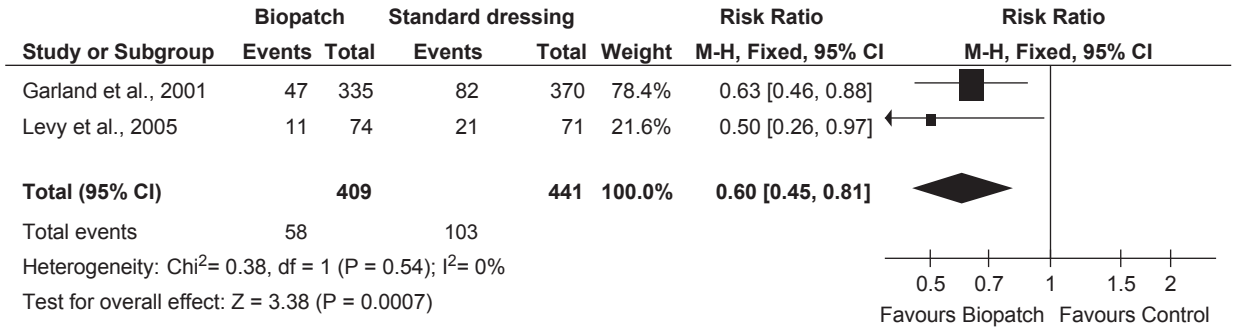

Figure 2. Efficacy of Biopatch in the prevention of catheter-tip colonization in children.

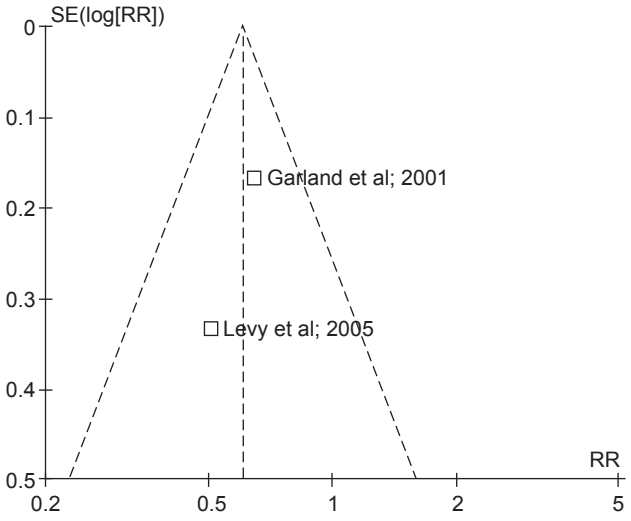

Figure 3. Funnel plot of the standard error by the log RR for two comparisons. Treatment on the x-axis and standard error on the y-axis.

concluded that chlorhexidine dressings could reduce cost, local infections, CRI, and deaths.[23]

In pediatric patients, CHGp has been used for several years but as shown in the present systematic review very few RCTs have been published in order to assess its efficacy and safety. Only one cohort and two RCTs were found. We found that the most important benefit was the reduction of CTC, which is highly associated with CVC bacteriemia. However, we did not find any difference in BSI, probably because this outcome has a multifactorial cause, especially in newborns. This study clearly shows that CHGp use in the pediatric population and in newborns is safe because the main adverse event of the use of CHGp in pediatric patients was contact dermatitis. Newborns are at high risk compared with the pediatric population, perhaps because of the immature skin of these patients. Its use must have special considerations. There were no systemic adverse

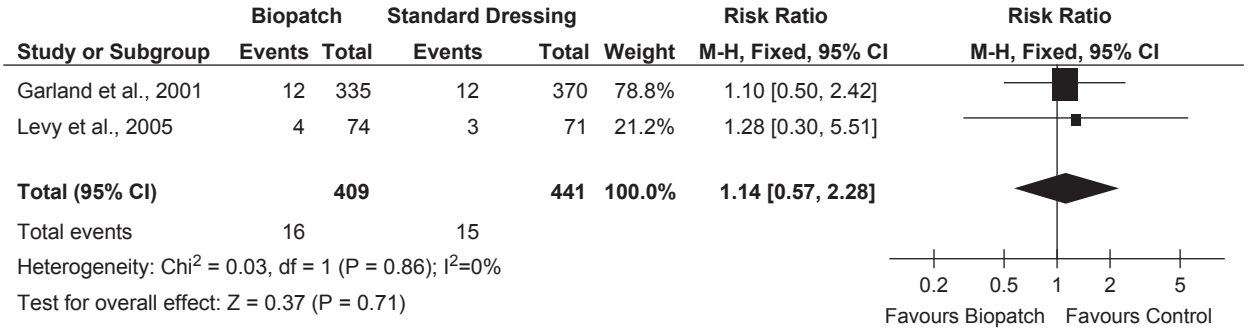

Figure 4. Efficacy of Biopatch in the prevention of bloodstream infections in children.

Table 2. Outcomes, population, statistical methods and effect size studied in this meta-analysis

Outcome	*No. of studies*	*No. of participants*	*Statistical method*	*Effect estimate [95% CI]*
Catheter-tip colonization	2	850	RR (M-H, fixed, 95% CI)	0.60 [0.45, 0.81]
Bloodstream infection	2	850	RR (M-H, fixed, 95% CI)	1.14 [0.57, 2.28]
Contact dermatitis	2	850	RR (M-H, fixed, 95% CI)	8.17 [1.19, 56.14]

RR, risk ratio; 95% CI, 95% confidence interval; RR, relative risk; M-H, Mantel-Haenszel.

reactions to CHGp in any of the pooled studies in this systematic review.

For more than 15 years, the use of Biopatch has been recommended because of its efficacy in reducing infections and because of its ease of use.[24,25] These capabilities seem to provide an additional advantage that is translated into decreased costs derived from patient care. This decrease in costs is due to savings in time devoted by health care personnel in catheter care[26] as well as to savings generated for not requiring extra material because of the need for less frequent changes of the standard dressing with the use of CHGp.[27]

Our results showed a statistically and clinically significant protection for CTC of ~40% of risk reduction with a relatively lower NNT of 11. Garland et al. in 2001 included only newborns,[17] whereas Levy et al. in 2005 included pediatric patients.[18] Despite this difference, both studies show CTC risk reduction. When we carried out the funnel plot we found that those studies did not show a statistically significant publication bias because they were distributed on both sides of the graph (Figure 3). Although this meta-analysis shows a low incidence of complications with the use of CHGp in children, we found only two RCT; therefore, it is possible that our findings may change with large-size RCTs (>900 patients).

According to our results, the recommendations from the new guidelines of the CDC[11] for using CHGp seem to be accurate. This patch represents a tool to reduce the risk of developing infections in addition to saving time in cleansings carried out by health care personnel. Likewise, decrease in costs and other unquantifiable variables in the trials should be considered such as secondary infections due to manipulation (catheter fracture, premature catheter removal, etc.) and secondary infections due to the cleansing process itself (where more manipulation implies more infection).

Furthermore, the use of chlorhexidine in children has been documented as a safe therapy in the prevention of CRI, even in newborns, with no reports of systemic adverse reactions. Despite the fact that two clinical trials in children reported adverse events with the use of Biopatch, these adverse events were mild, such as the presence of contact dermatitis. Pressure necrosis was found in one clinical trial, in addition to the fact that some of the patients tested had contact dermatitis.

The controversy lies in the fact that Biopatch is effective in the prevention of CRI, but the presence of those adverse events suggest caution in its use on children. The recommendation for the use of Biopatch in pediatrics is limited to children >2 months of age.[11] A well-designed controlled clinical trial is needed for newborns in order to correctly and accurately evaluate safety and the effect in that population group.

Moreover, use of this device may have further advantages such as time saved with less-frequent dressing changes by nurses and health care personnel, preventing other complications (e.g., premature catheter removal), offering patient comfort or providing economic savings derived from its use. Of note, these outcome measures have not been studied. Therefore, in the future there may be a new line of research regarding the use of this device.

The authors reached the following conclusions: in this systematic review and meta-analysis the authors found evidence based on clinical trials that support the use of Biopatch to prevent CVC-related infections in a pediatric population. Regarding safety with the use of Biopatch, only one vulnerable group was found: very low birth weight newborns for gestational age. A well-designed controlled clinical trial is needed for that age group to correctly and accurately evaluate safety in that population group.

Disclaimer: Use of trade names and commercial sources is for identification only and does not imply endorsement by the authors.

Acknowledgments

This study was presented in part at the 1st Surgical Infection Society: Latin America (SISLA) Meeting in Buenos Aires, Argentina (April 2010).

We wish to thank Johnson & Johnson for the economic support for translation and acquisition of some articles included in this paper.

REFERENCES

1. O'Grady NP, Alexander M, Dellinger EP, Gerberding JL, Heard SO, Maki DG, et al. Guidelines for the prevention of intravascular catheter-related infections. Centers for Disease Control and Prevention. MMWR Recomm Rep 2002;51:1-29.
2. Smith MJ. Catheter-related bloodstream infections in children. Am J Infect Control 2008;36:S173.e1-3.
3. Lau CE. Transparent and gauze dressings and their effect on infection rates of central venous catheters: a review of past and current literature. J Intraven Nurs 1996;19:240-245.
4. Safdar N, Maki DG. The pathogenesis of catheter-related bloodstream infection with noncuffed short-term central venous catheters. Intensive Care Med 2004;30:62-67.
5. Hoffmann KK, Weber DJ, Samsa GP, Rutala WA. Transparent polyurethane film as an intravenous catheter dressing. A meta-analysis of the infection risks. JAMA 1992;267:2072-2076.
6. Egol KA, Paksima N, Puopolo S, Klugman J, Hiebert R, Koval KJ. Treatment of external fixation pins about the wrist: a prospective, randomized trial. J Bone Joint Surg Am 2006;88:349-354.
7. Lethaby A, Temple J, Santy J. Pin site care for preventing infections associated with external bone fixators and pins. Cochrane Database Syst Rev 2008;4:CD004551.
8. Mann TJ, Orlikowski CE, Gurrin LC, Keil AD. The effect of the biopatch, a chlorhexidine impregnated dressing, on bacterial colonization of epidural catheter exit sites. Anaesth Intensive Care 2001;29:600-603.
9. Shapiro JM, Bond EL, Garman JK. Use of a chlorhexidine dressing to reduce microbial colonization of epidural catheters. Anesthesiology 1990;73:625-631.
10. Camins BC. Trial Evaluating the Efficacy of a Chlorhexidine-Impregnated Sponge (BIOPATCH®) to Reduce Catheter-Related Bloodstream Infections in Hemodialysis Patients. ClinicalTrials.gov Identifier: NCT00550693. Available at: http://clinicaltrials.gov/ct2/show/NCT00550693
11. Centers for Disease Control and Prevention (CDC). Guidelines for the Prevention of Intravascular Catheter-Related Infections. Available at: http://www.cdc.gov/hicpac/pdf/guidelines/bsi-guidelines-2011.pdf
12. Reynolds MG, Tebbs SE, Elliott TS. Do dressings with increased permeability reduce the incidence of central venous catheter related sepsis? Intensive Crit Care Nurs 1997;13:26-29.
13. Mimoz O, Pieroni L, Lawrence C, Edouard A, Costa Y, Samii K, et al. Prospective, randomized trial of two antiseptic solutions for prevention of central venous or arterial catheter colonization and infection in intensive care unit patients. Crit Care Med 1996;24:1818-1823.
14. International Contact Dermatitis Research Group (ICDRG). Available at: http://www.iscd2001.edu.uy/icdrg.htm (accessed: December 2010)http://www.iscd2001.edu.uy/icdrg.htm.
15. Bero L, Rennie D. The Cochrane Collaboration. Preparing, maintaining, and disseminating systematic reviews of the effects of health care. JAMA 1995;274:1935-1938.
16. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-634.
17. Garland JS, Alex CP, Mueller CD, Otten D, Shivpuri C, Harris MC, et al. A randomized trial comparing povidone-iodine to a chlorhexidine gluconate-impregnated dressing for prevention of central venous catheter infections in neonates. Pediatrics 2001;107:1431-1436.
18. Levy I, Katz J, Solter E, Samra Z, Vidne B, Birk E, et al. Chlorhexidine-impregnated dressing for prevention of colonization of central venous catheters in infants and children: a randomized controlled study. Pediatr Infect Dis J 2005;24:676-679.
19. Onder AM, Chandar J, Coakley S, Francoeur D, Abitbol C, Zilleruelo G. Controlling exit site infections: does it decrease the incidence of catheter-related bacteremia in children on chronic hemodialysis? Hemodial Int 2009;13:11-18.
20. Mimoz O, Villeminey S, Ragot S, Dahyot-Fizelier C, Laksiri L, Petitpas F, et al. Chlorhexidine-based antiseptic solution vs alcohol-based povidone-iodine for central venous catheter care. *Arch Intern Med* 2007;167:2066-2072.
21. Roberts B, Cheung D. Biopatch™--a new concept in antimicrobial dressings for invasive devices. Aust Crit Care 1998;11:16-19.
22. Maki DG, Mermel LA, Kluger D, Narans L, Knasinski V, Parenteau S, et al. The efficacy of a chlorhexidine-impregnated sponge (Biopatch™) for the prevention of intravascular catheter-related infection: a prospective, randomized, controlled, multicenter study. Abstr Intersci Conf Antimicrob Agents Chemother 2000;40:422-424 (abstr 1430).
23. Crawford AG, Fuhr JP Jr, Rao B. Cost-benefit analysis of chlorhexidine gluconate dressing in the prevention of catheter-related bloodstream infections. Infect Control Hosp Epidemiol 2004;25:668-674.
24. Timsit JF, Schwebel C, Bouadma L, Geffroy A, Garrouste-Orgeas M, Pease S, et al. Chlorhexidine-impregnated sponges and less frequent dressing changes for prevention of catheter-related infections in critically ill adults: a randomized controlled trial. JAMA 2009;301:1231-1241.
25. Chaiyakunapruk N, Veenstra DL, Lipsky BA, Saint S. Chlorhexidine compared with povidone-iodine solution for vascular catheter-site care: a meta-analysis. Ann Intern Med 2002;136:792-801.
26. Vandijck DM, Labeau SO, Secanell M, Rello J, Blot SI. The role of nurses working in emergency and critical care environments in the prevention of intravascular catheter-related bloodstream infections. Int Emerg Nurs 2009;17:60-68.
27. Vokurka S, Bystricka E, Visokaiova M, Scudlova J. Once-versus twice-weekly changing of central venous catheter occlusive dressing in intensive chemotherapy patients: results of a randomized multicenter study. Med Sci Monit 2009;15:CR107-CR110.