Biological contamination of insulin pens in a hospital setting

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Purpose. Biological contamination of insulin pens in a hospital setting was studied.
Methods. This prospective study, conducted at two hospitals within a multihospital system, examined 125 insulin pens that had been returned to the inpatient pharmacies after patient discharge and were refrigerated for up to 48 hours before laboratory testing. Insulin was removed from the 125 pens and examined microscopically for the presence of nucleated cells and red blood cells (RBCs). Positive samples were examined by a pathologist to determine the cell types present. An immunochromatographic assay was used to determine the presence of free hemoglobin in the insulin. The 10 control samples were negative on microscopic examination.
Results. Out of 125 insulin pens, 7 (5.6%) tested positive for cells or hemoglobin. Microscopic examination revealed six positive samples containing a total of nine cells, including macrophages, squamous cells, and an RBC. The sample containing the RBC was not the same sample that tested positive for hemoglobin. Based on findings of intact cells and hemoglobin in insulin pens after administration, the potential exists for transmission of infectious agents from patient to patient if a single pen cartridge is used to administer insulin to multiple patients, even if a new needle is used for each individual.
Conclusion. Examination of 125 insulin pens used in hospitals revealed hemoglobin in 1 pen and at least one cell in another 6 pens. The nine detected cells consisted of four squamous epithelial cells, four macrophages, and one RBC.
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From March to May 2009, the Food and Drug Administration (FDA) issued statements through several outlets warning against using the same insulin pen to administer insulin to multiple patients.[1-4] These alerts were issued following the release of information that two military hospitals inappropriately used insulin pens to administer medication to multiple patients, and over 2000 patients were at risk of contracting blood-borne pathogens, including viral hepatitis and human immunodeficiency virus (HIV).[5,6] Insulin pens are only approved for single-patient use, and FDA indicated that even though the needles were changed between uses, the patients were at risk due to possible biological contamination in the pen cartridges.[1-4,7] While insulin pen cartridges contain preservatives, the complete spectrum of their antimicrobial activity is unknown, and intracellular pathogens are most likely not exposed to the preservatives; these facts have led to concern that pathogens may be transmitted during insulin pen misuse.[8,9] Immediately after the initial press release from one of the hospitals involved and before the FDA alert, the Institute for Safe Medication Practices (ISMP) issued a similar warning concerning the improper use of insulin pens,[10] and then other groups, such as the American Medical Association, passed along the warnings to their constituents.[11-14] Despite these widely disseminated warnings, Dean Health System in Madison, Wisconsin, reported that over 2000 patients were

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at risk of contracting blood-borne illness through inappropriate reuse of insulin demonstration pens and fingerstick devices by a diabetes nurse educator during patient education training sessions between 2006 and 2011.[15-17] One patient has filed a lawsuit claiming that he contracted hepatitis C as a result of the nurse's negligence. The Centers for Disease Control and Prevention addressed proper insulin pen use again after this most recent incident, including reminders that pens are only to be used for 1 patient, pens should be properly labeled, health care facilities should review policies and educate staff on proper use, and facilities should notify patients if reuse occurs so they may undergo proper testing.[18] But even with reiteration of the warnings, Veterans Affairs Western New York Healthcare System in January 2013 notified approximately 700 patients that they were possibly exposed to blood-borne pathogens between October 2010 and November 2012 due to improper use of insulin pens on multiple patients.[19] After this incident and a similar occurrence at a different New York hospital,[20] ISMP issued a Medication Safety Alert urging hospitals to consider eliminating insulin pen use for inpatients because education and monitoring may not be enough to stem misuse.[21]

While there is widespread concern about disease transmission due to repeated instances of misuse of insulin pens in hospitals, to our knowledge no studies have been conducted in the United States to determine if contamination occurs with repeated use of insulin pens. The objective of this study was to determine whether intact patient cells infiltrate sterile insulin pen reservoirs during repeated use.

Methods

Sample collection. This prospective study, conducted at two hospitals within a multihospital system, examined 125 insulin pens (NovoLog FlexPen, Novo Nordisk, Princeton, NJ) that had been returned to the inpatient pharmacies after patient discharge and were refrigerated for up to 48 hours before laboratory testing. For study inclusion, each pen must have contained less than 250 units of insulin by visual inspection, indicating the pen had been used. Any pen marked with any patient identifier that had not been removed by the pharmacy staff was excluded from the study to protect patient privacy. Ten unused pens of the same type (lot VZF0367) were used for control comparison. Pens were collected from January to March 2009.

Sample preparation. Insulin vials were removed from their plastic pen casing, and all samples were kept on ice during processing. The plunger was removed from the vial, and the insulin was transferred to a 15-mL conical tube. The tube was centrifuged for five minutes at 125*g* and 4 °C. After centrifugation, 150 µL of supernatant was removed for hemoglobin testing (described below). The empty vial was rinsed with 2 mL of sterile insulin (NovoLog, Novo Nordisk) to remove any residual sample. The rinse insulin was added to the original insulin, and the tube was centrifuged again under the same conditions. Most of the supernatant was removed and discarded. The sediment was resuspended in the remaining 0.5 mL of supernatant for microscopic examination.

Hemoglobin analysis. Free hemoglobin from damaged red blood cells (RBCs) was detected using a direct immunochromatographic assay (ABAcard Hematrace, Abacus Diagnostics, Inc., West Hills, CA, lot 3280604), which is specific for the hemoglobin molecule and detects hemoglobin concentrations of >0.05 µg/mL. The assay was performed according to the manufacturer's instructions. Briefly, 150 µL of supernatant was added to the sample area of the test cartridge. The test cartridge was allowed to remain flat on the counter for 10 minutes, and the results were then determined. A single line (the control line) in the sample window indicated a negative result, and two lines (the control line and the sample line) indicated a positive result. All cartridges showing a positive result were photographed, and a representative negative sample was also photographed. Photographs were taken for record-keeping purposes, as test cartridges are not stable for long-term storage of results.

All test kits were from the same lot, and positive- and negative-control experiments were performed on each new box. The positive control was fresh blood from a finger stick, and the negative control was sterile insulin (NovoLog).

Microscopic examination. The sediment from each insulin vial was resuspended in the supernatant and transported on ice to a second laboratory for testing. The cell suspension was transferred to a Cyto-Tek specimen chamber (Cardinal Health, Dublin, OH). The sample was centrifuged (Cyto-Tek, Miles Scientific, Melrose Park, IL) at 8000 rpm for 10 minutes at room temperature. After centrifugation, the microscope slide was removed from the device and allowed to air dry. The slide was then stained on an automated slide stainer (Hema-tek 2000, Bayer Corporation, Tarrytown, NY) using Wright stain. The slides were examined microscopically (Axiostar plus, Zeiss, Thornwood, NY) for cells. The Cyto-Tek technique of sample preparation concentrates all cellular material in a small square, so essentially all cellular material from the insulin pen vial was viewed during microscopic examination of each slide. The entire square was scanned, first at 100× and then at 400×, to confirm cell presence. All slides were prepared and initially read by a trained biomedical scientist. The identity of all cells was confirmed by a pathologist. Photographs (AxioCam MRc, Zeiss) were taken of all detected cells.

Results

Hemoglobin assay. Of the 125 samples examined, 1 (0.8%) was positive for hemoglobin (sample 98). Two samples gave an inconclusive reading, consisting of a partial line in the test area and a full line in the control area. Of these inconclusive samples, 1 could not be retested because the sample volume was insufficient. The second inconclusive sample was retested, and the result was negative. All control experiments yielded appropriate results.

Microscopic examination. One slide was made for each sample, and slides were deemed positive when at least one intact, nucleated cell of any kind or an RBC was present. Microscopic examination revealed at least one cell in 6 (4.8%) of the 125 samples (Figure 1). A total of nine cells were observed in those 6 samples: four squamous epithelial cells (three in sample 45 and one in sample 95), four macrophages (two, one of which was binucleate, in sample 85; one in sample 96; and one in sample 111), and one RBC (in sample 103). The sample that contained the RBC was not the one that tested positive for hemoglobin with the immunoassay (sample 98), so a total of 7 (5.6%) of 125 samples tested positive for the presence of biological contamination. The 10 control samples were negative on microscopic examination.

Discussion

Introduced in the 1980s, insulin pens have become popular among patients and health care workers.[22-26] Studies have indicated that patients prefer insulin pens over the traditional syringe-and-needle administration method.[22-24] Hospital personnel appreciate insulin pens because they are already labeled with the product name and strength. Pens are also convenient because they provide insulin in a ready-to-administer form and reduce preparation time and medication waste.[25,26]

Safety concerns have been brought to the forefront since the introduction of insulin pens. Even before the army hospital incidents described previously, FDA, ISMP, and various researchers were debating the advantages and disadvantages of insulin pen devices.[26-30] A French study indicated that hospital workers sustained six times more needlestick injuries when using injection devices compared with syringes.[30] One of the early issues with insulin pens was leakage of insulin at the administration site, leading to dosage concerns; this is still a problem that is addressed through education on proper usage guidelines for both patients and health care workers.[25,30-32] Biological contamination issues were initially brought forward due to patient complaints of bubbles in their insulin pen cartridges or small amounts of blood in the cartridge. These problems were potentially related to similar improper technique that led to leakage and were possibly due to backflow pressure during the time the needle pathway was open to administer insulin if the pen was withdrawn too soon or too quickly.[26-28,33]

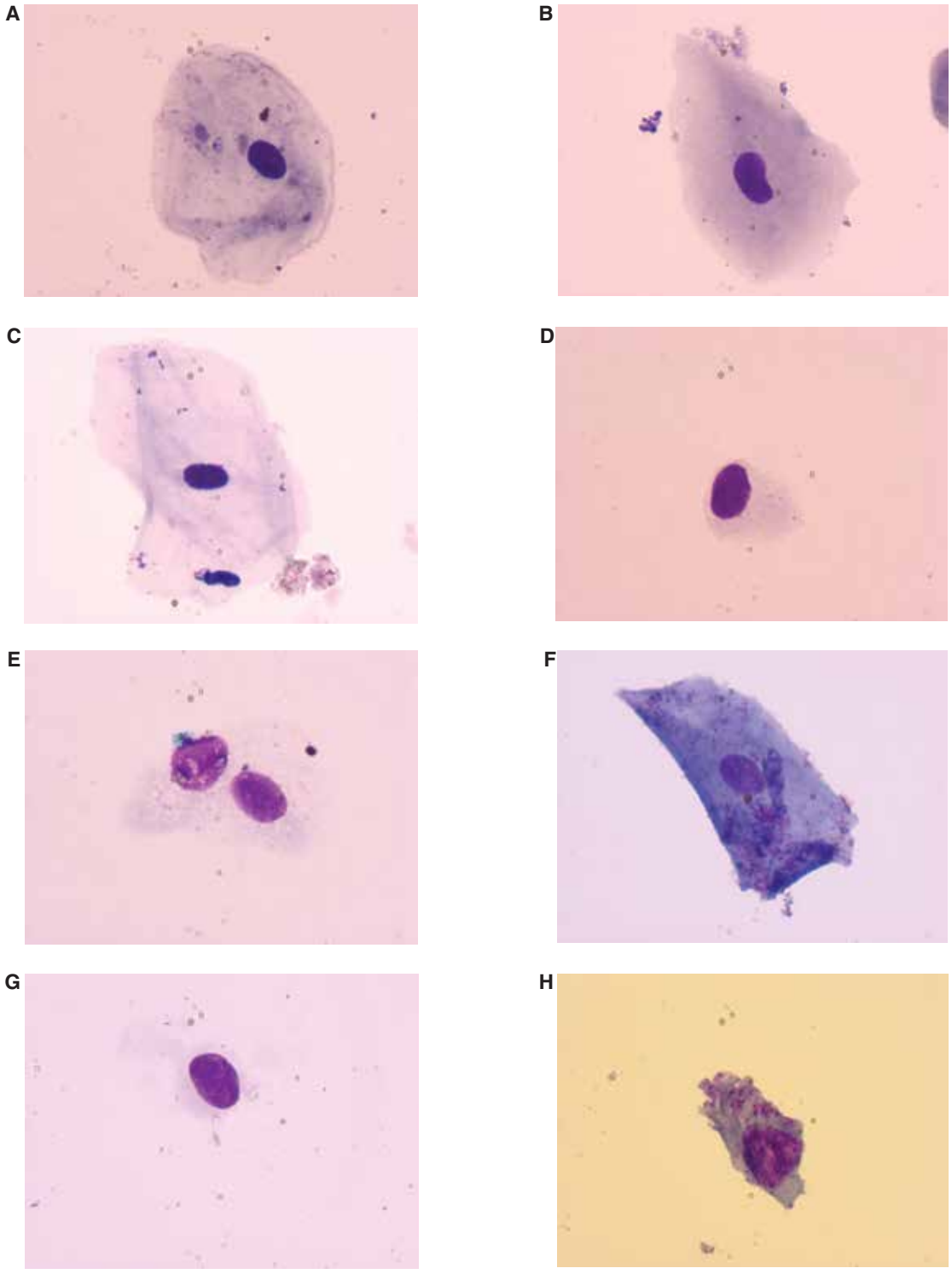
Until 1998 there were no studies investigating possible biological contamination from backflow during medication administration. Le Floch et al.[33] examined potential contamination by testing 120 insulin pens of French patients during regular ambulatory visits. The investigators found squamous cells in 30% of needles and 58% of cartridges in Omnipen, Novolet, and Novopen 3 devices. Air bubbles were found in 45% of cartridges. However, this study was unable to find blood cells and did not check for the presence of hemoglobin. The authors speculated that since cells were found more frequently in cartridges than needles, this might suggest total aspiration of cells into the cartridge.

In 2001, Sonoki et al.[34] described a Japanese study examining the effect of hydrostatic pressure on insulin pens and the movement of material back into the pens. A dye-filled rubber tube was used to mimic the injection site, and insulin pens were used to administer medication to determine if dye flowed back into the pen cartridge. Dye was detected in 17 of 57 cartridges of three different brands of insulin pens. The same authors used an immunochromatographic assay with anti-human-hemoglobin antibody to test 146 insulin pens that had been used by patients. Hemoglobin was found in 6 (4.1%) of the pens, and the volume of blood per contaminated pen was calculated to be >0.3 μL; the investigators did not check for the presence of cells.

Newer models of insulin pens have been introduced since the publication of these studies, and no recent investigations have examined the current potential for biological contamination. Furthermore, no studies to date have been conducted in the United States to investigate this topic. Only one study has investigated hepatitis C transmission following insulin pen misuse, and the researchers found no evidence of pathogen transmission in these patients.[35]

Our study analyzed insulin pens following patient use to determine the frequency of cartridge contamination and is the first to detect evidence of contamination by searching for both intact cells and hemoglobin. We also identified the cell types present. The presence of hemoglobin indicates contamination with blood and the potential for transmission of blood-borne microorganisms, most notably hepatitis B and C viruses and HIV. Contamination by squamous cells and macrophages indicates the potential for transmitting various pathogens, including viruses, intracellular and extracellular bacteria, and fungi. The results of this study are particularly enlightening following numerous reports of insulin pen misuse by health care professionals and the resultant FDA warnings about the potential hazards associated with using a single insulin pen

Figure 1. Cells detected during microscopic examination (400×) of contents of used insulin pens. Panels A–C: separate squamous cells from sample 45. Panel D: macrophage from sample 85. Panel E: binucleate macrophage from sample 85. Panel F: squamous cell from sample 95. Panel G: macrophage from sample 96. Panel H: macrophage from sample 111. Not shown is a red blood cell from sample 103.



for multiple patients. Our study found intact cells in the pens and also detected free hemoglobin from damaged RBCs, with contamination present in 5.6% of samples.

The cell types detected in our study—squamous cells, macrophages, and RBCs—are of concern. Squamous cells are from the epidermis of the skin, and they indicate the possibility of contamination with pathogens that infect squamous cells, including herpes simplex, varicella zoster, human papilloma virus, and molluscum contagiosum.[36] The "dirty hands" bacteria and fungi are also of concern, including *Staphylococcus aureus*, methicillin-resistant *S. aureus*, *Pseudomonas aeruginosa*, enterohemorrhagic *Escherichia coli*, and dermatophytes.[37] Macrophages are located below the epidermis and are capable of harboring and transmitting intracellular infections, including HIV and viral hepatitis.[36] The presence of an RBC and hemoglobin indicates that blood components can enter the pen cartridge and confirms the potential for transmission of blood-borne pathogens.

The insulin pens examined contain the preservative metacresol, which studies indicate can kill gram-positive bacteria and, to a lesser degree, gram-negative bacteria and fungi.[9,10,38,39] However, metacresol cannot kill viruses and spores. The pens also contain the preservative phenol, which studies suggest is bacteriostatic only at the lower concentrations found in insulin pens but has some antimicrobial activity against mycobacteria, fungi, and viruses. However, the studies on preservatives are limited regarding the spectrum of activity against potential pathogens. To our knowledge, there are no published studies indicating that the preservatives kill intracellular pathogens. Specifically, phenol is inactivated by organic material, suggesting that it would not be effective inside a cell. In addition, the studies that reported antimicrobial activity for metacresol and phenol used higher experimental levels than the amounts found in the NovoLog pen (Kothari M, Novo Nordisk, personal communication, 2013 May 16), leaving open the possibility that pathogens could remain viable in the insulin pen's cartridge after contamination. Our study suggests that passing infection from one patient to another is possible if a single insulin pen is used for multiple patients.

To our knowledge, this is the first formal, prospective observational study examining the frequency of biological contamination of insulin pens after administration to patients. These findings should be interpreted with consideration of the study's limitations. Of the 125 insulin pens examined, 5.6% tested positive for contamination, but this frequency may have been different if more pens were tested or if pens from different manufacturers were tested. Therefore, a larger prospective study may be beneficial for statistical analysis of the overall frequency and different types of contamination, including variations among different pens currently available. In addition, the hemoglobin assay was appropriately sensitive to detect hemoglobin in one sample, but there may have been more positive tests if a more-sensitive test were used. Positive controls using a set amount of blood injected into unused pens may also have provided information regarding the degradation of cells in the pens. Finally, since only laboratory data were collected, it may be beneficial in the future to collect information about device usage, such as the number of doses administered, to further examine the mechanism of contamination.

Based on findings of intact cells and hemoglobin in insulin pens after administration to a single patient, the potential exists for transmission of infectious agents from patient to patient if a single pen cartridge is used to administer insulin to multiple patients, even if a new needle is used for each individual. Therefore, shared use of one pen among multiple patients should be prohibited to prevent the transmission of viral, bacterial, and fungal infections. Health care providers should ensure that proper staff and patient education is provided and that proper infection-control procedures are in place to protect patients from harm related to shared insulin pens.

Conclusion

Examination of 125 insulin pens used in hospitals revealed hemoglobin in 1 pen and at least one cell in another 6 pens. The nine detected cells consisted of four squamous epithelial cells, four macrophages, and one RBC.

References

1. Food and Drug Administration. Insulin pens and insulin cartridges must not be shared. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149546.htm (accessed 2010 Jan 20).
2. Food and Drug Administration. Information for healthcare professionals: risk of transmission of blood-borne pathogens from shared use of insulin pens. www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm133352.htm (accessed 2010 Jan 20).
3. Food and Drug Administration. Insulin pens: risk of transmission of blood-borne pathogens from shared use. www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm127783.htm (accessed 2010 Jan 20).
4. Food and Drug Administration. Don't share insulin pens between patients. www.accessdata.fda.gov/psn/printerfull.cfm?id=126 (accessed 2010 Jan 20).
5. William Beaumont Army Medical Center. Insulin pen advisory. www.wbamc.amedd.army.mil/newsitems.aspx?articleid=02062009 (accessed 2010 Jan 20).
6. KPLC Channel 7 News. Fort Polk health warning. www.kplctv.com/story/9798908/fort-polk-health-warning?redirected=true (accessed 2012 Mar 20).
7. Novolog FlexPen (insulin aspart [rDNA origin] injection) package insert. Princeton, NJ: Novo Nordisk; 2009 Oct.
8. Meyer BK, Ni A, Hu B et al. Antimicrobial preservative use in parenteral products: past and present. *J Pharm Sci*. 2007; 96:3155-67.

9. Rowe RC, Sheskey PJ, Cook WG et al., eds. Handbook of pharmaceutical excipients. 7th ed. London: Pharmaceutical Press; 2012.
10. Institute for Safe Medication Practices. Reuse of insulin pen for multiple patients risks transmission of bloodborne disease. www.ismp.org/newsletters/acutecare/articles/20090212-2.asp (accessed 2010 Jan 20).
11. Kuehn BM. FDA warns against shared insulin pens. *JAMA*. 2009; 301:1527. News.
12. Dallas S, Holquist C. Shared insulin pens can transmit blood-borne pathogens. http://license.icopyright.net/user/viewFreeUse.act?fuid=NjcxMzU3OA%3D%3D (accessed 2010 Jan 26).
13. Cohen MR. Medication errors. *Nursing*. 2008; 38:17.
14. Cohen MR. ISMP medication error report analysis. *Hosp Pharm*. 2008; 43:445-8.
15. Dean Health Clinics. Important patient safety notification. www.deancare.com/about-dean/news/2011/important-patient-safety-notification/ (accessed 2012 Mar 7).
16. Superior Telegram. Man sues Dean Health after contracting hepatitis C. www.superiortelegram.com/event/article/id/63377/group/homepage (accessed 2012 Mar 7).
17. NBC15 News. Update: man who contracted hepatitis C sues Dean Health. www.nbc15.com/home/headlines/128599118.html (accessed 2012 Mar 26).
18. Centers for Disease Control and Prevention. Clinical reminder: insulin pens must never be used for more than one person. www.cdc.gov/injectionsafety/clinical-reminders/insulin-pens.html (accessed 2012 Mar 26).
19. Zremski J. 716 patients at VA may have been exposed to HIV. www.buffalonews.com/apps/pbcs.dll/article?AID=/20130111/CITYANDREGION/130119728/1002 (accessed 2013 Mar 15).
20. Olean General Hospital. Dear patient of Olean General Hospital letter. www.ogh.org/programs-and-services/diabetes/01-2013-OGH-Patient-LETTER.pdf (accessed 2013 Mar 28).
21. Institute for Safe Medication Practices. Ongoing concern about insulin pen reuse shows hospitals need to consider transitioning away from them. www.ismp.org/newsletters/acutecare/showarticle.asp?id=41 (accessed 2013 Mar 28).
22. Kroon L. Overview of insulin delivery pen devices. *J Am Pharm Assoc*. 2009; 49:118-31.
23. Molife C, Lee LJ, Shi L et al. Assessment of patient-reported outcomes of insulin pen devices versus conventional vial and syringe. *Diabetes Technol Ther*. 2009; 11:529-38.
24. Davis EM, Christensen CM, Nystrom KK et al. Patient satisfaction and costs associated with insulin administration by pen device or syringe during hospitalization. *Am J Health-Syst Pharm*. 2009; 65:1347-57.
25. Davis EM, Bebee A, Crawford L et al. Nurse satisfaction using insulin pens in hospitalized patients. *Diabetes Educ*. 2009; 35:799-809.
26. Institute for Safe Medication Practices. Considering insulin pens for routine hospital use? Consider this. www.ismp.org/Newsletters/acutecare/articles/20080508.asp (accessed 2010 Jan 20).
27. Institute for Safe Medication Practices. Cross contamination with insulin pens. www.ismp.org/Newsletters/acutecare/articles/20080327_1.asp?ptr=y (accessed 2009 Jun 10).
28. Food and Drug Administration. Potential problems with insulin pens in hospitals. www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/printer.cfm?id=840 (accessed 2010 Jan 20).
29. Edwards C. Reducing the risk of injuries to staff from insulin pens. *Nurs Times*. 2005; 101:34-6.
30. Pellissier G, Miguéres B, Tarantola A et al. Risk of needlestick injuries by injection pens. *J Hosp Infect*. 2006; 63:60-4.
31. Jamal R, Ross SA, Parkes JL et al. Role of injection technique in use of insulin pens: prospective evaluation of a 31-guage, 8-mm insulin pen needle. *Endocr Pract*. 1999; 5:245-50.
32. Wittmann A, Köver J, Kralj N et al. Insulin leakage value in relation to pen needle length and administration dose after subcutaneous injection. *Diabetes Technol Ther*. 2010; 12:587-90.
33. Le Floch JP, Herbreteau C, Lange F et al. Biological material in needles and cartridges after insulin injection with a pen in diabetic patients. *Diabetes Care*. 1998; 21:1502-4.
34. Sonoki K, Yoshinari M, Iwase M et al. Regurgitation of blood into insulin cartridges in the pen-like injectors. *Diabetes Care*. 2001; 24:603-4. Letter.
35. Hakre S, Upshaw-Combs DR, Sanders-Buell EE et al. An investigation of bloodborne pathogen transmission due to multipatient sharing of insulin pens. *Mil Med*. 2012; 177:930-8.
36. Nicol NH, Huether SE. Structure, function, and disorders of the integument. In: McCance KL, Huether SE, eds. Pathophysiology: the biologic basis for disease in adults and children. 6th ed. Maryland Heights, MO: Mosby Elsevier; 2010.
37. Mandell G, Bennett J, Mandell DR. Douglas and Bennett's principles and practice of infectious diseases. 7th ed. Philadelphia: Churchill Livingstone Elsevier; 2010.
38. Srivastava RB, Thompson RE. Influence of bacterial cell age on phenol action. *Nature*. 1965; 206:216.
39. Cooper EA. On the relations of phenol and meta-cresol to proteins; a contribution to our knowledge of the mechanism of disinfection. *Biochem J*. 1912; 6:362-87.