Review Article

CME Infusate Contamination in Regional Anesthesia: What Every Anesthesiologist Should Know

Stephen Head, MD, FRCPC*†

F. Kayser Enneking, MD‡§

Infection can be a devastating complication of regional anesthesia. Contaminated infusate as a cause of infection in neuraxial anesthesia or peripheral nerve blockade has rarely been reported in the literature. However, it may be an important source of morbidity, especially as increasing numbers of patients are being discharged with perineural catheters and portable pumps of local anesthetic, which may infuse for several days at home. Two important issues related to infusate contamination in regional anesthesia are that of "hang-time" and sterile compounding practices. Hang-time can be defined as the maximum length of time during which an admixture preparation (infusate) can be safely administered without risk of microbiological or chemical instability. In the United States, there are currently no national guidelines on the hang-times of regional anesthesia infusates. On the other hand, guidelines for the sterile compounding of infusions used in regional anesthesia are now established by United States Pharmacopeia and The National Formulary Chapter 797, entitled "*Pharmaceutical Compounding, Sterile Preparations*." These guidelines have significant implications for the anesthesiologist. In this review, we examined the available literature regarding contaminated infusate as a cause of infection in regional anesthesia, to discuss strategies for the prevention of such contamination including the appropriate hang-time for infusates, and to discuss the implications of United States Pharmacopeia and The National Formulary Chapter 797 for anesthesiologists.

(Anesth Analg 2008;107:1412–8)

Introduction of pathogens into the neuraxial or perineural space may occur in three ways: through skin contamination and subsequent spread along the needle or catheter track, by direct extension or hematogenous spread from a distant focus, or from contaminated infusate.[1] Of these three causes, infusate contamination is generally believed to be the least common,[2] and has received relatively little attention in the literature. However, it is an important mechanism of infection to consider, especially as increasing numbers of patients are being discharged with continuous perineural infusions of local anesthetics, which may infuse for several days at home. The sterile compounding practices for these mixtures vary among institutions, and the maximum safe duration of infusion (i.e., hang-time) is unknown.

In the United States, regional anesthesia infusions via epidural, perineural, or intraarticular catheters may be prepared by a variety of health care professionals, including pharmacists, anesthesiologists, surgeons, or nurses. Regardless of who prepares the mixtures, compounding practice should be in accordance with the United States Pharmacopeia and The National Formulary (USP) Chapter 797 Guidelines, entitled "*Pharmaceutical Compounding, Sterile Preparations*." These guidelines were introduced in 2004 and these specify the requirements and procedures that should be used to compound these sterile preparations.[3] They have important implications for anesthesiologists and will be discussed below.

Although USP 797 provides explicit guidelines regarding the mixing and labeling of sterile mixtures, they do not pertain to their clinical administration. The issue of hang-time (the maximum time during which an infusion can be safely administered without risk of microbiological or chemical instability) also has important implications for the anesthesiologist. Duration of infusion has been found to be an independent

From the *Department of Anesthesia, Saint Paul's Hospital; †Department of Anesthesiology, Pharmacology, and Therapeutics, University of British Columbia, Vancouver, British Columbia, Canada; Departments of ‡Anesthesiology, and §Orthopedics and Rehabilitation, University of Florida College of Medicine, Gainesville, Florida.

Accepted for publication July 27, 2007.

The authors have no conflicts of interest.

Reprints will not be available from the author.

Address correspondence to F. Kayser Enneking, MD, Department of Anesthesiology, PO Box 100254, Gainesville, FL 32610-0254. Address e-mail to kenneking@anest.ufl.edu.

DOI: 10.1213/01.ane.0000286228.57455.91

risk factor for infectious complications in continuous peripheral nerve blockade.[4] In some case series, the mean duration of perineural catheter infusion was more than 3 days,[5,6] and in one inpatient series, the mean duration of infusion was 9 days.[7] In none of these studies was the hang-time (i.e., frequency of bag-changes) described, and there are no national guidelines regarding hang-time. The purpose of this article, therefore, is to summarize published literature regarding contaminated infusate as a cause of infection in regional anesthesia, and to provide suggestions on how the anesthesiologist may reduce these risks. The topic of hang-time will also be reviewed, as will the implications of USP Chapter 797 to anesthetic practice.

INFECTIOUS COMPLICATIONS IN NEURAXIAL ANESTHESIA

Epidural abscess and meningitis are two of the most devastating complications in regional anesthesia. Of the three mechanisms of infection, it is generally believed that skin flora contamination and hematogenous spread are much more common than contaminated infusate.[1,2,8] Emphasis in the literature has therefore been placed on the efficacy of various topical skin antiseptics and optimal sterile technique during insertion.[9–12] The potential for bacteria to migrate centrally within a disconnected epidural catheter has also been investigated, and recommendations have been made regarding safe practice in the event of an epidural disconnect.[13]

Although infection introduced during needle insertion or from lapses in sterile technique are important sources of infection in neuraxial anesthesia, cases of contaminated injectate have also been reported. North and Brophy[14] reported two cases of epidural abscess secondary to *Staphylococcus aureus* contamination of lidocaine from a multidose vial. In another series, 10 cases of meningitis and epidural abscess occurred after the epidural injection of betamethasone, which had been contaminated with *Serratia marcescens*.[15] In 2002, the Centers for Disease Control (CDC) reported five cases of fungal meningitis secondary to contaminated epidural methylprednisolone.[16] In the latter two case series, contamination resulted from nonsterile compounding practices in the respective pharmacies.

Although several authors have postulated that skin contamination is the most common cause of neuraxial infection in regional anesthesia, it is important to understand that conclusions about the cause of such infections are most often based on cultures of epidural catheter tips, without microbiologic investigation of the infusate itself.[17–19] The microorganisms most often cultured, *S. aureus* and *S. epidermidis*, would also be expected to be common sources of infusate contamination (i.e., skin contamination during the compounding procedure), making the definitive cause of infection difficult to prove. For example, Du Pen et al.[20] evaluated both superficial and deep space infections in 350 terminally ill patients who were treated with long-term tunneled epidural catheters. The incidence of infection was 1:1702 catheter days. Eight cases of deep space infection were attributed to contaminated injectate based on clinical and radiological evidence of infection in the absence of superficial tract infection. However, the study did not include cultures from the epidural infusate itself, and so definite conclusions as to the underlying cause of infection are not possible.

Another study example whose design did not allow for the determination of infectious cause is that by Holt et al.[1] In this study, infectious complications were investigated in 78 patients who had culture-positive epidural catheter tips. The two most common organisms cultured were *S. aureus* and coagulase-negative staphylococcus (usually *S. epidermidis*). The authors concluded that because these organisms are also common skin flora, the most likely mechanism of infection was from skin contamination. Contaminated infusate was discounted as a potential cause because cultures of epidural infusate from 50 asymptomatic and unrelated patients were negative. Unfortunately, the authors did not culture the infusate from the epidural solutions of the infected individuals.

INFECTIOUS COMPLICATIONS IN PERIPHERAL NERVE BLOCKADE

In recent years, single injection and continuous peripheral nerve blockade techniques have gained in popularity, and infectious complications relating to these techniques have also been the subject of investigation and review.[4,7,21,22] Capdevila et al.[4] prospectively studied continuous peripheral nerve blocks in 1416 inpatients, with a mean duration of infusion of 56 h. Cultured catheter tips were positive in 28.7% of patients, and the organisms most commonly found were *S. epidermidis* (61%), Gram-negative bacillus (21.6%), and *S. aureus* (17.6%). Only 3% of patients had signs of inflammation at the catheter site. One psoas abscess requiring surgical drainage related to a femoral nerve catheter occurred in a diabetic patient. The authors postulated that the high rate of catheter tip colonization (versus the low rate of clinical infection) reflected colonization of the skin at the catheter insertion site and subsequent colonization of the tip upon catheter removal despite an "aseptic" (unspecified) removal technique.

Nseir et al.[23] reported a case of fatal streptococcal necrotizing fasciitis as a complication of axillary block in an elderly patient with diabetes. The source of contamination was thought to have arisen either from the patient's skin at the needle entry site or from the anesthesiologist's oropharyngeal airway. Catheter colonization at the skin entry site was also the presumed source of infection in case reports of a thigh abscess complicating continuous popliteal nerve block,[24] and

a psoas abscess complicating continuous femoral nerve blockade.[25]

Cuvillon et al.[26] cultured the tips of 211 consecutive femoral nerve catheter tips 48 h after insertion and found that 57% were colonized. The most frequent organisms were *S. epidermidis* (71%), *Enterococcus* (10%), and *Klebsiella* (4%). No cellulitis or abscess occurred. In a retrospective review of 405 continuous axillary catheters, Bergman et al.[21] found one case of cellulitis, which was treated effectively with catheter removal and antibiotics. No explicit discussion of underlying infectious cause was made in either of these studies.

Duration of infusion has been considered a risk factor for the development of infectious complications in regional anesthesia,[4] although there is a paucity of data on the topic.[2] Most peripheral nerve catheters are removed within 72 h. However, Stojadinovic et al.[7] reported a mean duration of infusion of 9 days in a case series of 361 continuous peripheral nerve blocks on Iraq war casualties at the Walter Reed Army Medical Center in Washington, DC. The infection rate was only 1.9%. The fact that the patients were generally young and otherwise healthy, and were concurrently treated with antibiotics at the time of catheter insertion may have contributed to the low incidence of infection.

In many of the studies discussed above, a relatively high rate of catheter colonization, but a low rate of clinical infection, is reported. The underlying cause of infection is most often attributed to bacteria entry at the site of insertion. However, no study has been specifically designed to distinguish between contaminated infusate versus skin contamination as a cause of infection. In fact, the only documented case of contaminated injectate as a cause of infection in regional anesthesia, aside from those reported in association with neuraxial anesthesia, is that of soft-tissue and intraarticular *S. aureus* infection in five patients after injection of contaminated lidocaine, which had been drawn from the same multidose vial.[27] In this case series, three patients developed septic arthritis after intraarticular knee injection, one patient developed a subcutaneous abscess after posterior hip injection, and one patient developed an IM abscess after trigger-point injection of the posterior neck.

USP CHAPTER 797: IMPLICATIONS FOR ANESTHESIOLOGISTS

For the purposes of this discussion, it is important to distinguish between a compounded sterile preparation (CSP) and a sterile product. A CSP is a sterile drug or nutrient prepared according to the order of a licensed prescriber, which may or may not contain sterile products (e.g., prepared by a hospital pharmacy). A sterile product is a commercially manufactured (i.e., prepackaged) sterile drug or nutrient that has been evaluated for safety and efficacy by the US Food and Drug Administration.[28]

Before 2004, standards for the compounding of sterile preparations had been provided by individual state pharmacy boards. These guidelines were less stringent than those for manufactured sterile products, which operate under the Federal Good Manufacturing Practices.[29] In 2004, the USP published Chapter 797: *Pharmaceutical Compounding, Sterile Preparations* to improve the compounding practices for all sterile preparations.[3] These guidelines specify the requirements and procedures with which all health care professionals must comply when compounding sterile preparations, and they are applicable to all practice settings.[30] The purpose of the guidelines is to "prevent harm, including death, to patients that could result from the following: 1) microbial contamination, 2) excessive bacterial endotoxins, 3) variability in the intended strength of correct ingredients, 4) unintended chemical and physical contaminants, and 5) incorrect types and qualities of ingredients in CSPs".[31]

Unlike previous publications on the subject, USP Chapter 797 is considered to be a national standard for sterile compounding, and is therefore enforceable by the Food and Drug Administration, State Boards of Pharmacy, and State Boards of Health.[28] The Joint Commission on Accreditation of Healthcare Organizations has begun using USP Chapter 797 when surveying hospitals.[30,32] Full compliance with these standards was expected by 2008.[33]

This has implications to the anesthesiologist, who often prepares multiple syringes of sterile compounds for both general and regional anesthesia. In its original form, Chapter 797 made no specific recommendations regarding CSPs that were intended for immediate administration. However, several months after the original publication, a revision was made that exempted all preparations whose administration will be complete within 12 h of preparation (i.e., the majority of medications prepared by the anesthesiologist).[28,33] On the other hand, all multiday infusions, including perineural, intraarticular, epidural, and intrathecal preparations, are required to meet USP standards. These standards will be discussed below.

USP LEVEL OF RISK

The USP specifies three levels of microbial contamination risk associated with the compounding of sterile preparations, and outlines quality assurance requirements for each level. Although examples of the risk level of various compounds are provided in the guidelines, the assigning of risk level is ultimately left to the discretion of the compounding practitioner. Examples of risk levels and compounding requirements are outlined in Table 1.[3,31] Recommended environmental air quality standards (referred to in Table 1) are defined in Table 2, which summarizes the International Standards Organization (ISO) air quality categories.

Of importance to the anesthesiologist is that all sterile preparations that are to be administered over

Table 1. Risk Levels and Recommended Compounding Practices for Admixtures and Solutions[31]

Compounding activity	Example	USP 797 requirements
Low-risk	Simple admixtures compounded using closed system transfer methods	Routine disinfection and air quality testing to maintain ISO Class 5 environment (i.e., laminar airflow workbench required)
	Reconstitution of single-dose vials of antibiotics	Located within an ISO Class 7 buffer room (i.e., no >352,000 air particles >0.5μm/m^3) with ante area (gown room)
	Preparation of hydration solutions	Adequate personnel garb for sterile preparation Visual inspection of the preparation Annual "media-fill test" of aseptic technique of the person compounding
Medium-risk	Admixtures compounded using multiple additives and/or small volumes	All of the above, plus:
	Batch preparations (e.g., syringes) that do not contain bacteriostatic components	More stringent annual media-fill test of aseptic practice
	Pain management infusions administered over several days	
	Complex manipulations (e.g., TPN)	
High-risk	Solutions made from nonsterile bulk powder ingredients (e.g., morphine and other opiates)	All of the above
	Open transfer systems	

Source: United States Pharmacopeia Chapter 797[31].

ISO = International Standards Organization; TPN = total parenteral nutrition.

Table 2. Air Quality

ISO Class	No. of air particles >0.5 μg/m^3	Example
1	0	Robotically controlled biohazard room
2	3.5	
3	35.2	
4	352	Nanofabrication facility
5	3520	Sterile hood with laminar flow
6	35,200	Operating room with HEPA filtration and >100 air exchanges per hour
7	352,000	
8	3,520,000	Fresh air
9	35,200,000	Urban ambient air

Source: United States Pharmacopeia Chapter 797[31].

ISO = International Standards Organization; HEPA = high-efficiency particulate air filters; OR = operating room.

several days are defined as medium-risk preparations, [34] and thus should be prepared in an ISO Class 5 environment (i.e., using a laminar flow workbench) within an ISO Class 7 buffer room. These conditions, of course, would not be met on a hospital ward, in the operating room, or in virtually any other environment in which the anesthesiologist is likely to work. Even in empty operating rooms equipped with high-efficiency particulate air filters, the particulate count varied between 0 and 46,262 per cubic meter (ISO Class 0–6) in a study by Landrin et al.[35] Even in laminar airflow-equipped operating rooms, the particulate count can be expected to be higher based on the turbulent airflow associated with movement of the surgeon and other personnel at the operative site and in and out of the room.[36] It is therefore recommended that such compounds be prepared by pharmacy personnel in accordance with USP guidelines. It is also recommended that anesthesiologists become aware of the compounding practices and conditions of the pharmacies in which infusions for regional anesthesia are prepared, because full compliance with USP 797 was expected by January 2008.[33]

THE HANG-TIME OF REGIONAL ANESTHETIC COMPOUNDS

The term "hang-time"[37] refers to the maximum length of time over which an admixture preparation can be safely infused. Determining the maximum allowable hang-time of infusions in regional anesthesia is important, as more patients are being discharged with peripheral nerve catheters and multiday infusions of local anesthetic. The term hang-time should be distinguished from "beyond-use dating," which is the maximum storage time between the end of manufacturing of the solution and commencement of its clinical use.[28] Although USP Chapter 797 sets standards for all preadministration manipulations of CSP, including beyond-use dating, it does not set standards for their clinical administration (i.e., hang-time).

Determination of hang-time should be based on both the chemical stability and microbiological stability of the solution in question. Much attention has been given to the assessment of chemical stability of local anesthetics alone or in combination with epinephrine or opioids. [38–43] These admixtures have been studied in

Table 3. Recommended Hang-Times at the Authors' Institutions

Product	Shands at the University of Florida	University of British Columbia, Saint Paul's site
Manufactured sterile solutions not prepared by the hospital pharmacy (e.g., prepackaged ropivacaine 0.2%)	72 h	24 h
Manufactured solutions containing dextrose	24 h	24 h
Pharmacy admixtures not containing dextrose (e.g., bupivacaine 0.1% with fentanyl 3 μg/mL)	48 h	24 h
Pharmacy admixtures containing dextrose	24 h	24 h

Source: Department of Pharmacy, Shands Hospital, University of Florida, Gainesville, Florida and Saint Paul's Hospital, Vancouver, BC.

both polyvinylchloride bags and in portable infusion pumps. In general, compounds commonly used in regional anesthetic practice, including lidocaine, bupivacaine, ropivacaine, morphine, fentanyl, and hydromorphone, are chemically stable for periods of weeks to months and are not the limiting factor in determining hang-time.[38–43] However, relatively little has been written about the microbiological stability of local anesthetics or about the potential impact on stability of different preparation techniques.

Because of a lack of data on the microbiological stability of anesthetic compounds, the hang-times for epidural and perineural solutions have traditionally been determined by the infection control policies of individual hospitals, which were traditionally extrapolated from the CDC guidelines for IV solutions. For example, Table 3 lists the hang-times of some mixtures used at the institutions of the authors.

The CDC guidelines were originally based on data for lipid-containing parenteral nutrition solutions, which were proposed after an outbreak of bloodstream infections from contaminated solutions in the early 1970s.[44–46] It is interesting to note that in the most recent CDC guidelines,[47] a hang-time of 24 h for lipid-containing solutions is recommended, but no recommendation is made for nonlipid containing IV solutions. This clearly suggests that hang-times for these solutions are not known, but could potentially extend beyond 24 h.

As applied to epidural solutions, the current CDC guidelines are considered by several authors to be overly stringent, as they generally do not consider the fact that epidural and peripheral nerve catheters are placed using aseptic technique, and that the mixtures generally do not contain dextrose, which supports bacterial growth.[37,48] In addition, it has been shown that many local anesthetics, including bupivacaine and lidocaine, possess antimicrobial properties, although the results of studies on their minimum bactericidal concentration are inconsistent.[49–52] Whether the dilute concentration of local anesthetics used in regional anesthesia today affords protection against infection is unknown. Furthermore, levobupivacaine and ropivacaine, two local anesthetics that have gained popularity recently because of a reduced risk of central nervous system and cardiac toxicity,[53,54] have shown less promise as antimicrobial drugs.[55–57] In one study, the bactericidal activity of levobupivacaine was only 50% that of bupivacaine.[55] Ropivacaine has been shown to have either poor[56] or no antimicrobial properties.[57]

To investigate the microbiological stability of epidural solutions, Sevarino et al.[48] tested 115 samples from 54 administered and nonadministered epidural infusion bags containing bupivacaine (0.03%–0.063%), hydromorphone (10 μg/mL), or a bupivacaine/hydromorphone mixture. These compounds had been prepared by the pharmacy department under aseptic conditions and laminar flow hoods. Samples were studied over a mean duration of 70 days and were maintained at room temperature to approximate the conditions of therapeutic administration, considering that higher ambient temperatures favor bacterial growth. Of the 115 samples, only five reported initial positive cultures, yet no growth was reported from repeat samples. The authors concluded that because subsequent cultures were negative, and because these samples did not contain local anesthetic (hydromorphone only), the underlying cause of the initial positive culture was because of touch contamination in the sample retrieval process (and not because of the possible bactericidal properties of local anesthetics). Based on the findings of this study, it was recommended that the CDC develop hang-time guidelines specific to epidural infusions. In the meantime, the authors recommend an epidural hang-time of 72 h.

Wulf et al.[43] examined mixtures of bupivacaine 0.3%, morphine 6.7 mg/mL, and clonidine 0.03 mg/mL from portable pump reservoirs intended for intrathecal infusion. They found that at room temperature, these mixtures were microbiologically stable over a period of 90 days. In a study of long-term epidural infusions in cancer patients, McIntosh et al.[58] cultured 84 samples from refrigerated epidural solutions over a 7-mo period, and found no evidence of colonization. They proposed that it would be safe to extend the epidural solution hang-time to 7–10 days in this population.

In another study of long-term epidural infusions in cancer patients, Ohlsson et al.[59] cultured residual morphine/dextrose samples from 211 portable pumps that had infused subcutaneously or epidurally for a mean of 3.7 days. Pumps had been prepared in the

hospital pharmacy under a laminar flow hood and sterile conditions. Although no patient demonstrated clinical evidence of infection, colonization occurred in 16 (7.6%): *Staphylococcus albus* in 13, *Escherichia coli* in two, and *Candida albicans* in one. The fact that the solutions contained dextrose and not local anesthetic may have accounted for the relatively high rate of colonization.

Jäppinen et al.[60] studied the microbiological stability of mixtures of sufentanil 1 μg/mL, levobupivacaine 0.9%, and 0.9% normal saline over a 28-day period. Compounding was done under a laminar flow hood and ISO Class 5 conditions. They found no bacterial growth at storage temperatures of 4°C, 21°C, and 36°C. They concluded that such solutions remain sterile for much longer than the 24 h expiration limit at their institution.

In further support of the proposal that hang-times for regional anesthesia solutions should be extended is the growing body of evidence that an important source of infection in IV solutions is from contamination at the catheter hub site, which likely occurs during "top-ups" or line changes.[47,61,62] In fact, a prospective study of 135 patients receiving total parenteral nutrition found that catheter hub contamination was the most common source of infection, whereas skin contamination, infusate contamination, and hematogenous spread were relatively less common.[63] Several authors have suggested that infection risks can be decreased by extending hang-time and minimizing the number of top-ups or bag-changes of these solutions.[37]

In a study by Langevin et al.,[1] six IV bags containing combinations of normal saline, lactated Ringer's solution, or dextrose were inoculated with *S. aureus*. The authors found that the bacterial count actually decreased over time. In their discussions, the authors state that "the common idea that microorganisms multiply in these fluids is a misconception," and that the risk of infection decreases over time if repetitive contamination is avoided.

Based on the reports above, and recognizing that data are still lacking regarding the maximum hang-time of regional anesthetic solutions, an argument can be made that the risk associated with extending the hang-time of local anesthetic solutions to at least 72 h is less than that of a shorter hang-time with more frequent reservoir changes.

CONCLUSIONS

Although not widely reported, contaminated infusate can lead to devastating infectious complications in regional anesthesia. Adopting compounding practices that minimize contamination should be a priority to the anesthesiologist, especially when such compounds will be infused in the unmonitored outpatient setting. Given that multiday infusions are considered by the USP to be medium-risk compounds, these infusions should be purchased as premanufactured sterile products, or should be compounded in accordance with USP 797 guidelines. It is also important for anesthesiologists to be aware of the compounding conditions in the pharmacies with which they work, as compliance with USP Chapter 797 was expected by January 2008.

Several recommendations can also be made regarding hang-times of regional anesthetic infusions. Evidence suggests that when local anesthetic or local anesthetic/opioid mixtures are prepared using sterile procedure, microbiological stability is maintained for much longer than 72 h. There is also evidence to suggest that breaks in the sterile circuits of regional anesthetic infusions, including top-ups or bag changes, increase infectious risk. A hang-time of at least 72 h for such solutions can be endorsed. Further research is needed to quantify the risks and benefits of prolonging hang-time beyond 72 h.

[1]Langevin PB, Gulig PA, Gravenstein N. Time to re-evaluate routine 24-hr syringe discard policy in the operating room [abstract]. Anesthesiology 1995;83:A1037.

REFERENCES

1. Holt HM, Andersen SS, Andersen O, Gahrn-Hansen B, Siboni K. Infections following epidural catheterization. J Hosp Infect 1995;30:253–60
2. Grewal S, Hocking G, Wildsmith JAW. Epidural abscesses. Br J Anaesth 2006;96:292–302
3. Kastango ES, Bradshaw BD. USP chapter 797: establishing a practice standard for compounding sterile preparations in pharmacy. Am J Health Syst Pharm 2004;61:1928–38
4. Capdevila X, Pirat P, Bringuier S, Gaertner E, Singelyn F, Bernard N, Choquet O, Bouaziz H, Bonnet F. Continuous peripheral nerve blocks in hospital wards after orthopedic surgery: a multicenter prospective analysis of the quality of postoperative analgesia and complications in 1,416 patients. Anesthesiology 2005;103:1035–45
5. Ilfeld BM, Wright TW, Enneking FK, Mace JA, Shuster JJ, Spandoni EH, Chmielewski TL, Vandenborne K. Total shoulder arthroplasty as an outpatient procedure using ambulatory perineural local anesthetic infusion: a pilot feasibility study. Anesth Analg 2005;101:1319–22
6. Ilfeld BM, Enneking FK. A portable mechanical pump providing over four days of patient-controlled analgesia by perineural infusion at home. Reg Anesth Pain Med 2002;27:100–4
7. Stojadinovic A, Auton A, Peoples GE, McKnight GM, Shields C, Croll SM, Bleckner LL, Winkley J, Maniscalco-Theberge ME, Buckenmaier CC III. Responding to challenges in modern combat casualty care: innovative use of advanced regional anesthesia. Pain Med 2006;7:330–8
8. Barreto RS. Bacteriologic culture of indwelling epidural catheters. Anesthesiology 1962;23:643–6
9. Hebl JR. The importance and implications of aseptic techniques during regional anesthesia. Reg Anesth Pain Med 2006;31:311–23
10. Hebl JR, Neal JM. Infectious complications: a new practice advisory [editorial]. Reg Anesth Pain Med 2006;31:289–90
11. Hebl JR, Horlocker TT. You're not as clean as you think! The role of asepsis in reducing infectious complications related to regional anesthesia. Reg Anesth Pain Med 2003;28:376–9
12. Sellors JE, Cyna AM, Simmons SW. Aseptic precautions for inserting an epidural catheter: a survey of obstetric anaesthetists. Anaesthesia 2002;57:584–605
13. Langevin PB, Gravenstein N, Langevin SO, Gulig PA. Epidural catheter reconnection: safe and unsafe practice. Anesthesiology 1996;85:883–8
14. North JB, Brophy PB. Epidural abscess: a hazard of spinal epidural anaesthesia. Aust N Z J Surg 1979;49:484–5
15. Civen R, Vugia DJ, Alexander R, Brunner W, Taylor S, Parris N, Wasserman R, Abbot S, Werner SB, Rosenberg J. Outbreak of

Serratia marcescens infections following injection of betamethasone compounded at a community pharmacy. Clin Infect Dis 2006;43:831–7
16. Centers for Disease Control and Prevention. Exophiala infection from contaminated injectable steroids prepared by a compounding pharmacy—United States, July–November 2002. MMWR Morb Mortal Wkly Rep 2002;51:1109–12
17. Sato S, Sakuragi T, Dan K. Human skin flora as a potential source of epidural abscess. Anesthesiology 1996;85:1276–82
18. Darchy B, Forceville X, Bavoux E, Soriot F, Domart Y. Clinical and bacteriologic survey of epidural analgesia in patients in the intensive care unit. Anesthesiology 1996;85:988–98
19. James FM, George RH, Naiem H, White GJ. Bacteriologic aspects of epidural analgesia. Anesth Analg 1976;55:187–90
20. Du Pen SL, Peterson DG, Williams A, Bogosian AJ. Infection during chronic epidural catheterization: diagnosis and treatment. Anesthesiology 1990;73:905–9
21. Bergman BD, Hebl JR, Kent J, Horlocker TT. Neurological complications of 405 consecutive continuous axillary catheters. Anesth Analg 2003;96:247–52
22. Neuburger M, Breitbarth J, Reisig F, Lang D, Büttner J. Komplikationen bei peripherer katheterregionalanästhesie [Complications and adverse events in continuous peripheral regional anesthesia. Results of investigations on 3491 catheters]. Anaesthetist 2006;55:33–40 [German] (Abstract in English)
23. Nseir S, Pronnier P, Soubrier S, Onimus T, Saulnier F, Mathieu D, Durocher A. Fatal streptococcal necrotizing fasciitis as a complication of axillary brachial plexus block. Br J Anaesth 2004;92:427–9
24. Compère V, Cornet C, Fourdrinier V, Maitre AM, Mazirt N, Biga N, Dureuil B. Thigh abscess as a complication of continuous popliteal sciatic nerve block. Br J Anaesth 2005;95:255–6
25. Adam F, Jaziri S, Chauvin M. Psoas abscess complicating femoral nerve block catheter. Anesthesiology 2003;99:230–1
26. Cuvillon P, Ripart J, Lalourcey L, Veyrat E, L'Hermite J, Boisson C, Thouabtia E, Eledjam JJ. The continuous femoral nerve block catheter for postoperative analgesia: bacterial colonization, infectious rate and adverse effects. Anesth Analg 2001;93:1045–9
27. Kirschke DL, Jones TF, Stratton CW, Barnett JA, Schaffner W. Outbreak of joint and soft-tissue infections associated with injections from a multiple-dose medication vial. Clin Infect Dis 2003;36:1369–73
28. Trissle LA. An update on USP Chapter 797: the New National Standard for Sterile Preparation. 2005. From the American Society of Health-System Pharmacists (ASHP) website: http://www.ashp.org/SterileCpd/USP797_Update_Trissel.pdf
29. Rusho WJ. Extemporaneously compounded sterile medications: relevance of new United States pharmacopeial standards to pain clinicians. J Pain Palliat Care Pharmacother 2004;8:69–76
30. Candy TA, Schneider PJ, Pedersen CA. Impact of United States Pharmacopeia chapter 797: results of a national survey. Am J Health Syst Pharm 2006;63:1336–43
31. USP Chapter 797 with proposed revisions 2006. From the United States Pharmacopeia website Dec. 2006: http://www.usp.org/pdf/EN/USPNF/PF797redline.pdf
32. Thompson CA. USP Chapter 797 enforceable but not often enforced. Am J Health Syst Pharm 2006;63:988–90
33. Bernstein WN. AIA, Architectural and environmental changes required for USP 797. From the USP website: http://www.usp797.org/Articles-PharmacyFacts.htm. Accessed July 2005
34. Buchanon C. "Clarification to USP 797." American Society of Health-System Pharmacists Website: http://www.ashp.org/SterileCpd/interview.cfm?cfid=3425592&CFToken=86248059
35. Landrin A, Bissery A, Kac G. Monitoring air sampling in operating theatres: can particle counting replace microbiological sampling? J Hosp Infect 2005;61:27–9
36. Brohus H, Balling KD, Jeppesen D. Influence of movements on contaminant transport in an operating room. Indoor Air 2006;16:356–72
37. Langevin PB. How should we handle epidural solutions? One view. Reg Anesth Pain Med 2000;25:343–6
38. Priston MJ, Hughes JM, Santillo M, Christie IW. Stability of an epidural analgesia admixture containing epinephrine, fentanyl, and bupivacaine. Anaesthesia 2004;59:979–83
39. Kjønniksen I, Brustugun J, Niemi G, Breivik H, Anderssen E, Klem W. Stability of an pidural analgesic solution containing adrenaline, bupivacaine, and fentanyl. Acta Anaesthesiol Scand 2000;44:864–7
40. Sánchez del Águila MJ, Jones MF, Vohra A. Premixed solutions of diamorphine in ropivacaine for epidural anaesthesia: a study on their long-term stability. Br J Anaesth 2003;90:179–82
41. Allen LV Jr, Stiles ML, Wang DP, Tu YH. Stability of bupivacaine hydrochloride, epinephrine hydrochloride, and fentanyl citrate in portable infusion-pump reservoirs. Am J Hosp Pharm 1993;50:714–5
42. Tu YH, Stiles ML, Allen LV. Stability of fentanyl citrate and bupivacaine hydrochloride in portable pump reservoirs. Am J Hosp Pharm 1990;47:2037–40
43. Wulf H, Gleim M, Mignat C. The stability of mixtures of morphine hydrochloride, bupivacaine hydrochloride, and clonidine hydrochloride in portable pump reservoirs for the management of chronic pain syndromes. J Pain Symptom Manage 1994;9:308–11
44. Maki DG, Martin WT. Nationwide epidemic of septicemia caused by contaminated infusion products. IV. Growth of microbial pathogens in fluids for intravenous infusion. J Infect Dis 1975;131:267–72
45. Maki DG, Goldman DA, Rhame FS. Infection control in intravenous therapy. Ann Intern Med 1973;79:867–87
46. Centers for Disease Control. Nosocomial bacteriemia associated with intravenous fluid therapy. MMWR Morb Mortal Wkly Rep 1971;20(suppl 9):81–2
47. Centers for Disease Control and Prevention. Guidelines for the prevention of intravascular catheter-related infections. MMWR Morb Mortal Wkly Rep 2002;51(No. RR-10):1–36
48. Sevarino FB, Pizarro CW, Sinatra R, Sterility of epidural solutions—recommendations for cost-effective use. Reg Anesth Pain Med 2000;25:368–71
49. Rosenberg PH, Renkonen OV. The antimicrobial activity of bupivacaine and morphine. Anesthesiology 1985;62:178–9
50. Sakuragi T, Ishino H, Dan K. Bactericidal activity of preservative-free bupivacaine on microorganisms in the human skin flora. Acta Anaesthesiol Scand 1998;42:1096–9
51. Feldman JM, Chapin-Robertson K, Turner J. Do agents used for epidural analgesia have antimicrobial properties? Reg Anesth 1994;19:43–7
52. Zaidi S, Healy TEJ. A comparison of the antibacterial properties of six local analgesic agents. Anaesthesia 1977;32:69–70
53. Casati A, Putzu M. Bupivacaine, levobupivacaine and ropivacaine: are they clinically different? Best Pract Res Clin Anaesthesiol 2005;19:247–68
54. Simpson D, Curran MP, Oldfield V, Keating GM. Ropivacaine: a review of its use in regional anaesthesia and acute pain management. Drugs 2005;65:2675–717
55. Hodson M, Gajraj R, Scott NB. A comparison of the antibacterial activity of levobupivacaine vs bupivacaine: an in vitro study with bacteria implicated in epidural infection. Anaesthesia 1999;54:683–702
56. Pere P, Lindgren L, Vaara M. Poor antibacterial effect of ropivaine: comparison with bupivacaine. Anesthesiology 1999;91:884–6
57. Aydin ON, Eyigor M, Aydin N. Antimicrobial activity of ropivacaine and other local anaesthetics. Eur J Anaesthiol 2001;18:687–94
58. McIntosh D, Spaven J, Hagen NA. How long do prepared epidural solutions remain sterile? J Pain Symptom Manage 1999;18:137–9
59. Ohlsson LJ, Rydberg TS, Edén T, Glimhall BAK, Thulin LA. Microbiologic and economic evaluation of multi-day infusion pumps for control of cancer pain. Ann Pharmacother 1995;29:972–6
60. Jäppinen A, Turpeinen M, Kokki H, Rasi A, Ojanen T, Pelkonen O, Naaranlahti T. Stability of sufentanil and levobupivacaine solutions and a mixture in a 0.9% sodium chloride infusion stored in polypropylene syringes. Eur J Pharm Sci 2003;19:31–6
61. De Cicco M, Matovic M, Castellani GT, Basaglia G, Santini G, Del Pup C, Fantin D, Testa V. Time-dependent efficacy of bacterial filters and infection risk in long-term epidural catheterization. Anesthesiology 1995;82:765–71
62. De Cicco M, Panarello G, Chiaradia V, Fracasso A, Veronesi A, Testa V, Santini G, Tesio F. Source and route of microbial colonization of parenteral nutrition catheters. Lancet 1989;2:1258–61
63. Liñares J, Sitges-Serra A, Garau J, Pérez JL, Martin R. Pathogenesis of catheter sepsis: a prospective study with quantitative and semiquantitative cultures of catheter hub and segments. J Clin Microbiol 1985;21:357–60