Update on vascular catheter-related infections

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The present article is an update of the literature on intravascular catheter-related infections. A multidisciplinary group of Spanish physicians with an interest in catheter-related infections selected the most important papers produced in the field during 2004 and 2005. One of the members of the group discussed the content of each of the selected papers, with a critical review by other members of the panel. After a review of the state of the art, papers from the fields of epidemiology, new causative microorganisms (bacterial and fungal), laboratory diagnosis, antimicrobial-lock therapy, prevention based on educative measures, and prevention based on new connectors were discussed by the group.

Key words: **Catheter-Related Infections. Bacteremia. Catheter-Related Bloodstream infections. Epidemiology. Laboratory diagnosis. Antibiotic-Lock therapy. Prevention. Education measures.**

Actualización de las infecciones relacionadas con catéteres

El artículo presente recoge una actualización bibliográfica de las infecciones intravasculares relacionadas con catéteres. Un grupo multidisciplinario de clínicos españoles con experiencia en las infecciones relacionadas con catéteres seleccionó las publicaciones más importantes en este campo aparecidas en la bibliografía en 2004 y 2005. El contenido de cada uno de los artículos seleccionados fue expuesto y discutido por uno de los miembros del grupo, después de lo cual los miembros restantes efectuaron una revisión crítica. Tras la revisión de la situación actual, el grupo discutió las publicaciones procedentes de los campos de la epidemiología, los nuevos microorganismos causales (bacterias y hongos), el diagnóstico de laboratorio, el tratamiento mediante sellado endoluminal con antibióticos, la prevención fundamentada en medidas educativas y la prevención basada en nuevos dispositivos de conexión.

Palabras clave: **Infecciones relacionadas con catéteres. Bacteriemia. Sepsis relacionada con catéteres. Epidemiología. Diagnóstico de laboratorio. Tratamiento mediante sellado endoluminal con antibióticos. Prevención. Medidas educativas.**

State of the art (Dr. E. Bouza, Dr. C. León)

An estimated 5 million central venous catheters (CVCs) are implanted in patients in the United States every year[1-6]. These devices provide access to the circulatory system to administer therapeutic drugs, total parenteral nutrition, and blood products, and enable us to monitor hematologic and hemodynamic status. While CVCs are usually deployed safely and the incidence of complications is about 6%[7], they are subject to mechanical malfunction and clot formation[8], and expose the catheterized patient to the risk of thrombophlebitis, catheter-related microbial infection (CRI), or bacteremia. Between 2% and 19% of patients with a CVC inserted develop a CRI, representing perhaps 100,000 to 950,000 nosocomial infections per year. Catheter-related bloodstream infection (CR-BSI) occurs in 1% to 10% of CRI cases, is the second most important cause of nosocomial infection in the intensive care unit (ICU)[9-11], and has an attributable mortality rate reported to range from 10% to 20%. Patients who develop CRI add about 6 days (median length of stay) to their hospitalization with an extra attributable cost of approximately $29,000 per survivor[12-15].

Most infections associated with the use of intravascular devices in critically ill patients requiring short-term catheterization are preventable, and extensive reviews of our current understanding of vascular catheter infections have recently been published[16-18]. Prevention relies mainly on a strict observation of the basic rules of hygiene, of which hand washing is the most important.

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Before insertion, skin preparation should include hair-cutting rather than shaving[19]. *Maximal sterile barrier* precautions during insertion—fenestrated drapes, sterile gloves, gown, cap, mask, and a large drape—can minimize catheter colonization and subsequent CRI[20-22]. However, the use of full sterile barriers does not reduce the risk of infection for arterial catheters[23].

In *skin preparation*, povidone iodine 10% and alcohol 70% are effective, but aqueous chlorhexidine 2% has been shown to be superior in preventing CVC colonization[24].

The *location* of the CVC placement is an important risk factor for infection and is probably due to the density of skin flora at the insertion site. The actual risk of infection at the three most commonly used insertion sites—subclavian, internal jugular and femoral—remains controversial. Although Merrer et al[25] showed an increase at the femoral site, others reported no increased risk[26-28], even in immunocompromised patients[29]. Available evidence suggests that subclavian catheterization is less likely to result in CRI than internal jugular catheterization, although the two approaches have not been compared in randomized trials[30-32].

Several trials have evaluated the effect of *tunneling* on catheter-related infections. Current evidence does not support the routine use of tunneling CVCs until its efficacy is clearly demonstrated at different insertion sites and relative to other interventions (e.g., antimicrobial catheters)[33].

The *number of lumina* does not directly affect the rate of catheter-related complications[34-36]. One quantitative systematic review[37] provides evidence that the risk of catheter-related bloodstream infection may be lower with single-lumen than with multi-lumen CVCs.

Several studies have shown that *CVCs impregnated with antiseptic or antibiotic agents* decreased the risk of catheter colonization and catheter-related bloodstream infections (CR-BSI)[30,38-46], in comparison with non-impregnated catheters. The best studied antimicrobial catheters are those impregnated with a combination of *chlorhexidine and silver sulfadiazine (C-SS)*[38-41] or *minocycline and rifampin* (M-R)[42-44]. Catheters coated with C-SS have been shown to decrease the risk of colonization by twofold and the risk of CR-BSI by at least fourfold compared with uncoated catheters[30]. Thus, these catheters are particularly efficacious in reducing the risk of CR-BSI associated with short-term CVCs[40], but failed to reduce the risk for CR-BSI in situations requiring long-term catheterization[41]. A new generation of C-SS-coated catheters, featuring higher concentration of antiseptics and enhanced bonding to both the internal and external surface of the catheter, has recently become available. The use of this type of catheter was associated with a relative reduction in the CRI rate of about 60%, but did not produce a significant decrease in the bloodstream infection rate[45].

M-R-impregnated catheters have been associated with a lower rate of infection than have C-SS-impregnated catheters. (CR-BSI 0.3% vs 3.4%, respectively)[42]. However, the duration of catheterization may have played a role. All antimicrobial-impregnated catheters failed to prevent CRIs in neutropenic cancer patients with a longer mean catheterization time of 20 days, compared with less than 8 days in other studies[38,42]. Walde et al confirmed in a meta-analysis that the potential benefit of these devices may be lost after 7-10 days[47.] Munson et al[48], found that the exposure of Gram-positive cocci to either rifampin or minocycline in vitro can lead to the development of resistance. However, exposure of bacteria to these antibiotics in combination does not lead directly to resistance. The major finding of this study is that M-R-impregnated catheters do not appear to select for resistance among those bacteria that are responsible for the majority of CRI. In vitro data demonstrate that neither distance from the catheter nor duration of exposure to the catheter results in the reliable selection of significant antimicrobial resistance. However, a thorough investigation is required to determine the risk of emergence of resistance to minocycline-rifampin associated with long-term use of these catheters.

Polyurethane catheters combined with silver, carbon and platinum (oligon-treated catheters) are a new option for the prevention of CR-BSI[49,50.] Another technology is the silver iontophoretic device, in which silver ions are released through a low voltage current to carbon-impregnated CVCs[51], or through silver wires that are attached to the proximal segment of a silicone catheter[52]. Although this technology has been shown to prevent CRI, the clinical safety and efficacy of this device have not been demonstrated.

Catheter hubs are a common source of contamination, especially during prolonged catheterization[53]. Two types of antiseptic-containing hub have been shown to decrease the risk of CR-BSI[54-56]. One of them[54], a catheter hub containing an *antiseptic chamber filled with 3% iodinated alcohol*, has been shown to reduce the rate of CR-BSIs by fourfold compared with a standard hub model. This model will be most useful with long-term CVCs, in which hub and lumen colonization are the leading causes of CR-BSI. Nevertheless, a recent clinical trial failed to show any benefit from the use of this hub in preventing CR-BSI[57].

Another model, which uses a *povidone-iodine connection shield* to encase the catheter hub significantly reduced the rate of CR-BSI when compared with a control hub (0% vs 24%; $p < 0.05$) in a randomized controlled clinical trial involving patients receiving total parenteral nutrition[58]. Certain needleless connectors may have a lower risk of contamination than conventional luer locks, and in this way, other authors using CLAVE, a *new needleless closed system device*, and a disinfectable, needle-free system, found a reduction in the number of CRIs[59,60].

Sherertz and other investigators reported that an *educational program* for physicians-in-training can decrease the risk of CRIs[61-66]. A multiple approach including an educational strategy aimed at specific problems observed during a careful evaluation of CVC care practices and policy changes can decrease rates of CVC-BSI. Accordingly, the concept of preventing CRI has evolved, and education-based programs are now recommended as a first-line strategy in the recently revised guidelines for the prevention of these infections[67].

With regard to *diagnosis*, Safdar et al[68] performed a meta-analysis to determine the most accurate diagnostic methods (8 diagnostic methods) for intravascular device (IVD)-related bloodstream infection. They concluded that the paired quantitative blood culture is the most accurate test for diagnosis of IVD-related bloodstream infection. A

concentration of at least 5-fold more colony forming units of bacteria per mL in catheter-drawn blood was a reasonable cut-off point for diagnosing CR-BSI. The study by Raad et al, comparing the time necessary for the blood cultures from the CVC and the peripheral vein to become positive, shows that a differential time to positivity of 120 minutes or more was associated with high sensitivity and specificity in the diagnosis of CR-BSI[69]. Catheters should not be cultured routinely, but only if IVD-related bloodstream infection is suspected clinically.

The *antibiotic-lock technique* is a controversial method used to prevent and treat CRIs[70]. Antimicrobial lock is a novel technique in which an antimicrobial solution, often consisting of an anticoagulant and an antibiotic agent, is instilled into the lumen of the catheter and allowed to remain for a defined period, usually 6-12 hours, after which it is removed. Antimicrobial-lock solutions have mostly proven to be effective for the prevention of infections associated with long-term CVCs. Studies that evaluate the antibiotic-lock technique vary in the type of antibiotic (vancomycin-heparin, vancomycin-ciprofloxacin-heparin solutions, minocycline, EDTA gentamicin, linezolid, and eperezolid, taurolidine citrate)[71-79] and concentrations used, the addition of heparin to the solutions, time in the catheter lumen, and use of the technique for the prevention or treatment of CVC infection. The frequency of antibiotic locks and appropriate time are not well established and must be tailored according to drug stability and frequency of intravenous drugs or fluids infused. Large, prospective, randomized trials are needed to determine the most appropriate concentration of antibiotics, duration of therapy, and role of concomitant systemic antibiotics with antibiotic-lock therapy for catheter-related sepsis.

Other treatments include analyzing the rate of noncompliance with the Infectious Diseases Society of America guidelines for treatment of CR-BSI, and the physicians who provided care for the next 46 patients with CR-BSI received standardized treatment advice by electronic mail[80]. Another procedure is the watchful waiting method of Rijnders et al[81], who show that waiting until CRI has been determined is a safe and effective strategy in the management of suspected vascular catheter infections in ICU patients.

In summary, full sterile barriers are not necessary for the insertion of arterial catheters. Subcutaneous tunneling may decrease the risk of femoral catheter infection. M-R catheter coating still appears to be the most efficacious. Further studies demonstrating that education of healthcare personnel reduces the risk of catheter infection now exist. Paired quantitative blood culture and differential time to positivity are the most accurate tests for diagnosis of IVD-related bloodstream infection. Not all catheters suspected of infection need to be removed. The management of vascular catheter infections can be improved using the watchful waiting method.

Below, a group of Spanish physicians with an interest in the field of CRI, discusses the most remarkable papers produced in this area during the last two years. The following are the publications selected for discussion.

Epidemiology

Zurcher M, Tramer MR, Walder B. Colonization and bloodstream infection with single- versus multi-lumen central venous catheters: a quantitative systematic review. Anesth Analg. 2004;99:177-82.

Does the number of lumens in a CVC have any impact on the incidence of CR-BSI? This is a systematic review for full reports included in different databases on randomized comparisons of single-lumen and multi-lumen catheters implanted in adult patients, with the endpoint of catheter colonization or CR-BSI. Thirty-five randomized studies were selected, and five trials published between 1987 and 1995 were finally included in the meta-analysis. These trials provided data on 255 single-lumen catheters (average insertion time 9 to 24 days) and 275 multi-lumen catheters (average insertion time 8 to 21 days). The rate of colonization was 14.7% in single-lumen and 13.1% in multi-lumen catheters (odds ratio [OR] 0.92, 95% confidence interval [CI], 0.49-1.72), whereas the rate of bloodstream infection was 3.1% vs 8.1% (OR 2.58, 95% CI, 1.24-5.37). None of the trials was double blind and none of the following were monitored: efficiency and experience of catheter insertion, the number of punctures required and catheter manipulation in each group, use of antibiotics after placement of the device, or type of infusions administered through the line. The evidence level of these studies is low.

Comments

Although it may be concluded that, in identical circumstances, the insertion of a single-lumen line is preferable to a multi-lumen catheter, a study with 400 patients per arm is necessary, in which difficulties of CVC insertion, levels of care in both study groups, number and type of manipulations, and use and type of antibiotics administered should be appropriately assessed.

Deshpande KS, Hatem C, Ulrich HL, Currie BP, Aldrich TK, Bryan-Brown CW, Kvetan V. The incidence of infectious complications of central venous catheters at the subclavian, internal jugular, and femoral sites in an intensive care unit population. Crit Care Med. 2005;33:13-20.

Controversy continues regarding the risk of CVC infection with respect to insertion site, which seems to be higher when the catheter is inserted through the femoral vein. This prospective observational study compares the risk of infection of a femoral, subclavian and internal jugular CVC. The setting of the study was a 30-bed adult ICU. Only CVC of a particular brand, with a maximum insertion time of 14 days (catheters were systematically removed at 14 days even in the absence of catheter-related problems) were analyzed. A total of 831 central venous catheters and 4735 catheter days in 657 patients were studied. The colonization rate was 2.89% (5.07/1,000 catheter days) and the CR-BSI rate was 2.29% (4.01/1, catheter days).

Comments

The limitations of this study are as follows: the CVCs assessed had very short indwelling times (they were systematically removed after 14 days), the insertion sites were not randomized, the rate of catheter colonization and CR-BSI was low, and the risk of deep venous thrombosis was not evaluated. The three insertion sites were associated with a low infection rate, although a higher risk for the femoral vein did not reach statistical significance. The risk of infection does not justify foregoing the most convenient insertion site or that with fewer complications for the patient.

Cartwright DW. Central venous lines in neonates: a study of 2186 catheters. Arch Dis Child Fetal Neonatal Ed. 2004;89:F504-8.

It is well known that the insertion of CVC in neonates may cause complications, such as cardiac tamponade, pleural effusion or ascites, so that some authors recommend that the catheter tip should not be positioned in the right atrium.

The aim of this study was to describe the use of percutaneously inserted CVCs in neonates at the Royal Brisbane and Women's Hospital, Australia. The study is particularly interesting because it addresses complications such as pericardial and pleural effusion, CR-BSI, and the reasons for catheter removal in a specific patient population (neonates). Data for all infants admitted from 1 January 1984 until 31 December 2002 who had a central venous line were examined in the neonatal database, and autopsy reports of all babies who died with a catheter in place were reviewed. There were 18,761 admissions and 2,186 catheters in 1862 babies for a total of 35,159 days. The colonization rate was 58.6% (1282 positive catheter tips) and the CR-BSI rate 3.82/1000 line days. The highest risk groups for CR-BSI were babies with a birth weight of < 750 g (8.62/1000 line days) followed by those weighing 750-999 g at birth (3.53/1000 line days). The lowest incidence was in babies of 1000-1499 g (1.7/1000 line days). There were no cases of pleural effusion or cardiac tamponade.

Comments

This is one of the largest series of CVC in neonates reported in the literature and confirms the safety of placing catheter tips in the right atrium using contrast radiography to determine the tip position. Following strict guidelines for insertion and care of the line, low rates of CR-BSI and candidemia are obtained.

Uncommon microorganisms (bacteria)

Hanna H, Afif C, Alakech B, Boktour M, Tarrand J, Hachem R, Raad I. Central venous catheter-related bacteremia due to gram-negative bacilli: significance of catheter removal in preventing relapse. Infect Control Hosp Epidemiol. 2004;25:646-9.

There is little information regarding the incidence and clinical outcome of CR-BSI caused by Gram-negative bacilli. The purpose of this study was to assess the characteristics of catheter-related Gram-negative bacteremia (GNB) and the role of CVC removal. This 7-year retrospective study (1990-1996) was conducted in cancer patients. Catheter-related GNB was defined as (1) a positive catheter tip culture with at least 15 colony-forming units (cfu) measured semiquantitatively, (2) isolation of the same organism from the tip and peripheral blood cultures, (3) no other source of bacteremia except the CVC, and (4) clinical manifestations of infection (fever or chills).

Seventy-two cases met the criteria of catheter-related GNB. In 93% of patients (n = 67), CVCs were removed in response to the bacteremia and the remaining 7% (n = 5) were treated with appropriate antibiotics and the catheters left in place. Of the first group, only 2 patients (3%) relapsed with the same organism, whereas in the second group all 5 patients relapsed after responding ($p < 0.001$). The most commonly isolated organisms were *Enterobacter* spp., *Klebsiella* spp., *Stenotrophomonas maltophilia*, *Pseudomonas* spp., and *Acinetobacter* spp. Catheter removal within 72 hours of the onset of the catheter-related GNB was the only independent protective factor against relapse (OR 0.13, 95% CI, 0.02-0.75, $p = 0.2$). A high APACHE II score was the only variable associated with a poor prognosis (OR 1.35, 95% CI, 1.08-1.68, $p = 0.007$). The authors conclude that in cancer patients with documented catheter-related GNB, CVCs should be removed within 48 to 72 hours to prevent relapse.

Comments

Limitations of the study include its retrospective design and the fact that results were published 8 years after finishing the study. Conceptual errors include considering some enterobacteriaceae as non-fermenting Gram-negative bacilli. Patients should be evaluated by means of standard microbiological procedures.

Lee SA, Raad, II, Adachi JA, Han XY. Catheter-related bloodstream infection caused by *Mycobacterium brumae*. J Clin Microbiol. 2004;42:5429-31.

Kiska DL, Turenne CY, Dubansky AS, Domachowske JB. First case report of catheter-related bacteremia due to *Mycobacterium lacticola*. J Clin Microbiol. 2004;42:2855-7.

Rapidly growing mycobacteria, such as those reported in these studies, have occasionally been implicated as the cause of CVC infection in immunocompromised patients. With regard to the microbiological diagnosis, emphasis should be placed on the importance of prolonged incubation time of the blood culture bottles, the need to use appropriate staining techniques, prolonged incubation at different temperatures or subcultures, and identification of strains by sequence analysis of the 16S rRNA gene. In these cases, catheter removal is mandatory.

Uncommon microorganisms (fungi)

Muñoz P, Bouza E, Cuenca-Estrella M, Eiros JM, Pérez MJ, Sánchez-Somolinos M, Rincón C, Hortal J, Peláez T. *Saccharomyces cerevisiae* fungemia: an emerging infectious disease. Clin Infect Dis. 2005; 40:1625-34.

Saccharomyces cerevisiae is well known in the baking and brewing industry. *Saccharomyces boulardii* is adminis-

tered orally as a probiotic for the treatment and prevention of *Clostridium difficile*-associated diarrhea. An outbreak of 3 patients with fungemia caused by *Saccharomyces cerevisiae* that occurred in a Spanish ICU over a period of 15 days is analyzed. All patients received treatment with *Saccharomyces boulardii* for the prevention of *C. difficile*-associated diarrhea. A review of the literature identified a total of 57 cases of *S. cerevisiae* fungemia reported since 1996. In the epidemiological study of these 3 patients, strains from the probiotic capsules and the clinical isolates were identified as *S. cerevisiae*, with identical DNA fingerprinting. Flucytosine and voriconazole were the most active drugs. Discontinuation of the product in the unit stopped the outbreak of infection. Of the 60 cases of fungemia reviewed, 45.6% had received probiotics, 9% were in close contact with patients treated with the product, 93% had a CVC in place, 60% were ICU patients, 71% received enteral or parenteral nutrition, and 88% were given broad spectrum antibiotics. The mortality rate was 29.5%.

Comments

Two similar outbreaks have previously been reported in the ICU. The possibility of airborne transmission when opening the probiotic capsules and posterior colonization of the insertion site has been suggested. *S. boulardii* is a variant of *S. cerevisiae* and not an independent species. Invasive infection by *Saccharomyces* is indistinguishable from invasive candidiasis and the use of this probiotic should be weighed up in patients with a CVC. Discontinuation of the probiotic, removal of the CVC, and administration of amphotericin B or fluconazole is recommended. Voriconazole may be a good therapeutic alternative.

Laboratory diagnosis of catheter colonization and CR-BSI

Bouza E, Alvarado N, Alcalá L, Pérez MJ, Muñoz P, Martín-Rabadn P, Rodríguez-Creixems M. A prospective, randomized, and comparative study of 3 different methods for the diagnosis of intravascular catheter colonization. Clin Infect Dis. 2005;40:1096-100.

This single-center prospective study, carried out between September 2002 and April 2003, makes a randomized comparison of three different culture techniques on the tip of CVCs to examine their ability to detect colonization and determine their reliability for predicting CR-BSI: these are Maki's semiquantitative technique and the quantitative methods of sonication and vortexing of Brun-Buisson. A total of 1000 catheter tips from 831 patients (539 short-term tips, 461 long-term tips) were processed, and 329 (32.9%) had positive results for at least 1 of the 3 techniques when a breakpoint of ≥ 100 cfu/catheter segment was used for the quantitative techniques and a breakpoint of ≥ 15 cfu was used for Maki's technique. Eighty-two of the catheter tips for which results were positive were from patients with catheter-related bacteremia. For each technique, the likelihood of detection decreased progressively depending on the order in which the technique was performed (i.e., second vs first and third vs. second). The likelihood of detection of catheter colonization for each technique, when the technique was performed first and when 2 breakpoints (≥ 100 cfu/catheter segment [criterion B] or ≥ 1000 cfu/catheter segment [criterion A]) were used for the quantitative techniques and a breakpoint of ≥ 15 cfu was used for Maki's technique, was as follows: 99.1% and 100% for Maki's technique, 95.1% and 92.9% for sonication, and 93.1% and 72.8% for vortexing (for criteria B and A, respectively). The authors concluded that the quantitative techniques of sonication and vortexing were not superior to Maki's technique, and that the greater simplicity of Maki's semiquantitative technique makes it the procedure of choice for routine work in the microbiology laboratory.

Comments

This is the first randomized study including a large number of catheter segments in which the sequence of three culture techniques was assessed, as was the likelihood of detecting catheter-tip colonization when the technique is performed first, second, or third. The authors observed that the diagnostic usefulness of each technique decreases progressively and significantly depending on the order in which the technique was performed, a fact that was not assessed in previous comparative studies of different methods for the diagnosis of catheter colonization.

The study also evaluated the reliability of quantitative techniques in the diagnosis of catheter colonization when different breakpoints (≥ 100 cfu/catheter segment or ≥ 1000 cfu/catheter segment) are considered, and confirms the superiority of the ≥ 100 cfu/catheter segment breakpoint over the ≥ 1000 cfu/catheter segment breakpoint. However, when CR-BSI is used as the gold standard, significant differences between the three techniques were not found. This finding is highly relevant for clinical microbiologists due to the greater simplicity of Maki's semiquantitative technique in comparison with the quantitative techniques. Therefore, Maki's semiquantitative technique continues to be the technique of choice for the diagnosis of catheter colonization, and the addition of a quantitative technique has a very limited value. Future studies addressing the comparison of different techniques should take into account the order in which the technique is performed.

Raad I, Hanna HA, Alakech B, Chatzinikolaou I, Johnson MM, Tarrand J. Differential time to positivity: a useful method for diagnosing catheter-related bloodstream infections. Ann Intern Med. 2004; 140:18-2569.

This was a prospective study carried out between September 1999 and November 2000 to evaluate differential time to positivity as a method for diagnosing catheter-related bacteremia caused by both short-term and long-term use of CVCs in cancer patients. A total of 6138 simultaneous blood cultures of samples drawn from the catheter and a peripheral vein were analyzed: both were negative in 5128 (84%) cases, both positive in 216 (3%), catheter blood culture-positive and peripheral blood culture-negative in 603 (10%), and catheter blood culture-negative and pe-

ripheral blood culture-positive in 191 (3%). The definitions of CR-BSI were as follows: composite definition (Infectious Diseases Society of America, IDSA), i.e., positive simultaneous blood cultures from the CVC, peripheral vein and catheter tip (Maki), or number of cfu from blood drawn through the CVC at least 5-fold greater than the number isolated from blood drawn percutaneously; partial definition based on simultaneous quantitative blood cultures (at least 5 times the number of cfu from the CVC compared with the peripheral vein); and partial definition based on semiquantitative catheter culture (catheter tip culture with ≥ 15 cfu of the same organism isolated from peripheral vein culture). Of the 191 patients with CR-BSI, 108 (56%) had catheter-related bacteremia and 83 had non-catheter-related bacteremia, according to the composite definition. Differential time to positivity of ≥ 120 min was associated with 81% sensitivity and 92% specificity for short-term catheters, and 93% sensitivity and 75% specificity for long-term catheters. As a diagnostic tool for catheter-related bacteremia (using a composite definition reference standard according to the IDSA guidelines), differential time to positivity is a useful method for patients who have short-term and long-term catheters.

Comments

The definition CR-BSI selected influenced the results obtained, with a higher sensitivity and specificity when quantitative blood cultures (at least 5 times the number of cfu) were considered as the gold standard compared with the semiquantitative culture technique of the catheter tip (≥ 15 cfu). However, the simultaneous use of CVC and peripheral blood quantitative cultures represents an important workload for clinical microbiology laboratories and should only be performed in selected patients.

Treatment. Antiobiotic-lock therapy

Koldehoff M, Zakrzewski JL. Taurolidine is effective in the treatment of central venous catheter-related bloodstream infections in cancer patients. Int J Antimicrob Agents. 2004;24:491-5.

Taurolidine is a derivative of tauronimide which was developed in the 1960's, and is active against Gram-positive and Gram-negative pathogens. It has antifungal activity and is available as a 2% solution. It is non-toxic, metabolizes to taurine+CO_2+H_2O, and can be administered intravenously and intraperitoneally.

In an open-label, pilot study, 11 cancer patients with catheter-related bacteremia not responding to 48-72 hours of systemic antibiotic therapy were treated with taurolidine solution as an intravenous lock in totally implanted intravascular devices. There were 3 men and 8 women with a mean age of 64.5 years. Solid tumors had been diagnosed in 8 patients, lymphoma in 2, and chronic lymphocytic leukemia in 1. Catheter lock was accomplished with 3 mL of 0.5% taurolidine-Ringer lactate in place for 24 hours. The catheter was then washed with 10 mL of 0.9% saline solution. Taurolidine i.v. lock therapy was performed once in 6 patients, twice with a 24-hours interval in 2 patients, and three times after 24 and 48 hours in 3 patients. In addition, all patients were given systemic antibiotics according to results of antibiotic susceptibility testing. All patients recovered completely from the infection (disappearance of clinical symptoms, normalization of PCR, and negative blood cultures) without removal of the intravascular line. Three patients were successfully retreated for a recurrent infection. No adverse drug effects were observed. The authors conclude that the application of taurolidine i.v. lock is feasible and could be especially useful in infections resistant to antibiotic chemotherapy.

Comments

Taurolidine may be an effective treatment in patients with bacteremia associated with intravascular devices caused by multiresistant organisms. The use of this agent has no relevant toxic or adverse effects. Treatment with taurolidine does not induce the development of resistant bacterial strains.

Rijnders BJ, Van Wijngaerden E, Vandecasteele SJ, Stas M, Peetermans WE. Treatment of long-term intravascular catheter-related bacteraemia with antibiotic lock: randomized, placebo-controlled trial. J Antimicrob Chemother. 2005;55:90-4.

Different studies have shown that the use of an antibiotic lock (AB-lock) is a useful strategy for the prevention of CR-BSI in neutropenic patients with long-term catheters. Evidence for the use of AB-lock in the treatment of infected catheters is based on non-randomized studies with historical controls.

A multicenter, randomized, double-blind, and placebo-controlled study was conducted at 3 hospitals in Belgium. The study population included pediatric and adult patients with oncohematological diseases, on dialysis, or receiving parenteral nutrition with long-term catheters (Hickman or Port-a-cath) and associated bacteremia. The study compared an AB-lock containing vancomycin for Gram-positive or ceftazidime for Gram-negative bacteria with placebo, in addition to parenteral antibiotic therapy. Bacteremia was confirmed by differential blood cultures. Patients with complicated infections (endocarditis, suppurative thrombophlebitis) and candidemia were excluded. Antibiotic solutions were prepared by the hospital pharmacy on days 0 and 7 and contained heparin (100 IU/mL) and vancomycin or ceftazidime (0.5 g/mL both). The placebo solution contained heparin only. AB-lock was maintained for 7 to 14 days, the same as systemic antibiotic therapy.

During a 30-month study period, 174 patients with a long-term intravascular device and bacteremia were evaluated: 111 cases of bacteremia were related to the catheter. Finally, only 44 patients were evaluable: 21 in the AB-lock group and 23 in the placebo group. On day 180 by Kaplan-Meier analysis, failure to cure the CR-BSI or relapse with the same strain, occurred in 33% (7 of 21) in the AB-lock arm and in 57% (13 of 23) in the placebo arm (hazard ratio 0.55, p = 0.10). The multivariate analysis did not reveal differences in relation to parenteral nutrition, causative organism (80% of bacteremias in each group were caused by coagulase-negative *Staphylococcus*), type of catheter, or presence of neutropenia. A relapse with the same strain occurred in 9/23 with the placebo and

in 3/21 with the AB-lock (p = 0.06). Although differences were not statistically significant given the small number of patients analyzed, the study shows that AB-lock is associated with a 24% reduction in failures to cure CR-BSI in patients with long-term catheters.

Comments

The study was discontinued due to difficulties for the enrollment of patients, and a few organisms such as *S. aureus* or *Candida* spp. were documented. Although not conclusive, the study supports the usefulness of AB-lock with vancomycin or ceftazidime.

Grill F, Fortún J, Blázquez J et al. Treatment of long-term intravascular catheter-related bacteremia with antibiotic lock-technique. Abstract K-2221. 45th ICAAC; Washington, USA, 2005.

At the annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), the results of a comparative, retrospective study of bacteremia associated with long-term catheters in 801 patients with oncohematological diseases or parenteral nutrition were recently reported. CR-BSI was confirmed in 92 patients, 48 of whom fulfilled the inclusion criteria. Of these patients, 19 were treated with AB-lock (vancomycin or gentamicin or ciprofloxacin, 2 mg/mL) and 29 received antibiotic therapy only. A favorable response was observed in 84% of patients treated with AB-lock and in 65% of patients treated with systemic antibiotics (p = 0.27).

Curtin J, Cormican M, Fleming G, Keelehan J, Colleran E. Linezolid compared with eperezolid, vancomycin, and gentamicin in an in vitro model of antimicrobial lock therapy for *Staphylococcus epidermidis* central venous catheter-related biofilm infections. Antimicrob Agents Chemother. 2003;47: 3145-8.

Vancomycin is the most common antibiotic agent in most studies on AB-lock in Gram-positive infections. In this respect, the results of Curtin et al. in an in vitro model of biofilm formation are interesting. This study shows that linezolid (2 mg/mL) or eperezolid (4 mg/mL) eradicate *S. epidermidis* biofilms more rapidly than vancomycin (10 mg/mL) and gentamicin (10 mg/mL).

Percival SL, Kite P, Eastwood K, Murga R, Carr J, Arduino MJ, Donlan RM. Tetrasodium EDTA as a novel central venous catheter lock solution against biofilm. Infect Control Hosp Epidemiol. 2005;26:515-9.

Studies carried out with non-antibiotic-lock substances have shown promising results, with the potential benefit of preventing the development of resistance to glycopeptides in the management of these infections. Percival et al demonstrate that antimicrobial lock treatment using 40 mg/m of EDTA for at least 21 hours could significantly reduce or potentially eradicate CVC-associated biofilms of clinically relevant microorganisms, such as *S. epidermidis*, *S. aureus* (including methicillin-resistant *S. aureus*), *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Candida albicans*.

Prevention bases on education programs

Warren DK, Zack JE, Mayfield JL, Chen A, Prentice D, Fraser VJ et al. The effect of an education program on the incidence of central venous catheter-associated bloodstream infection in a medical ICU. Chest. 2004;126:1612-8.

The impact of education programs on the reduction of catheter-related infections has received little attention. This pre-intervention and post-intervention observational study was carried out in a 19-bed medical ICU at a 1400-bed teaching hospital. The program consisted of a 10-page self-study module on risk factors and practice modifications involved in CR-BSI; fact sheets and posters reinforcing the information in the study module were also posted throughout the ICU. Each participant was required to complete a pretest before reviewing the study module and an identical test after completion of the study module. Following implementation of the intervention, the rate of CR-BSI decreased from 9.4 to 5.5 per 1,000 catheter-days (p = 0.019), with estimated cost savings of between $103,600 and $1,573,000.

Comments

This study has important limitations, including the fact that it was performed in a single ICU with poor catheter-care measures at the pre-intervention phase, catheters were inserted by residents, and interventions made were inadequately quantified. Data reported in the literature are assumed for cost analysis and the impact of other variables is not measured.

Lobo RD, Levin AS, Gomes LM, Cursino R, Park M, Figueiredo VB et al. Impact of an educational program and policy changes on decreasing catheter-associated bloodstream infections in a medical intensive care unit in Brazil. Am J Infect Control. 2005; 33:83-7.

Higuera F, Rosenthal VD, Duarte P, Ruiz J, Franco G, Safdar N. The effect of process control on the incidence of central venous catheter-associated bloodstream infections and mortality in intensive care units in Mexico. Crit Care Med. 2005;33:2022-7.

Gnass SA, Barboza L, Bilicich D, Angeloro P, Treiyer W, Grenovero S et al. Prevention of central venous catheter-related bloodstream infections using non-technologic strategies. Infect Control Hosp Epidemiol. 2004;25:675-7.

Comments

These studies are limited to the ICU setting. Most of them had very poor catheter insertion and maintenance conditions before intervention, thus making success more

plausible. The impact of other variables on catheter-related bacteremia is not considered.

Prevention based on new connetors

Yebenes JC, Vidaur L, Serra-Prat M, Sirvent JM, Batlle J, Motje M et al. Prevention of catheter-related bloodstream infection in critically ill patients using a disinfectable, needle-free connector: a randomized controlled trial. Am J Infect Control. 2004; 32:291-5.

Yebenes et al evaluated, in critically ill patients, the usefulness of a multilumen, needle-free connector with a valve mechanism in each lumen that closes the connection by means of an endoluminal silicone embolus. The device can be disinfected before each use, which theoretically reduces the likelihood of contamination of connectors during catheter manipulation. In this randomized controlled trial, patients who needed multi-lumen CVC were randomly assigned to the study group (catheters with disinfectable, needle-free connectors) or the control group (catheters with 3-way stopcocks). The primary efficacy variable was the frequency of CR-BSI. The ports of the connection system were disinfected before use with 70% alcohol. The authors mention that all catheters were inserted and manipulated according to the Centers for Disease Control and Prevention (CDC) recommendations, but no details regarding manipulations of the 3-way stopcocks are provided. The study included 139 catheters in each arm. Mean indwelling time was 9.9 days. In both study groups, a similar distribution of medical, surgical and trauma patients (approximately one third per group) was recorded, and almost 30% of patients in each group received total parenteral nutrition. The incidence rate of CR-BSI was 0.7 per 1000 indwelling days the study group, compared with 5.0 per 1000 days of catheter use in the control group ($p = 0.03$). The use of catheters with 3-way stopcocks was an independent risk factor for CR-BSI in the logistic regression analysis (OR 11.9, 95% CI, 1.2-113.5) together with younger age, length of ICU stay, and obesity. The frequency of colonization in CVCs that were removed was similar in both study groups. The authors concluded that adding a disinfectable, needle-free connector to the CDC recommendations reduces the incidence of CR-BSI in critically ill patients with CVCs.

Comments

Since a blind condition for the study design is impossible, a limitation of the study could be the higher level of adherence to general preventive measures among patients assigned to the new connector device.

Leon C, Ruiz-Santana S, Rello J, De la Torre MV, Valles J, Alvarez-Lerma F et al Cabaña Study Group. Benefits of minocycline and rifampin-impregnated central venous catheters. A prospective, randomized, double-blind, controlled, multicenter trial. Intensive Care Med. 2004;30:1891-9.

This was a prospective, randomized, double-blind, controlled trial, in which seven Spanish ICUs participated. At catheter insertion, 228 patients were randomized to minocycline and rifampin-impregnated catheters and 237 to non-impregnated catheters. A trend towards a reduction in catheter-related infectious complications (local infection or catheter-related bacteremia) (relative risk [RR] 0.67, 95% CI, 0.31-1.44) and catheter-related bacteremia (RR 0.53, 95% CI, 0.2-1.44) was observed. A statistically significant decrease in tip colonization (RR 0.43, 95% CI, 0.26-0.73) was found. Antimicrobial-impregnated catheters were associated with a significant decrease in coagulase-negative staphylococci colonization (RR 0.24, 95% CI, 0.13-0.45) and a significant increase in Candida spp. colonization (RR 5.84, 95% CI, 1.31-26.1). Differences in the rate of bacteremia, ICU length of stay, or 30-day survival rate were not observed. However, a decrease in infectious complications with the use of antibiotic-impregnated catheters for parenteral nutrition or intravenous lipid emulsion was recorded.

Comments

This study confirms the results of previously reported clinical trials in which antibiotic-impregnated catheters were associated with a decrease in the rate of catheter colonization. However, the final objective of this technique is to reduce the rate of bacteremia and episodes of catheter-related sepsis, variables that remained unchanged throughout the study with the use of minocycline and rifampin-impregnated catheters. Although a cost/benefit analysis was not performed, it may be reasonable to argue whether the use of antibiotic-impregnated catheters is justified in all patients, or only in those at high risk of infection, or in intravenous lines used for parenteral nutrition as recommended by published guidelines.

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