



Evaluation of the mortality of neonates and children related to the use of central venous catheters: a systematic review*

Avaliação da mortalidade de neonatos e crianças relacionada ao uso do cateter venoso central: revisão sistemática

Evaluación de la mortalidad de neonatos y niños relacionada al uso del cateter venoso central: revisión sistemática

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ABSTRACT

Objective: To analyze mortality related to infections in the use of central venous catheters in newborns and hospitalized children. **Methods:** This was a systematic review, using studies that were identified in the databases of MEDLINE, EMBASE, Lilacs, CINAHL, SciELO and Cochrane, in bibliographical references of articles, and other reviews. Two reviewers independently identified relevant studies, analyzed the methodological quality, and subsequently, extracted data. **Results:** We encountered 1,000 articles, of which 16 were related to catheter infection and only two mentioned mortality. Findings of these two studies verified that sepsis was the principal complication related to the use of central venous catheters, and the most prevalent microorganisms in these infections were *Candida sp.* and *Enterococcus sp.*, with significant impact on neonatal and child mortality. **Conclusion:** It was observed in this review that sepsis was most prevalent complication related to central catheters. **Keywords:** Mortality, catheter-related infections; Literature review as a subject

RESUMO

Objetivo: Avaliar a mortalidade relacionada às infecções no uso de cateter venoso central em recém-nascidos e crianças hospitalizadas. **Métodos:** Trata-se de uma revisão sistemática, cujos estudos foram identificados nas bases de dados Medline, Embase, Lilacs, Cinahl, SciELO e Cochrane, em referências bibliográficas de artigos e outras revisões. Dois revisores independentes identificaram os estudos relevantes, analisaram a qualidade metodológica e, posteriormente, os dados foram extraídos. **Resultados:** Foram encontrados 1.000 artigos, dos quais 16 se relacionavam à infecção de cateter e só dois mencionaram mortalidade. Dos estudos achados, verificou-se que a sepse primária foi a principal complicação relacionada ao uso de cateter venoso central, e sendo os micro-organismos mais prevalentes nestas infecções a *Candida sp* e *Enterococcus sp* com impacto significante para a mortalidade em neonatos e crianças. **Conclusão:** Observou-se nesta revisão que a sepse primária foi a complicação mais prevalente relacionada ao cateter central.

Descritores: Mortalidade; Infecções relacionadas a cateter; Literatura de revisão como assunto

RESUMEN

Objetivo: Evaluar la mortalidad relacionada a las infecciones en el uso del cateter venoso central en recién nacidos y niños hospitalizados. **Métodos:** Se trata de una revisión sistemática, cuyos estudios fueron identificados en las bases de datos Medline, Embase, Lilacs, Cinahl, SciELO y Cochrane, en referencias bibliográficas de artículos y otras revisiones. Dos revisores independientes identificaron los estudios relevantes, analizaron la calidad metodológica y, posteriormente, los datos fueron extraídos. **Resultados:** Se encontraron 1.000 artículos, de los cuales 16 se relacionaban a la infección del cateter y sólo dos mencionaron mortalidad. De los estudios encontrados, se verificó que la sepsis primaria fue la principal complicación relacionada al uso del cateter venoso central, y siendo los microorganismos más prevalentes en estas infecciones la *Candida sp* y *Enterococcus sp* con impacto significativo para la mortalidad en neonatos y niños. **Conclusión:** Se observó en esta revisión que la sepsis primaria fue la complicación más prevalente relacionada al cateter central.

Descriptores: Mortalidad; Infecciones relacionadas con catéteres; Literatura de revisión como asunto

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INTRODUCTION

The use of central venous catheters (CVC) has become indispensable practice in the care of hospitalized patients, particularly the most severe. In Europe, 60% of hospitalized patients make use of the CVC at some time during hospitalization⁽¹⁾. Over 150 million CVC are purchased in the United States of America (USA), and seven million are inserted each year⁽²⁻³⁾.

The use of CVC represents a significant advance in health, diagnostically and therapeutically. In newborns and children, they are indicated for drug therapy, hemodynamic monitoring, and administration of total parenteral nutrition. Surgical and medical procedures are performed with the development of this technology. However, despite the observed benefits, because it is a device that directly accesses the bloodstream, the use of CVC is associated with mechanical and infectious complications, local or systemic, described as: cellulitis at the insertion site, septic thrombophlebitis, endocarditis, bacteremia and metastatic infection (osteomyelitis, arthritis) resulting in hematogenous dissemination based on the colonized catheter⁽⁴⁾.

Infection is the principal complication related to use of the CVC, since they result in increased hospital costs, prolonged hospitalization, and increased morbidity and mortality, among other issues⁽⁵⁾. Annually, 250,000 cases of bloodstream infection are recorded in the U.S.A., with a mortality rate ranging from 12% to 25%, of which the majority is associated with the nontunneled catheter^(2,4). With regard to the mortality of patients with episodes of infection related to CVC, it is estimated that it is 30% greater than when compared to peripheral lines⁽⁶⁾.

The time of CVC use is related to the occurrence of death in the Neonatal Intensive Care Unit (NICU), which highlights the need for new studies to seek the real causes of the connection between the use of CVC and death in newborns and children⁽⁷⁾.

Therefore, it is acknowledged that CVC are widely used in infants and children, and assist in therapy. On the other hand, we must consider the risk to which this population may be exposed, which demands that we seek scientific evidence to assess the mortality related to intravascular devices. The objective of this systematic review was to assess mortality related to infections and the use of CVC in hospitalized newborns and children.

METHODS

The study was conducted through a systematic literature review, which for evidence-based practice becomes an important resource, since the survey results are collected, categorized, evaluated and synthesized.

The scientific evidence presented by studies with adequate design and statistically sound results assists in decision-making⁽⁸⁾.

The studies for this review were selected by searching the electronic databases of the Cochrane Library, SciELO, EMBASE, LILACS, PubMed and CINAHL, bibliographical references of articles, conference papers, review articles and guidelines. In the search, we included: randomized clinical trials, quasi-randomized studies, randomized controlled trials, and prospective and retrospective observational studies.

The specific terms adopted for the search strategy were: “*Catheterization*” OR “Catheterization, Central Venous” OR “Catheters, Indwelling” AND “*Infant*” [Mesh] OR “Infant, Very Low Birth Weight” [Mesh] OR “Infant, Low Birth *Weight*” [Mesh] OR “Infant, Extremely Low Birth Weight” [Mesh] OR “Infant, *Premature*” [Mesh] OR “Infant, Postmature” [Mesh] OR “Infant, Newborn” [Mesh] OR “*Infant*, Small for Gestational Age” [Mesh] OR “*Child*” [Mesh] OR (“*Child*, *Preschool*” [Mesh] OR “*Child*”) AND “*Infection*” [Mesh] OR “Cross Infection” [Mesh] OR “*Catheter-Related Infections*” [Mesh].

The search in electronic databases included research published between January 1982 and July 2009, as shown for each database: PubMed (1984-2009), LILACS (1982-2009) SciELO (1997-2009), EMBASE (1982 - 2009), and CINAHL (1987-2009). In the search strategy, there is no purpose for filtering the publication date of studies, because the quality of evidence is not related to the date of publication⁽⁹⁾, therefore we did not limit the year of publication of the studies.

For the selection of articles, two reviewers independently analyzed the titles and abstracts of the publications found. Studies in English, Portuguese and Spanish, independent of design, were included which analyzed hospitalized newborns or children who used CVC and who had mortality related to CVC infection. In case of disagreement or doubt between reviewers, a third reviewer was asked to issue a final opinion about the inclusion of the study.

We excluded studies that did not have newborns or children as subjects of the research, those conducted in outpatient clinics and home care, or those that included pulmonary artery catheters (Swan-Ganz®), fully implanted devices (port-a-cath®), and arterial, peripheral and umbilical devices, because of the specificity of these devices and their placement in the vessel.

To describe the intensity of agreement between reviewers, the measurement of Kappa was used, which is based on the number of concordant responses, i.e., the frequency at which the result is the same between reviewers⁽¹⁰⁾. There was agreement between the two reviewers (Kappa = 0.862). In assessing the method-

ological quality of the observational studies, we applied the STROBE (*Strengthening the reporting of observational studies in epidemiology*) recommendations⁽¹¹⁾.

For data extraction, we used a predelineated form that included: variables that defined eligibility criteria, study identification, design characteristics, the population included in the study, number of subjects in each group, intervention (for trials), outcomes, results, ethical aspects, financing, and the opinion of the reviewer.

The data reported in this study are part of a comprehensive systematic review on infections related to the use of CVC. For this research, the outcome of interest concerned catheter-related infections related with mortality in newborns and children.

RESULTS

The search results identified 1000 primary studies: 686 in PubMed, 214 in EMBASE, 30 in LILACs, 21 in CINAHL, 19 in SciELO, and 30 from manual searches. After a consensus meeting for the selection of articles, 16 studies addressed infection related to the use of CVC, only two of which were related to mortality in newborns and children with the CVC device, as shown in Figure 1.

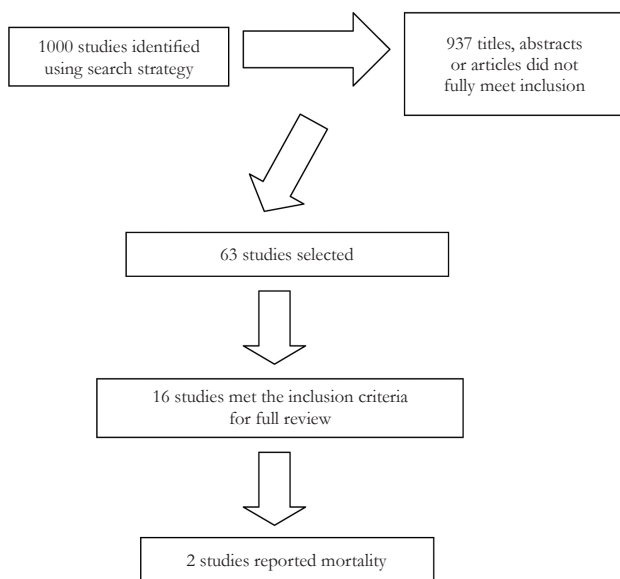


Figure 1. Flowchart of the process of identifying and selecting studies.

In the two studies that addressed this outcome, the STROBE value presented was B, conforming to 50% to 79% of the established criteria. The data in Table 1 describe the included studies.

Table 1. Description of studies included in the morbidity and mortality outcomes:

Author, publication year & country	Study design	Participants	Outcomes	STROBE
Pandit, P.B. et al. (1999) – Canada	Retrospective cohort	2934 children with birth weights ≤ 1500 g, admitted to three NICUs	14.5 episodes/1000 catheters/day	B
Johnson, P.R. et al. (1982) – USA	Retrospective cohort	64 children with cancer	2.8 infections/1000 catheters/day	B

The first study was conducted by Pandit et al.⁽¹²⁾ and was a retrospective cohort study with the objective of determining the incidence of surgically inserted CVC complications in newborn infants of low birth weight. There were 2934 neonates evaluated with birth weights less than or equal to 1,500g, admitted to three NICUs; of these, 104 (3.5%) used 112 catheters, of which 55 were boys and 49 girls. It was observed that 85 infants had a weight of 1.000g, and 19 had weights ranging from 1,001 to 1,500g.

In ninety-seven patients, the indication for use of CVC was administration of parenteral nutrition and antibiotic therapy. The 112 CVC were tunneled, with an average duration of 21 days, with a range of 1 to 130 days. In 43 neonates, the device was surgically inserted, 112 catheters in the jugular: 84 in the right internal jugular, seven in the right external jugular, 20 in the left internal jugular vein, and 1 in the left external jugular vein⁽¹²⁾.

Of the 104 neonates, 59 (57%) had one or more complications associated with a catheter, for a ratio of 27 complications/1,000 catheters/day. Sepsis was the most common infectious complication (43 episodes in 38 patients), resulting in 14.5 episodes/1,000 catheters/day. Multivariate analysis indicated that sepsis was associated with birth weight ($p = 0.015$), male gender ($p = 0.016$), CVC duration ($p < 0.001$), and duration of parenteral nutrition ($p < 0.001$)⁽¹²⁾. Sepsis was a complication associated with mortality in newborns, but was not related to gestational age, birth, age (at time of CVC insertion), surgical procedure, number of ventilation, or death. More male patients developed sepsis (OR = 2.76, 95% CI 1.1 to 7.0)⁽¹²⁾.

The 43 episodes of sepsis were isolated for: 34 (79%) *Coagulase negative Staphylococcus*; 3 cases of *Enterococcus*; 1 case each of *Serratia*, *Staphylococcus aureus*, *Alpha-hemolytic Streptococcus*, *Pseudomonas species*; 4 cases of *Candida albicans*;

and, 1 instance of *Malassezia furfur*⁽¹²⁾. There was evidence that three patients died from sepsis when the CVC was inserted, one from sepsis related to *Candida sp.* and the other two with *Enterococcus sp.*⁽¹²⁾.

The second study was presented by Johnson et al.⁽¹³⁾. In this retrospective cohort study, 64 pediatric oncology patients with 70 Broviac catheters were evaluated: 35 were boys (55%) and 29 (45%) girls; 51 were white (80%) and 13 were black (20%). Exclusion criteria were not reported in the study. Subject age was reported by age range: newborn (one year or less) = 3 (5%); child (1-4 years) = 38 (59%); school-aged children (5-10 years) = 11 (17%); and, adolescents (11-17 years) = 12 (19%).

Of the 70 Broviac catheters, 34 permanently inserted, 13 were removed for infection, and 23 were extracted for other reasons⁽¹³⁾. In the 50 infection occurrences, 34 episodes of infection were associated with length of time the catheter was in place, and 25 were infected only once; 6 had two infections; and, the other 3 devices had three, four and six infections, respectively. The 70 implanted devices represented a total of 17,581 catheters/day, with 50 infectious episodes; the mean was 2.8 infections/1,000 catheters/day⁽¹³⁾. Also, 25 had septic infections, 17 infections of the exit site, and eight surrounding the site of the insertion and tunnel⁽¹³⁾.

Age was not significantly associated with the development of one or more infections. Young children were more susceptible to infection than adolescents: 2 (17%) of 12 devices in adolescents presented with one or more episodes of infection, compared with 25 (58%) of 43 catheters in children, and 7 (58%) of 12 school-aged children (OR = 6, P=0.02); 3 catheters in children were not infected⁽¹³⁾. The infection rate for each age group per 1,000 catheters, in infants was zero; in children was 2.7, and in adolescents was 0.5 (children and school-aged children *versus* adolescents, P = 0.0002)⁽¹³⁾. Age was significantly correlated with the total number of infections per patient (P = 0.03). More babies had multiple episodes of infection: 10 of 38 infants had multiple catheter infections, as compared with 9 of 26 other children (OR > 20, P < 0.005)⁽¹³⁾.

In regard to microorganisms, these were isolated in the second study: *gram-positive Cocci* and *gram-negative Bacilli* were found in equal frequency, representing 92% of the microorganisms isolated. The most commonly isolated were: *Pseudomonas aeruginosa* (20%), *Staphylococcus aureus* (20%) e *Staphylococcus negative* (14%). *Pseudomonas aeruginosa* was more frequent at the exit site, with 12 (44%) of 27 exit sites isolated, and 3 (6%) of 47 blood cultures. *Gram negative* and showed a clear difference and was more common in the blood (34%) and the exit site (11%). *Gram negative Cocci* and *Gram positive bacilli* were uncommon⁽¹³⁾.

Regarding mortality related to the use of CVC, 23 of the studied 64 children died, and two deaths were directly associated with catheter infection. Twenty-one patients had no infection related to catheter use, accumulated in 4,574 patients/day of catheter use and 12 acquired infections, in a ratio of 2.6/1,000 catheters/day⁽¹³⁾.

DISCUSSION

There are some predisposing factors to bloodstream infection, such as extreme age, presence of immunodeficiency, neoplasms, neutropenia (four-fold increased risk) and patients with chronic renal failure on hemodialysis (rate of 0.6 episodes/1,000 patients/day)⁽¹⁴⁾. Issues related to infection associated with the use of CVC are discussed in the study of Pandit et al.⁽¹²⁾ and Johnson et al.⁽¹³⁾, as well as predisposing factors such as age, underlying disease and hospitalization time.

Children who require cardiac surgery are at increased risk for developing bloodstream infections related to use of CVC, the high complexity of the surgery, low body weight and extended time in the Pediatric Intensive Care Unit (PICU). A study in PICU patients after cardiac surgery showed high rates of bloodstream infection, with a six time increase in risk of mortality in infected patients⁽¹⁵⁾.

Children with leukemia are at risk of developing complications when compared to children with solid tumors. Treatment for childhood leukemia is followed by prolonged periods of myelosuppression, leukopenia, neutropenia, and greater manipulation of CVC, which favors the development of infections⁽¹⁶⁾. Retrospective studies show that patients with cancer or acquired immunodeficiency syndrome have four times greater risk of developing bloodstream infection. However, in patients with neutropenias and/or those receiving immunosuppressive therapy, this risk is even greater⁽¹⁷⁻¹⁸⁾.

Other studies show that infections related to use of CVC prolong hospitalization by 6.5 to 22 days, at a cost of USD \$29,000 to \$56,000 per episode of infection^(6,19). Noteworthy are the significant risks of morbidity and mortality for all patients, regardless of age^(4,20), as it shows the estimated risk is 13% to 28% higher compared to the patients of the same gravity without this complication^(6,19).

In the U.S.A., the average risk of bacteremia is 5.3/1,000 catheters /day, corresponding to approximately 80,000 cases per year, increasing mortality by 35%, at an estimated cost of USD \$34,508 to \$56,000 per episode. It is further considered that among hospitalized patients the total is approximately 250,000 cases annually, at an average cost of USD \$25,000 per case⁽²¹⁾.

Pandit et al.⁽¹²⁾ and Johnson et al.⁽¹³⁾ commented that the length of time the catheter is in place is crucial

to developing bloodstream infection. When the time of use of the device is less than three days, the risk of bloodstream infection is close to zero, at three to seven days, this risk is increased by 3% to 5%, and when more than seven days, it increases 5% to 10%⁽²²⁾.

Sepsis was cited as a factor in CVC-related mortality. A study in Brazil evaluated the profile of nosocomial infections in neonates and the principal risk factors of death in 2,402 newborns: the average rate of nosocomial infection was 18.3%. Sepsis was the most frequent infection (49.1%) and was related to hospital length of stay exceeding 60 days and invasive procedures, such as vascular catheter, which increased the risk of sepsis and the risk of death by 2.5%⁽¹⁸⁾.

According to Pandit et al.⁽¹²⁾, *Staphylococcus negative coagulase* was found in 79% of cultures, *Staphylococcus aureus*, in one episode, and, *Candida albicans* in four cases; in Johnson et al.⁽¹³⁾, micro-organisms commonly isolated were *Staphylococcus aureus* (20%) and *Staphylococcus negative coagulase* (14%), data similar to those found in the literature.

The *Staphylococcus negative coagulase* is the most frequent agent in bloodstream infection related to CVC, followed by *Staphylococcus aureus* and Gram-negative bacteria. Infection by *Candida sp.* occurs due to the use of broad-spectrum antibiotics, parenteral nutrition, and immunosuppressive therapies, among other factors⁽²³⁾. *Candida sp.* infections have an impact on mortality, and the CVC is a clearly identified risk factor for this type of fungus. In a study of adults, one fourth of patients affected by CVC had candidemia, with 58% of 77 catheters removed⁽²⁴⁾.

It was observed that for Pandit et al.⁽¹²⁾, patients weighed less than or equal to 1500g, but the authors did not address whether there is a significant relationship between mortality associated with weight.

In contrast, studies show that neonates, with birth weights below 1500g, showed a high risk of death compared to those weighing more than 1501g (RR = 2.81, confidence interval [CI] 95% = 2.26 -3.49). For neonates who had CVC, the risk of death was higher than in those who did not (RR = 4.49, 95% CI = 2.48 - 8,12). These findings suggest that CVC is an aggravating factor of mortality in low birthweight newborns, but it is not the cause of death (21).

It was observed in the study by Johnson et al.⁽¹³⁾ that boys had more infections than girls, which may be because they are more active and do not follow guidelines

for infection prevention⁽¹⁶⁾. Children under four years of age more often develop infectious complications related to the catheter, due to cognitive level immaturity and difficulty in understanding what is needed⁽¹⁶⁾.

These data demonstrate the importance of clear guidelines on the care of the CVC, and that the nurse should teach parents about care to reduce catheter-related complications. The CVC is a safe and effective tool for the management of chronic diseases, so there is need for early identification of any complication, as well as factors associated with mortality.

Thus, the need emerges to implement strategies to reduce the incidence of infections related to the use of the catheter, in order to minimize mortality. This effort should be multidisciplinary, involving health professionals and patients that can assist in care, implementation of protocols, and medical and nursing education activities aimed at reducing infections associated with these devices.

CONCLUSION

It was noted in this review that primary sepsis was the most prevalent complication related to the CVC. The incidence of infection was higher among children with lower birth weight, male gender and duration time of catheter. The most common microorganisms in cases of sepsis related to the use of CVC were *Candida sp.* and *Enterococcus sp.*, and they were related to mortality.

IMPLICATIONS FOR PRACTICE

Given the scarcity of data from quality randomized clinical trials to assess the mortality related with CVC use, it is appropriate to conduct new studies that may be incorporated into this review, so that complications associated with central venous devices can be evaluated statistically.

There is need to develop protocols for insertion, maintenance and prevention of infections related to use of CVC, which may help identify complications and possible treatments for patients with this type of device and, consequently, prevention of mortality.

We suggest the extension and construction of new systematic reviews on the subject to assess newborns and children separately, and that compare one or more devices in relation to mortality.

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