

Identification of central venous catheter-related infections in infants and children

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Objective: To define central venous catheter-related infections in infants and children for the purpose of enrolling children in sepsis studies, for epidemiology and surveillance studies, and for clinical management.

Methods: Review of the literature and consensus of experts.

Results: No changes were made to the current Centers for Disease Control and Prevention criteria for defining local catheter infection. Because catheter tips are not available as often in children as in adults, smaller blood volumes are drawn per culture decreasing sensitivity, and antibiotics are rarely withheld, slight modifications to the existing adult Centers for Disease Control and Prevention criteria were made to increase practical use. Catheter-related bloodstream infection was categorized as definite, probable, and possible based on culture results and clinical symptoms.

Conclusions: For the purposes of enrolling patients with sepsis in clinical trials, only patients who meet criteria for definite catheter-related bloodstream infection should be categorized as

having the catheter as the infection source. Because many patients suspected of having catheter-related bloodstream infection do not have positive blood culture results, which makes the confirmation of infection difficult, we recommend that these patients not be enrolled in sepsis trials. Because catheter tips are often not obtained for culture in children, the epidemiology of catheter-associated bloodstream infection (bloodstream infection in a patient who has a central venous catheter and no other obvious source of infection) is better understood than the epidemiology of confirmed catheter-related bloodstream infection in infants and children. Definitions for catheter-related bloodstream infection that compare the through-catheter and peripheral culture for time to positivity or for quantitative growth are unlikely to be falsely positive, but sensitivity requires further validation. (*Pediatr Crit Care Med* 2005; 6[Suppl.]:S19–S24)

KEY WORDS: central venous catheter; indwelling; infection; nosocomial; bloodstream

Intravascular central venous catheter (CVC)-related sepsis is an important and common cause of sepsis in infants and children with high associated morbidity and significant associated mortality rates. The rate of central catheter associated infections in pediatric intensive care units (ICUs) is, on average, 7.3 per 1000 catheter days and is more than double that reported nationally in adult medical ICUs (1). The rate is highest in neonates under 1000 g at birth at 11.3 per 1000 catheter days (1). Children with acquired and congenital immunodeficiencies and extremely pre-

mature neonates are at the highest risk for catheter-related infection. In children in the ICU, risk factors for catheter-related sepsis include use of extracorporeal membrane oxygenation, the presence of multiple intravascular access devices, and total duration of vascular access device use (2).

There is a large literature on the epidemiology and definitions of intravascular catheter-related infections in adults. In contrast, the data in children regarding validation of diagnostic criteria are sparse. Therefore, our recommendations must reference consensus guidelines that were based almost solely on adult studies (3–6). Management of CVCs differs in children compared with adults, necessitating modifications of the existing definitions. For example, vascular access may be very difficult to achieve in children, especially in small infants. Removal of the catheter may not be indicated for diagnostic purposes because catheter replacement may be associated with a high risk of complications or with reinsertion difficulties, and it may be prudent to attempt to eradicate the infection in the catheter. Therefore, it is more common to draw cultures through the catheter. In

addition, although recommended, it is not standard practice to send a peripheral culture because it may be difficult to obtain.

The amount of blood drawn from infants and young children for each culture is also markedly smaller, usually ≤ 3 mL (7). In adults, ≥ 10 mL of blood should be cultured to ensure optimal sensitivity (8). Culturing methods in pediatric hospitals usually use a smaller blood culture tube so that the amount of blood drawn will be in the right ratio to the volume of the media components that help to neutralize the host antimicrobial factors and antimicrobial agents. The yield of cultures for bloodstream infection in adults, however, increases by 3%/mL of blood cultured. When these pediatric blood culture bottles are used in adult-sized patients, detection of bloodstream infection drops from 92% to 69%, a difference of 23% (8). The baseline sensitivity of blood cultures in children using 3.5-mL pediatric blood culture bottles is not accurately known but may be $\leq 70\%$. In extremely premature neonates, when volumes of 1 mL of blood are sometimes sent, the sensitivity is markedly lower. If anaerobic infection is not suspected, it may be possible to put

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the entire blood volume into the aerobic bottle to optimize sensitivity, rather than splitting it with the anaerobic bottle.

Taking into account these limitations, we have attempted to write practical consensus definitions of intravascular catheter-related infection in infants and children. We will classify the certainty of our diagnoses as definite, probable, or possible. Definitions are listed in Table 1. These definitions are written for application in three situations:

1. Identifying infection early to enroll children in sepsis trials.
2. Identifying infections for surveillance and epidemiologic studies.
3. Identifying infections for diagnosis and optimal therapy.

For the purpose of enrolling children in sepsis trials, the diagnosis of catheter-related bloodstream infection (CRBSI) as a subcategory of infection is often a diag-

nosis of exclusion. At the time of early enrollment, the definitive diagnosis cannot be made because culture results are not available until 24–48 hrs after clinical suspicion of CRBSI and confirmation of absence of other sources of infection. Many more patients are suspected of having a CRBSI than have a confirmed CRBSI. Therefore, to decrease the probability that patients without CRBSI are enrolled in a clinical sepsis trial, we have focused on identifying those patients with definite CRBSI as defined in Table 1 or patients with uncommon clinical presentations where CRBSI is highly probable.

The clinical probability of CRBSI rises when a catheter has been in place for multiple days or when a catheter has been placed using nonsterile technique. Infusions of lipids or total parenteral nutrition solutions through the catheter are also risk factors, especially for neonates (9, 10). Many patients in the ICU, how-

ever, may have these risk factors. There are only a few clinical presentations that suggest a very high probability of CRBSI, which although uncommon are highly specific. Although it rarely occurs, hypotension on flushing the catheter is a strong sign that the catheter is infected. Local signs at the catheter exit site also increase the clinical probability of CRBSI. Local signs suggestive of CRBSI include, in increasing order of specificity, erythema or induration extending ≥ 2 cm of the catheter exit site, cellulitis along the subcutaneous tract of the catheter, and pus at the catheter exit site. Whereas the presence of pus is virtually diagnostic of infection, the other signs are nonspecific. Patients with the highest probability of catheter-related sepsis based on findings at clinical presentation share three characteristics: a) a severe presentation (severe sepsis or septic shock); b) no other “obvious source”; and c) a high clinical

Table 1. Clinical definitions for intravascular catheter infections

Local infections
Catheter colonization (i.e., “microbiological definition”)
Significant growth of a microorganism by semiquantitative (≥ 15 cfu) or quantitative (≥ 1000 cfu) culture of the catheter tip, subcutaneous segment of the catheter, or catheter hub
Exit site infection
Erythema or induration within 2 cm of the catheter exit site, in the absence of concomitant BSI and without concomitant purulence
Tunnel infection
Tenderness, erythema, site induration >2 cm or purulence from the catheter site along the subcutaneous tract of a tunneled (e.g., Hickman or Broviac) catheter, in the absence of concomitant BSI
Pocket infection
Purulent fluid in the subcutaneous pocket of a totally implanted intravascular catheter that might or might not be associated with spontaneous rupture and drainage or necrosis of the overlying skin, in the absence of concomitant BSI
Systemic infection
Infusate-related BSI
Concordant growth of the same organism from the infusate and blood cultures (preferably percutaneously drawn) with no other identifiable source of infection
Definite catheter-related BSI (i.e., the catheter is the proven source of infection)
One of the following should be present in addition to at least one peripheral positive blood culture:
1. A positive semiquantitative (≥ 15 cfu/catheter segment) or quantitative (≥ 1000 cfu/catheter segment) catheter culture, whereby the same microorganism (species and antibiogram) is isolated from the catheter segment and peripheral blood
2. Simultaneous quantitative blood cultures with a $>5:1$ ratio CVC vs. peripheral
3. Differential time to positivity of >2 hrs between peripheral and CVC blood culture positivity
4. Pus from the catheter exit site, growing the same microorganism as peripheral blood
Probable catheter-related BSI (i.e., the catheter is highly likely to be infected but criteria for definite infection are not met; catheter-associated BSI).
Either 1 or 2 should be met:
1. Clinical catheter-related sepsis: Positive (semi-) quantitative catheter tip or segment culture in a patient with clinical sepsis and no other apparent source than the catheter that resolves within 48 hrs of catheter removal in the absence of new antibiotic therapy
2. Bacteremia/fungemia: At least two positive blood cultures, including one peripheral) with a common skin commensal (e.g., diphtheroids, <i>Bacillus</i> spp., <i>Propionibacterium</i> spp., coagulase-negative staphylococci, or micrococci), in a patient with an intravascular catheter and clinical manifestations of infection (i.e., fever, chills, and/or hypotension), in the absence of catheter segment culture and no apparent source for the BSI except the catheter (e.g., so-called “primary bacteremia”)
Possible catheter-related BSI (i.e., cannot rule in or out a catheter-related infection). Either 1 or 2 should be met:
1. Clinical catheter-related sepsis: Positive (semi-) quantitative catheter tip or segment culture in a patient with clinical sepsis and no other apparent source than the catheter that resolves after catheter removal and initiation of antibiotic therapy
2. Bacteremia/fungemia: At least one positive blood culture, either through the catheter or peripheral, with a common skin commensal (e.g., diphtheroids, <i>Bacillus</i> spp., <i>Propionibacterium</i> spp., coagulase-negative staphylococci, or micrococci), in a patient with an intravascular catheter and clinical manifestations of infection (i.e., fever, chills, and/or hypotension), in the absence of catheter segment culture and no apparent source for the BSI except the catheter (e.g., so-called “primary bacteremia”)

cfu, colony-forming units; BSI, bloodstream infection; CVC, central venous catheter.
Adapted from Ref. 6. Other sources reviewed include Refs. 3 and 5.

probability that the infection is related to the catheter. The majority of CRBSI occurs in the absence of local symptoms, so it will be uncommon for a definite to highly probable diagnosis to be made on clinical presentation alone.

Ideally, when bacteremia occurs in a patient having an indwelling catheter and no other obvious source is identified (e.g., pulmonary, urinary tract, abdominal, surgical site), confirmation of whether bacteremia originates from the catheter (i.e., is "catheter-related") or is secondary to another source must be sought. This is done by taking appropriate cultures, which may or may not require catheter removal. A clinical suspicion of catheter infection in the presence of otherwise unexplained septic shock, however, should prompt catheter removal (if possible) and appropriate cultures of the catheter tip (i.e., quantitative or semiquantitative catheter segment culture), blood cultures (at least one peripheral and simultaneously one central blood culture), and exit site or hub cultures depending on the presentation. The feasibility of treating the catheter *in situ*, for which outcome data in children in septic shock are sparse, must be weighed against the possibility of harm from a new catheter insertion.

In definitions used for CRBSI surveillance purposes, all bacteremia originating from patients who have a CVC in place and no other identifiable source of infection are classified as "primary" bacteremia, probably/possibly catheter-associated. These patients currently fit under the Probable and Possible catheter-related bacteremia definitions in Table 1. This definition is sensitive but nonspecific. For the purposes of categorizing patients enrolled in sepsis trials as to the source of infection, only patients meeting criteria for definite CRBSI (Table 1) should be categorized as CRBSI. The most challenging problem that arises when evaluating a patient with possible CRBSI is ascribing a sepsis syndrome to catheter infection when bacteremia is due to a common skin commensal and only one positive blood culture (central or peripheral) is available or has been obtained. In this situation, repeat cultures, with culture of the catheter tip, must be performed to confirm CRBSI. The likelihood of CRBSI will depend on the microorganism, the number of bottles taken in a set, antibiotic exposure, and the clinical picture. Confirmation that the catheter is the true source of

infection requires that the criteria in Table 1 are met. When such information is not available for technical reasons (lack of cultures, defective processing), the positive blood culture arose from external contamination during collection of the sample or represents colonization of the catheter, or the infection is viewed as true bacteremia and no other source has been identified, the patient can only be categorized as probable or possible CRBSI (i.e., catheter-associated bloodstream infection).

The following clinical scenario is defined as "probable CRBSI," that is, clinical catheter-related sepsis. This diagnosis is usually made in retrospect, since it requires a positive (semi-) quantitative catheter tip or segment culture in a patient with clinical sepsis and no apparent source other than the catheter and the sepsis resolves within 48 hrs of catheter removal in the absence of new antibiotic therapy.

In reality, few physicians will wait to start or broaden antibiotics in a patient who shows signs of severe sepsis in an ICU. Therefore, this definition is problematic to use clinically as it would be difficult to confirm whether the sepsis would have resolved simply with catheter removal except in mild (nonsevere), hemodynamically stable patients with sepsis who can easily have the catheter replaced at a new site. It is important also to note that use of antibiotics either bonded to the catheter or systemically through the catheter may decrease the sensitivity of the catheter tip culture.

In summary, when enrolling patients in sepsis trials, it is important to identify patients with severe sepsis or septic shock with evidence of bloodstream infection. When a patient presents with signs of systemic inflammation and has a CVC in place and no other identifiable source of infection, it cannot be assumed that the patient has a catheter-related infection. Confirmation of catheter-related infection most often comes days later when appropriate diagnostic tests results become available. In the absence of cultures, only in those specific uncommon clinical situations described previously can a patient with presumed catheter-related sepsis be enrolled in a trial designed to evaluate agents to treat sepsis. For example, an oncology patient with an implanted CVC who presents with a tunnel infection, fever, shock, and no other infection source should be eligible for a sepsis trial. A toddler with fever, in-

creased white blood count, blood pressure instability, a central catheter in place for more than a week, and no identified source of infection may or may not have a catheter-related infection and, without a clearly identified infection, should not be enrolled in a sepsis trial. Another issue with enrolling patients with catheter-related infections in a sepsis trial is that device-related infections are somewhat different from other categories of infections such as pneumonia and meningitis, in that the infection may resolve quickly after the infected device is removed. This must be taken into account *a priori* by investigators designing sepsis trials.

For the purpose of identifying infections for epidemiologic and surveillance purposes, the consensus clinical definitions listed in Table 1 also apply. Catheter-associated bloodstream infection (probable or possible CRBSI) must be clearly differentiated from definite CRBSI. The majority of published surveillance studies in infants and children have reported rates of catheter-associated bacteremia. The true incidence of CRBSI in subpopulations of children is currently not known. As discussed later, various techniques for culturing the intravascular catheter segment can be used. These techniques have different sensitivities and specificities. It is important, for epidemiologic studies, that the techniques used across the hospitals enrolling patients be clearly specified and, optimally, standardized.

For the purpose of identifying infections for diagnosis and optimal therapy, the discussion points that follow should be noted regarding use of various diagnostic strategies to identify catheter-related infections. These points are excerpted from Mermel et al. (3), from the Centers for Disease Control and Prevention HICPAC guidelines (6), and from other sources.

Clinical Diagnosis

Clinical findings are unreliable for establishing a diagnosis of intravascular device-related infection, because of their poor specificity and sensitivity (11). For example, the most sensitive clinical findings, such as fever with or without chills, have poor specificity. Inflammation or purulence around the intravascular device and bloodstream infection have greater specificity but poor sensitivity (12). Blood culture results that are posi-

tive for *Staphylococcus aureus*, coagulase-negative staphylococci, or *Candida* species, in the absence of any other identifiable source of infection, increase the suspicion for CRBSI, but to confirm catheter-related infection, one must perform a peripheral culture paired with a catheter tip culture or blood culture through the catheter (3,4).

Rapid Diagnostic Techniques

These are not routinely used and are available mainly for research purposes. Gram-negative stain of blood drawn through the catheter hub may be helpful for the diagnosis of CRBSI, but it is significantly less sensitive than quantitative methods for the diagnosis of catheter-related infections (13). In one study, use of acridine orange stains for rapid diagnosis resulted in a positive predictive value of 91% and a negative predictive value of 97% (14). There are no data on the sensitivity of Gram-negative stain in children where smaller aliquots of blood are routinely used. Use of the bacterial 16S recombinant RNA gene using a polymerase chain reaction assay has been shown to have a sensitivity of 96%, specificity of 99.4%, and high positive and negative predictive value in neonates using blood volumes as small as 200 μ L with a turnaround time of as low as 9 hrs (15). For the diagnosis of fungal infections, buffy coat direct fluorescent antibody, buffy coat polymerase chain reaction, and buffy coat culture have been shown to be more sensitive than blood culture in laboratory studies (16,17). At this time, it is not clear how these rapid diagnostic techniques apply to the diagnosis of CRBSI in the child with sepsis.

Culturing Methods

Cultures of Samples of Intravascular Catheters. Laboratory criteria for the diagnosis of intravascular catheter-related infections are precise, but differences in the definitions and methodologies used in various studies have made data difficult to compare (4,18).

1. The most widely used laboratory technique for the clinical diagnosis of catheter-related infection is the semiquantitative method, in which the catheter segment is rolled across the surface of an agar plate and colony-forming units (cfu) are counted after overnight incubation (19).
2. Quantitative culture of the catheter

segment requires either flushing the segment with broth, vortexing, or sonicating it in broth, followed by serial dilutions and plating on blood agar (20).

A yield of ≥ 15 cfu from a catheter by means of semiquantitative culture, or a yield of ≥ 1000 cfu from a catheter by means of quantitative culture with accompanying signs of local or systemic infection, is indicative of catheter-related infection (4). In a prospective study that compared the sonication, flush culture, and roll plate methods, the sonication method was 20% more sensitive for the diagnosis of catheter infection than was the roll plate method, and it was 120% more sensitive than the method of flushing the individual catheter lumens (21). If only CRBSIs are considered, the sensitivities of the three methods are as follows: sonication, 80%; roll plate method, 60%; and flush culture, 40–50%. Summary receiver operating characteristic curve analysis has been recommended as a potentially more rigorous method for comparing the accuracy of different diagnostic tests for the same condition, because a given test may have one sensitivity at a given specificity and a different sensitivity at another specificity. Receiver operating characteristic curve analysis plots the true-positive rate against the false-positive rate for the different possible cut points of a diagnostic test, therefore showing the tradeoff between sensitivity and specificity. Using receiver operating characteristic curve analysis, a meta-analysis confirmed that quantitative cultures of catheter segments were more accurate than were the roll plate and qualitative methods (22). At this time, it is unclear whether any of these differences are clinically significant. The predictive value of quantitative or semiquantitative culture methods may vary depending on the type and location of the catheter, the culture methodology used, and the source of catheter colonization. For example, a recently inserted catheter (duration of placement < 1 wk) is most commonly colonized by a skin microorganism along the external surface of the catheter, and the roll plate method will be quite sensitive in the identification of such colonization. For longer dwelling catheters (duration of placement > 1 wk), in which intraluminal spread from the hub may be the dominant mechanism for catheter colonization, the roll plate method is less sensitive, and methods

that obtain samples of both the internal and external surfaces for culture are more sensitive (23). As use of antimicrobial-coated catheters becomes more prevalent, the existing definitions of catheter colonization and catheter-related infection may need to be modified, because such coatings may lead to false-negative culture results (24).

Paired Cultures of Blood Drawn Through the Catheter and Percutaneously. Patients with suspected intravascular catheter-related infection should have two sets of blood samples drawn for culture, with at least one set drawn peripherally. The clinical usefulness of cultures of blood samples drawn from an indwelling CVC was assessed in a study of hospitalized patients with cancer (25). In the study, the positive predictive value of catheter and peripheral blood cultures was 63% and 73%, respectively, and the negative predictive value was 99% and 98%, respectively. Therefore, a positive culture result for a blood sample drawn through a catheter requires clinical interpretation, but a negative result is helpful for excluding CRBSI. In infants and children, one must bear in mind the lower sensitivity of small volume blood cultures. If the culture is positive, antibiotics should be started and paired cultures should then be sent along with the catheter tip if the catheter is removed. If the culture is negative, it may be possible to withhold antibiotics in the child in the ICU if the child is otherwise stable, but one cannot completely rule out CRBSI with one set of cultures, and repeated cultures must be sent if symptoms recur.

Quantitative Cultures of Peripheral and CVC Blood Samples. Quantitative blood culturing techniques have been developed as an alternative for the diagnosis of catheter-related bloodstream infection in patients for whom catheter removal is undesirable because of limited vascular access. This technique relies on quantitative culture of paired blood samples, one of which is obtained through the central catheter hub and the other from a peripheral venipuncture site. In most studies, when blood obtained from the CVC yielded a colony count at least five- to ten-fold greater than that for blood obtained from a peripheral vein, this was predictive of CRBSI (26). Among tunneled catheters, for which the method is most accurate, a quantitative culture of blood from the CVC that yields ≥ 100 cfu/mL may be diagnostic without a companion culture of a peripheral blood sam-

ple. Franklin and colleagues (27) showed that in immunocompromised children with a single- or double-lumen CVC, CRBSI can be diagnosed when culture of blood from the CVC yielded ≥ 100 cfu/mL with sensitivity, specificity, positive predictive value, and likelihood ratio of 75.5, 69.1, 79.3, and 2.44, respectively. Using a greater than five-fold difference in cfu/mL between two lumens of a CVC as a definition, the sensitivity, specificity, positive predictive value, and likelihood ratio were 61.8, 93.3, 92.2, and 9.22, respectively.

Differential Time to Positivity for CVC Vs. Peripheral Blood Cultures. This new method, which correlates well with quantitative blood cultures, makes use of continuous blood culture monitoring for positivity and compares the differential time to positivity for qualitative cultures of blood samples drawn from the catheter and a peripheral vein. When studied with tunneled catheters, this method has offered accuracy comparable to that of quantitative cultures of blood samples and has had greater cost-effectiveness (28, 29). In a study of differential time to positivity, a definite diagnosis of catheter-related bacteremia could be made in 16 of the 17 patients who had a positive result of culture of a blood sample from the CVC ≥ 2 hrs earlier than they had a positive result of a peripheral blood culture; the overall sensitivity was 91% and specificity was 94% (28). This technique has also been validated in immunocompromised pediatric patients with tunneled catheters (30) and in critically ill cancer patients (31). In ICU patients, this method may require further validation as one ICU study showed no difference in time to positivity in patients with confirmed CRBSI and non-catheter-related bloodstream infection (32). Most hospitals do not have quantitative blood culture methodologies, but many will be able to use differential time to positivity for diagnosis.

Microorganism Identification

Skin commensals such as *Staphylococcus epidermidis* can contaminate a peripheral blood culture if adequate sterile technique is not used. It is important to distinguish contamination from actual infection. To do so usually requires comparison of genotypes of the actual organisms to ensure that both the peripheral and central cultures are growing the same organism (33). If the genotypes are

not confirmed, then catheter-related sepsis is not bacteriologically confirmed. Antibiotograms can also be used but are less specific; organisms with the same genotype should also have the same antibiotogram. Genotyping of organisms is recommended, when possible, to confirm CRBSI when both cultures are growing the same species of organism.

Infusate-Related Bloodstream Infection

Infusate-related bloodstream infection is uncommon and is defined as the isolation of the same organism from both infusate and separate percutaneous blood cultures, with no other source of infection. The sudden onset of symptoms of bloodstream infection soon after the initiation of an infusion, resulting from the administration of contaminated intravascular fluid, is often diagnostic (18). When this diagnosis is suggested, cultures of the infusate fluid should be part of an investigation of potential sources of infection. If the patient is in septic shock or has severe sepsis, the Gram-negative stain of the infusate may be positive. The fluid itself can be cultured by filtering it through a 0.22- μ filter and culturing the filter, or by taking 10 mL of fluid and putting it into concentrated broth of similar volume. Infusate-related infections are infrequent but can come from a contaminated lot and may result in a local epidemic that infects multiple patients.

CONCLUSIONS

For the purposes of enrolling patients with sepsis in clinical trials, only patients who meet criteria for definite CRBSI should be categorized as having the catheter as the infection source. Because many patients suspected of having CRBSI do not have positive blood culture results, thereby making the confirmation of infection difficult, we recommend that these patients not be enrolled in sepsis trials. There are only a few uncommon clinical presentations, which we have described, in which patients can be identified before cultures results are known as having a high probability of intravascular catheter-related sepsis. Because catheter tips are often not obtained for culture in children, the epidemiology of catheter-associated bloodstream infection is better understood than catheter-related bloodstream infection in infants and children. There is an urgent need for more re-

search in children to determine the test characteristics and positive and negative predictive values of clinical presentations and laboratory tests in critically ill children. When diagnosing an infection related to an indwelling catheter, clinicians should adhere to accepted definitions. They should also be aware of the sensitivity, specificity, and predictive values of the diagnostic strategies employed. Given the difficulty in obtaining catheter tip and peripheral blood cultures in children, the performance characteristics of diagnostic techniques that compare quantitative cultures between two lumens of a CVC (26), calculate the time to positivity (28, 29), or use a cutoff such as 100 cfu/mL from a single lumen (27) are promising but require further study in critically ill infants and children.

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