Fourth, for the statistical analysis, the authors use all catheters "infections confirmed" and "infections probable" in a single data pool.

These methodological flaws result in unreliable results, particularly those concerning the clinical significance of a positive skin culture and the discordance between clinical findings (temperature) and microbiological results. Thus, we cannot agree with the following conclusion written in the abstract: "Another source of fever is likely if inflammation is absent and there is...colonization by less than 50 colonies of coagulase-negative staphylococci at the insertion site." This approach would dismiss the catheter as cause of fever in all patients with hub-related catheter sepsis.

In our experience (unpublished observations), the sensitivity and specificity of surveillance skin cultures are too low to recommend their routine use. Furthermore, study protocols on catheter sepsis should incorporate means to detect endoluminal catheter contamination in order to properly identify those catheters infected through the hub.[4]

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The authors were asked to respond to this letter

We are pleased to respond to the comments of Drs. Segura and Sitges-Serra. First, we will respond to their methodological concerns, and then we will address the mechanism by which catheter infections develop as it relates to their comments about our conclusions.

The first concern was the criteria we used for catheter removal. These criteria have been published in a related article.[1] The second concern was the method used to remove the catheters to avoid contamination during withdrawal of the catheters. We state in the methods section that "the insertion site was cultured and then cleaned with an alcohol pledget. The catheter was withdrawn at a right angle to the skin to prevent contamination on removal." Alcohol also has been used by other investigators to cleanse the skin prior to catheter removal.[2-5]

Next, we will respond to the fourth comment and then discuss their third comment below when we examine the data on the pathogenesis of catheter infections. Drs. Segura and Sitges-Serra suggest that combining confirmed catheter infections and probable catheter infections could lead to unreliable results. We disagree with this comment. The only difference between confirmed catheter infections and probable catheter infections was that the latter were removed accidently. They were cultured promptly using the same technique. To compensate for possible contamination of these catheters during accidental withdrawal, we set the cutoff for colony counts at more than three times the criterion used for catheters removed under controlled conditions (50 rather than 15).

As stated in the discussion, we showed in a related publication that it was highly likely that these catheters were infected.' First, the lowest colony count on semiquantitative culture of catheters in the group with probable infections was 163. Second, the median colony counts for catheters with confirmed and probable infections were similar (>400 and >310, respectively), and the median colony count for uninfected catheters was zero. Thus, there was a wide margin between the median colony counts for catheters with confirmed and probable infections and catheters that were uninfected. Third, six of the isolates recovered on semiquantitative culture of the catheters with probable infections are common causes of catheter infection, and the catheter infected with *Serratia marcescens* yielded confluent growth on semiquantitative culture. For these reasons, we feel that pooling the catheters with confirmed infection and those with probable infection was entirely appropriate.

The remainder of the comments by Drs. Segura and Sitges-Serra relate to the pathogenesis of intravascular catheter infections. They contend that endoluminal catheter contamination by microorganisms that enter at the catheter hub is an important pathogenetic mechanism for infection of intravascular catheters. They state that failure to take this mechanism into account in our study invalidates our conclusions.

We strongly disagree. The overwhelming bulk of the evidence published in the literature supports migration of microorganisms on the skin surface into the subcutaneous catheter tract with extension to the fibrin sheath on the intravascular portion of the catheter as the primary pathogenetic mechanism for development of intravascular catheter-

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related infection. These studies have been published by many different investigators working in a variety of institutions in different geographic areas. On the other hand, studies implicating endoluminal contamination with spread of microorganisms down the lumen to the fibrin sheath on the intravascular portion of the catheter have, with few exceptions, been done only by Drs. Segura and Sitges-Serra and their co-workers.[6-12] Maki and Ringer cultured catheter hubs in a study of the effect of different types of dressings applied to the catheter site.[13] Although they found an association between positive hub cultures and catheter infection, they rarely found more than ten colony-forming units in any catheter hub. These authors concluded that most catheter infections occurred by migration of microorganisms into the catheter tract from the skin and listed eight categories of data that support this pathogenetic mechanism for catheter infection. Flowers and co-workers could implicate the hub as a source for catheter infection in only 8.3% of their patients.[14] Stotter and colleagues concluded that the catheter hub was the source of catheter infection in their patients.[15] They reported a drop in catheter infection rates from 39% to 8% after instituting new procedures to protect the hub from contamination. However, their conclusions may not have been valid, because they simultaneously changed to a new type of catheter (Broviac-type silicone rubber catheter), which was tunneled and had a Dacron cuff to block ingress of microorganisms into the catheter tract from the skin.

There are other weaknesses in this hypothesis. Drs. Segura and Sitges-Serra and their colleagues have reported difficulty in recovering bacteria on skin cultures taken at the catheter site.[7-10] This conflicts with other studies in which microorganisms were recovered from the skin at the catheter sites of many patients.[13,14,16-19] Dr. Sitges-Serra was the coauthor of an article in which it was suggested that coagulase-negative staphylococci from skin may be different from those on the catheter, and stated that there is no proof that coagulase-negative staphylococci recovered from skin and catheters are the same microorganisms.[20] However, in a study of peripheral intravenous catheters, Francioli and associates showed that microorganisms cultured from catheters correlated much better with the microorganisms recovered from skin than with those cultured from hubs.[21] Dr. Sitges-Serra cites the failure of tunneling to prevent catheter sepsis as evidence against migration of microorganisms from the skin surface into the catheter tract as the pathogenetic mechanism for catheter infection.[20] However, this argument conflicts with the apparent success of tunneling and incorporation of a Dacron cuff to block ingress of microorganisms into the subcutaneous tract in protecting catheters used for long-term venous access.

Another problem with the hub hypothesis is the absence of data on the source of microorganisms that contaminate the hub and the mode of transmission of microorganisms to the hub. Is hub contamination a random event or perhaps an epiphenomenon? Dr. Sitges-Serra and coworkers did a study of the effect of tubing changes on catheter infection rates when tubing was changed every two or four days rather than changed every day. They concluded from these data comparing study patients with historic controls that catheter hubs were contaminated during tubing changes.

One of the most diicult prob lems with the hub hypothesis has been trying to resolve the conflict between positive semiquantitative cultures of the external surfaces of catheters from patients with simultaneously positive cultures of the hubs.[8] Dr. Sitges-Serra and co-workers' failure to recover microorganisms from the skin does not, in our opinion, resolve this conflict in favor of hub contamination. In a recently published study using an experimental model, Drs. Segura and Sitgues-Serra observed that *Pseudomonas aeruginosa* was cultured from the hub of a catheter and the skin at the catheter site.[12] They postulated that "...the very mobile *P aeruginosa* may have reached the skin surface after extraluminal backwards migration from the tip by the capillary action of the catheter." Whether applied to an animal model or a clinical model, there are no data to support such a hypothesis. This hypothesis would require that microorganisms that contaminate the hub migrate down the lumen of the catheter, migrate to the fibrin sheath on the external surface of the catheter, and then migrate, against the direction of blood flow, to a point many centimeters upstream where the catheter penetrates the wall of the vein. This would have to be followed by migration of the microorganisms into and through the catheter tract to the surface of the skin. There is also the problem of the authors' observation that most of their infected catheters have microorganisms recovered from the external surfaces on semiquantitative culture.

The data in support of the migration of microorganisms from the skin surface into the subcutaneous tract as the primary pathogenetic mechanism for intravascular catheter infec-

tions are overwhelming compared with the data in support of the hub hypothesis. First, in addition to our article, there are six studies showing a relationship between colonization of the skin at the catheter site and subsequent catheter infection.[13,14,16-19] Five studies have shown a relationship between a positive semiquantitative catheter culture and catheter infection.[2,3,8,22,23] In a study in which catheter segments were cultured semiquantitatively and then gram-stained on removal, Cooper and Hopkins made an important observation in support of the skin- subcutaneous catheter tract pathogenesis of catheter infection.[23] They observed that catheters that were culture-positive on semiquantitative culture had microorganisms limited almost exclusively to the external surfaces of the catheters, and in the four catheters with microorganisms on both the external and lumenal surfaces, there were larger numbers of microorganisms on the external surface than on the lumenal surface. In addition, the large prospective study of Francioli and co-workers makes a strong case for the skin as the source of microorganisms that cause intravascular catheter-related infection.21 They found that microorganisms isolated from the external surfaces of colonized or infected peripheral intravenous catheters on semiquantitative culture were significantly more likely to correlate with isolates from skin than with isolates from the catheter hub.

Rounding out the evidence for migration of microorganisms on the skin into the catheter tract as the principal pathogenetic mechanism for intravascular catheter-related infections is the evidence that strategies designed to prevent ingress of microorganisms from the skin into the catheter tract are associated with significantly lower rates of infection. Thus, application of topical antimicrobial agents at the point where the catheter penetrates the skin has been associated with a significant decrease in catheter-related infections.[24,25] Finally, two studies of subcutaneous collagen catheter cuffs impregnated with silver ions designed to block the migration of microorganisms from the skin surface into the catheter tract have shown significant protection of catheters from infection when compared with controls.[14,19]

Given the evidence in favor of the migration of microorganisms from the skin surface into the subcutaneous catheter tract as the pathogenetic mechanism for intravascular catheter-related infection, we do not agree with the conclusions of Drs. Segura and Sitges-Serra from our study. In our opinion, the data supporting the hub hypothesis are too tenuous to necessitate inclusion of hub cultures in any study of intravascular catheter-related infections. The data and conclusions from our study are consistent with and extend the observations from the large number of studies from many different institutions that support the migration of microorganisms on the skin into the subcutaneous catheter tract as the pathogenetic mechanism by which catheter-related infections develop.

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