

Optimal Approach for the Diagnosis of Hemodialysis Catheter–Related Bacteremia

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Central venous catheter (CVC) use among patients on hemodialysis (HD) remains unacceptably high and is associated with an increased risk of all-cause infection, infection-related hospitalizations, and mortality (1–4). In CVC-dependent patients on HD who present with suspected infection (symptoms of fever, rigors, altered mental status, unexplained hypotension, or CVC exit site purulence) and in whom infection is confirmed by positive blood cultures, the CVC may be implicated as the probable source in approximately 80%–90% of patients, provided that clinical evaluation does not reveal an alternative source (5,6). In most United States outpatient HD units, concordant blood cultures are drawn from the CVC hub and the HD circuit when symptoms are present at the start of HD or two sets of blood cultures are both drawn from the HD circuit separated by a 15-minute period when symptoms are present during the HD session. It is not common practice to obtain peripheral vein cultures (PVCs) because of the desire to preserve future veins for vascular access or due to the presence of limited peripheral vein sites as a result of previous needle stick injury.

In the clinical setting, it is important to identify the CVC as the infectious source with a reasonable degree of certainty so that the appropriate CVC management strategy is applied (6–9). This real world definition of probable catheter–related bloodstream infection (CRBSI) is useful and practical for clinical practice. The definition of CRBSI in CVC-dependent patients on HD used for the purpose of study end points in clinical trials lacks uniformity in the existing nephrology literature. Many investigators defined HD CRBSI using the real world definition described above, whereas others categorized CRBSI as possible, probable, and definite, using varying criteria for each category (5,6,10–17). The most stringent criteria for defining definite CRBSI, published by the Infectious Disease Society of America (IDSA), has been required by the Federal Drug Administration for the approval of devices targeted for HD CRBSI prevention (7). This has resulted in blocking approval of devices that have met important clinical end points, such as bacteremia-free survival, when definite CRBSI measures have not been satisfied for the primary outcome (12). The updated 2009 IDSA guidelines define a definite CRBSI using one of three methods: (1) quantitative blood culture criteria, (2) differential time to positivity (DTTP)

criteria, or (3) obtaining concordant cultures from a peripheral vein and the CVC tip (7,18,19). All definite CRBSI definitions require that PVCs be obtained, preferably before antibiotics are administered, and the latter requires that the CVC be removed. Although the 2009 IDSA guidelines recognized the unique qualities of CVCs used for the provision of HD, the requirements for defining definite CRBSI are derived from data on CVCs used predominantly for chemotherapy infusion in patients with cancer. Quantitative cultures and DTTP have never been specifically tested in CVCs used for HD (7,8). Whether HD circuit–drawn blood cultures are appropriate surrogates to PVCs remains to be validated.

In this issue of the *Clinical Journal of the American Society of Nephrology*, Pelletier *et al.* (20) are the first to compare blood cultures drawn from CVC hubs, the HD circuit, and peripheral vein sites to evaluate the DTTP criteria in symptomatic patients on HD suspected of having CRBSI. To their credit, Pelletier *et al.* (20) designed a long-term study over a 2.5-year period that was meticulously implemented and elegantly analyzed. One of the major findings of the study is that blood cultures drawn from the HD circuit were superior in sensitivity, specificity, and accuracy compared with PVCs when all culture data and clinical information were factored into the assessment. The challenges of drawing PVCs in this HD population were evident; Pelletier *et al.* (20) reported that PVCs were successfully obtained in only 75% of suspected CRBSI events, and of these, 12% were drawn with difficulty. In addition, PVCs were more likely to be contaminated, whereas none of the HD circuit cultures were deemed contaminated by an independent subcommittee. Another important finding was that DTTP was not shown to be a reliable criterion because of the wide range of time to positivity in each blood culture category. Furthermore, the DTTP criteria used by the IDSA were met in only a minority of patients.

One of the important limitations of the study by Pelletier *et al.* (20) is that DTTP was not assessed in infections where an alternative (non-CVC) source was identified, thereby lacking appropriate negative controls. Furthermore, the number of events for which bacteria growth was detected in all or partial blood culture sets was small ($n=33$), and quantitative blood cultures were not evaluated. As postulated by Pelletier

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et al. (20), the active continuous two-way high-blood flow rate present in the dialysis circuit could theoretically lead to dilution of organisms in an infected catheter. One way to assess this theory is to perform quantitative blood culture sets before and at a prespecified time point after initiation of the HD procedure. That being said, there was no difference in the range of DTTP between culture sets obtained at earlier versus later time periods after HD initiation, and earlier culture sets obtained in the first 30 minutes of HD initiation were not associated with a higher likelihood of meeting the DTTP criteria.

Pelletier *et al.* (20), in their discussion, emphasize some of the barriers present in the HD setting that make meeting the definite CRBSI definition unrealistic. It is important to highlight the fact that performing DTTP was possible, because the study was performed in an in-center HD unit where there was a hospital-based venipuncture team on backup to assist with drawing PVCs. In countries like the United States, where 93% of HD units are free-standing units, the transport of blood cultures to a uniform laboratory in a timely fashion to satisfy the DTTP standards would be problematic and costly (18,21,22). The method of performing DTTP with the highest accuracy requires that blood cultures from the CVC hub and PVCs be drawn before antibiotic administration and transported immediately to a microbiology laboratory with an automatic culture detector (18,22). Additional obstacles are that trained phlebotomy teams are unavailable in free-standing HD units and that drawing PVCs may result in sclerosis of veins and jeopardize future HD vascular access sites. Paired quantitative blood cultures are the most accurate test for diagnosing CRBSI, and they require drawing cultures from both the CVC hub and a peripheral vein (19,22,23). Performing quantitative blood cultures is expensive, tedious, and associated with a high risk of contamination, and like the DTTP procedure, it requires proper processing in a microbiology laboratory (19,22,23). In one study, performed on CVCs used in the surgery-trauma intensive care unit, quantitative blood cultures were reported to be of low sensitivity and specificity, leading the investigators to conclude that they were of limited usefulness for the diagnosis of CRBSI (23). The use of quantitative blood cultures for CRBSI in the HD setting has not yet been validated.

Pelletier *et al.* (20) provide strong and convincing evidence that, in lieu of PVCs, HD circuit-derived blood cultures may be acceptable surrogates for defining CRBSI in CVC-dependent patients on HD. Furthermore, their DTTP findings are compelling and persuasively challenge the value of using DTTP in the outpatient HD setting. Until data from future well designed and adequately powered studies are available, the DTTP criteria seem insensitive and too widely variable to be reliably used to define CRBSI in HD CVCs. The findings of this study by Pelletier *et al.* (20) have a number of important additional implications. They underscore the need for critical appraisal and validation of the IDSA guidelines for diagnosis of CRBSI in CVC-dependent patients on HD. Future high-priority studies need to be conducted to validate the use and feasibility of the quantitative blood culture criteria for CRBSI in CVCs used for HD and determine if HD circuit cultures are appropriate surrogates for PVCs when comparing them with differential colony counts for CVC hub samples. In addition, the DTTP

results published by Pelletier *et al.* (20) should be confirmed using a larger number of suspected CRBSI events with positive blood cultures in all sets and include appropriate negative controls, such as CVC-dependent patients on HD with known non-CVC sources of bacteremia. It also highlights the need to establish standardized definitions for CRBSI in patients on HD which are agreed upon by a consensus of interested parties, including clinicians in nephrology, radiology, infectious diseases, and representatives of industry and federal regulators. To this end, the Kidney Health Initiative has been assembled by the American Society of Nephrology to establish a consensus around major definitions in HD vascular access. It is imperative that a compromise is reached with the goal of unifying end point definitions for HD CRBSI that are acceptable to all parties, so that future research in this field may continue to advance unhampered and result in much needed reductions in infection-associated morbidity and mortality in CVC-dependent patients on HD. This can only be achieved by identifying those diagnostic tools and procedures that are valid for CVCs used for HD and can be realistically implemented in the outpatient HD setting.

Disclosures

None.

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