CORRESPONDENCE

Complications of Central Venous Catheterization

TO THE EDITOR: The results of the randomized trial by Parienti et al. (Sept. 24 issue)¹ comparing insertion sites for central venous catheterization will help guide clinicians in their choice of sites. We were surprised, however, that the authors did not report the number of patients in each insertion-site group who were receiving positive-pressure ventilation. The increased positive end-expiratory pressure and large tidal volumes associated with mechanical ventilation can predispose a patient to the development of pneumothorax. Some evidence suggests that the risk of pneumothorax from subclavian-vein catheterization may be higher among patients receiving positive-pressure ventilation than among those not receiving it.² Without knowing how the outcomes are stratified according to ventilation status, it is hard to fairly assess the true risk profile of subclavian-vein access.

The authors correctly observe that “the cumulative risk of infectious and thrombotic complications increases with increasing catheter exposure.” We think the inference is worth stating more plainly: one means of preventing infectious complications from central venous catheterization is prompt removal of the catheter when it is no longer needed.³

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1. Parienti JJ, Mongardon N, Mégarbane B, et al. Intravascular complications of central venous catheterization by insertion site. *N Engl J Med* 2015;373:1220-9.

2. Vinson DR, Ballard DW, Hance LG, et al. Pneumothorax is a rare complication of thoracic central venous catheterization in community EDs. *Am J Emerg Med* 2015;33:60-6.

3. McGee DC, Gould MK. Preventing complications of central venous catheterization. *N Engl J Med* 2003;348:1123-33.

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TO THE EDITOR: We are concerned with the reporting by Parienti and colleagues of central-catheter-associated bloodstream infections with the use of *Medical Dictionary for Regulatory Activities* definitions. These rates are inconsistent with contemporaneous American and Australian data on central-catheter-associated bloodstream infections defined according to the Centers for Disease Control and Prevention (CDC).^{1,2}

Data from the Victorian Healthcare Associated Infection Surveillance System, based on 303,968 days of central venous catheter use at 29 intensive care units (ICUs) from 2009 through 2013, showed the statewide rate of catheter-associated bloodstream infections to be 1.26 per 1000 catheter-days.² This is approximately 60% of the aggregate 2.0 bloodstream infections per 1000 catheter-days reported in the 3SITES trial by Parienti et al.

Our institution is a typical Australian tertiary referral center. Local protocols for the insertion of central venous catheters mandate the following: skin preparation with topical chlorhexidine, chlorhexidine-impregnated catheters, and ultrasonographic guidance.³ The rate of central-catheter-associated bloodstream infections in local ICUs is 1.1 per 1000 catheter-days overall. Moreover, the rate of attributable iatrogenic pneumothorax in our ICU was 0 per 2221 insertions of central venous catheters from 2013 through 2015. We suggest that the findings of

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the 3SITES trial are of limited external validity to jurisdictions and sites that apply the above catheter-insertion principles and different definitions of central-catheter-associated bloodstream infections.

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1. Climo MW, Yokoe DS, Warren DK, et al. Effect of daily chlorhexidine bathing on hospital-acquired infection. *N Engl J Med* 2013;368:533-42.
2. Worth LJ, Spelman T, Bull AL, Brett JA, Richards MJ. Central line-associated bloodstream infections in Australian intensive care units: time-trends in infection rates, etiology, and antimicrobial resistance using a comprehensive Victorian surveillance program, 2009–2013. *Am J Infect Control* 2015;43:848-52.
3. Australian and New Zealand Intensive Care Society Safety and Quality Committee. Central line insertion and maintenance guideline. Melbourne, VIC, Australia: ANZICS, 2012 (http://www.anzics.com.au/Downloads/ANZICS_Insertion&maintenance_guideline2012_04.pdf).

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TO THE EDITOR: The 3SITES trial provides site-specific complication rates after central venous catheterization and suggests the preferential use of the subclavian vein in critical illness. Not considered, however, are long-term complications, which might influence the choice of site, particularly in the subgroup of patients who are likely to require long-term dialysis.

Chronic central-vein stenosis is asymptomatic in many persons but leads to malfunction of surgically created arteriovenous fistulae in patients receiving dialysis, in whom it often recurs after venoplasty. Central-vein stenosis is particularly associated with catheters in the subclavian vein (as opposed to the internal jugular or femoral vein),^{1,2} regardless of catheter size, even after short-term use.³

This is of relevance to a growing proportion of patients: between 1996 and 2010, the percentage of critically ill patients who initiated dialysis during intensive care increased by a factor of almost 4, with up to a quarter of surviving patients remaining permanently dependent on dialysis.⁴ The subclavian venous site may provide short-term benefits, but in those who may face permanent renal failure, this site has longer-term disadvantages that need consideration.

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1. Hernández D, Díaz F, Rufino M, et al. Subclavian vascular access stenosis in dialysis patients: natural history and risk factors. *J Am Soc Nephrol* 1998;9:1507-10.
2. Schillinger F, Schillinger D, Montagnac R, Milcent T. Post catheterisation vein stenosis in haemodialysis: comparative angiographic study of 50 subclavian and 50 internal jugular accesses. *Nephrol Dial Transplant* 1991;6:722-4.
3. Cimochoowski GE, Worley E, Rutherford WE, Sartain J, Blondin J, Harter H. Superiority of the internal jugular over the subclavian access for temporary dialysis. *Nephron* 1990;54:154-61.
4. Wald R, McArthur E, Adhikari NKJ, et al. Changing incidence and outcomes following dialysis-requiring acute kidney injury among critically ill adults: a population-based cohort study. *Am J Kidney Dis* 2015;65:870-7.

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TO THE EDITOR: In the trial reported by Parienti and colleagues, the authors conclude that subclavian catheterization was associated with a higher risk of pneumothorax than was jugular or femoral catheterization. We believe that this conclusion concerning the pneumothorax rate cannot be generalized to other ICUs for a number of reasons: both French and U.S. guidelines recommend the use of the ultrasonography-guided technique for all sites, but only 15% of the subclavian procedures in the present trial were performed with ultrasonographic guidance^{1,2}; it cannot be ruled out that the ultrasonography-guided technique was preferentially chosen by operators in patients who presented with risk factors for pneumothorax (e.g., obesity or emphysema); and the incidence of pneumothorax in subclavian procedures reported here was 1.5%, whereas in studies using ultrasonography-guided subclavian procedures, the rate was between 0 and 0.2%, similar to the pneumothorax rate reported in the jugular site in the present trial.^{3,4} For all these reasons, the authors' conclusion that subclavian procedures are associated with an increased risk of pneumothorax pertains only to physicians using the nonrecommended landmark technique.

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1. Haute Autorité de Santé. Check-list: pose d'un catheter

veineux central (CVC) ou autre dispositif vasculaire (DV) (http://www.has-sante.fr/portail/upload/docs/application/pdf/2011-01/11_01_check-list-cvc-dv.pdf).

2. O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. *Am J Infect Control* 2011;39:Suppl 1:S1-34.
3. O'Leary R, Ahmed SM, McLure H, et al. Ultrasound-guided infraclavicular axillary vein cannulation: a useful alternative to the internal jugular vein. *Br J Anaesth* 2012;109:762-8.
4. Fragou M, Gravvanis A, Dimitriou V, et al. Real-time ultrasound-guided subclavian vein cannulation versus the landmark method in critical care patients: a prospective randomized study. *Crit Care Med* 2011;39:1607-12.

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TO THE EDITOR: Parienti et al. report catheter-related infectious and thrombotic complications of central venous catheterization according to insertion site. They chose compression ultrasonography as the diagnostic standard for deep-vein thrombosis (DVT). Although compression ultrasonography alone has efficacy that is similar to that of combined-method ultrasonography (color Doppler ultrasonography combined with compression ultrasonography) in diagnosing DVT in the legs,¹ this might not be the case for DVT in the arms. The vascular insertion site of subclavian-vein catheterization is usually located beneath the clavicle, which makes it difficult for the site to be visualized or compressed with compression ultrasonography. Color Doppler ultrasonography has been shown to be more sensitive and accurate than compression ultrasonography in diagnosing DVT in the arms.² The American College of Chest Physicians guidelines also suggest initial evaluation with combined-method ultrasonography over other initial tests in patients with suspected DVT in the arms.³ Using compression ultrasonography alone to diagnose subclavian-vein thrombosis might lead to underestimation of the event rate.

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No potential conflict of interest relevant to this letter was reported.

1. Poppiti R, Papanicolaou G, Perese S, Weaver FA. Limited B-mode venous imaging versus complete color-flow duplex venous scanning for detection of proximal deep venous thrombosis. *J Vasc Surg* 1995;22:553-7.
2. Prandoni P, Polistena P, Bernardi E, et al. Upper-extremity deep vein thrombosis. Risk factors, diagnosis, and complications. *Arch Intern Med* 1997;157:57-62.
3. Bates SM, Jaeschke R, Stevens SM, et al. Diagnosis of DVT: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141:2 Suppl:e351S-418S.

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TO THE EDITOR: Parienti et al. report that use of the subclavian site for catheter insertion was associated with lower risks of infection and thrombosis but a higher risk of pneumothorax than use of the jugular or femoral sites. Although these results may be explained by the choice of anatomical site alone, there are other factors of equal or greater importance. Rates of ultrasonographic guidance for catheter insertion were low, which could explain the reported rates of insertion failure, hematoma, and pneumothorax. Systematic reviews show that the use of ultrasonographic guidance for central venous cannulation is associated with fewer complications than without such guidance.^{1,2} Chlorhexidine skin preparation was used less than 50% of the time, and chlorhexidine-impregnated dressings were not used.³ Less than 60% of the catheters were removed when no longer required. Appropriate indications for central-venous-catheter placement, the use of insertion bundles, proper catheter care (including the use of chlorhexidine-impregnated dressings),⁴ daily needs assessment, and prompt removal of catheters when no longer needed may be more important than the insertion site.

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1. Brass P, Hellmich M, Kolodziej L, Schick G, Smith AF. Ultrasound guidance versus anatomical landmarks for internal jugular vein catheterization. *Cochrane Database Syst Rev* 2015;1: CD006962.
2. Brass P, Hellmich M, Kolodziej L, Schick G, Smith AF. Ultrasound guidance versus anatomical landmarks for subclavian or femoral vein catheterization. *Cochrane Database Syst Rev* 2015;1: CD011447.
3. Mimoz O, Lucet JC, Kerforne T, et al. Skin antisepsis with chlorhexidine-alcohol versus povidone iodine-alcohol, with and without skin scrubbing, for prevention of intravascular-catheter-related infection (CLEAN): an open-label, multicentre, randomised, controlled, two-by-two factorial trial. *Lancet* 2015;386:2069-77.
4. Safdar N, O'Horo JC, Ghufuran A, et al. Chlorhexidine-impregnated dressing for prevention of catheter-related bloodstream infection: a meta-analysis. *Crit Care Med* 2014;42:1703-13.

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THE AUTHORS REPLY: Vinson et al. raise the issue of ventilation status. The majority of catheterizations were performed with positive-pressure ventilation (2859 of 3471 [82.4%]) and positive end-expiratory pressure (PEEP) ventilation (2676 of 3471 [77.1%]). The higher risk of pneumothorax

associated with the use of PEEP than with non-use is difficult to assess, because the PEEP was turned off at the inserter's discretion during catheterization.

In response to Urbancic et al.: we used a rigorous definition of catheter-related bloodstream infection,¹ not the less accurate surveillance definition of central-catheter-associated bloodstream infection to which they refer. The former definition requires specific laboratory testing in order to unambiguously identify the catheter as the source of the bloodstream infection, whereas the latter definition indicates a bloodstream infection that occurred in the presence of a central catheter or within 48 hours after its removal, without any obvious other cause except the catheter. The low incidence of central-catheter-associated bloodstream infection that they report may relate to a different case mix or the use of chlorhexidine-coated catheters, which were not used in our trial. Given their low rate of pneumothorax, they could decrease further their incidence of central-catheter-associated bloodstream infection by adding the CDC and Australian and New Zealand Intensive Care Society guidelines recommendation "prefer the subclavian site" to their local protocol.

The risk of subclavian-vein stenosis² described by Corbett and Ashby has been associated with dialysis catheters. We excluded these devices.

Maizel and Slama may have misinterpreted the guidelines for catheterization³ in the subclavian vein, which state, "We suggest that ultrasound dynamic guidance is of limited value for most operators to guide subclavian-vein catheterization in adult patients (and that landmark technique is used instead)." Our multicenter trial reflects current real-world practice in France, with ultrasonography used at the discretion of the operator.

Keng informs us about the sensitivity of compression ultrasonography to diagnose subclavian DVT. The rate of Doppler-defined subclavian DVT ranged from 2 cases per 107 catheters (1.9%) to 8 cases per 123 catheters (6.5%) in previous trials,⁴ and we found a rate of 21 cases per 401 catheters (5.2%).

We agree with Bauer and colleagues that factors other than the insertion site can influence the risk of intravascular complications, but the site access was randomized. The CDC guidelines available when our trial was initiated¹ stated, "No comparison has been made between using chlorhexidine preparations with alcohol and povidone-iodine in alcohol to prepare clean skin. Unsolved issue." The results of the CLEAN trial⁵ were not available when we initiated or conducted our trial. Nevertheless, the incidence of catheter-related bloodstream infections in that trial was similar with chlorhexidine preparations and povidone-iodine preparations ($P=0.51$) for central venous catheters.

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Since publication of their article, the authors report no further potential conflict of interest.

1. O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. *Am J Infect Control* 2011;39:Suppl 1:S1-34.
2. Parienti JJ, Thirion M, Mégarbane B, et al. Femoral vs jugular venous catheterization and risk of nosocomial events in adults requiring acute renal replacement therapy: a randomized controlled trial. *JAMA* 2008;299:2413-22.
3. Frankel HL, Kirkpatrick AW, Elbarbary M, et al. Guidelines for the appropriate use of bedside general and cardiac ultrasonography in the evaluation of critically ill patients — part I: general ultrasonography. *Crit Care Med* 2015;43:2479-502.
4. Ge X, Cavallazzi R, Li C, Pan SM, Wang YW, Wang FL. Central venous access sites for the prevention of venous thrombosis, stenosis and infection. *Cochrane Database Syst Rev* 2012;3:CD004084.
5. Mimos O, Lucet JC, Kerforne T, et al. Skin antisepsis with chlorhexidine-alcohol versus povidone iodine-alcohol, with and without skin scrubbing, for prevention of intravascular-catheter-related infection (CLEAN): an open-label, multicentre, randomised, controlled, two-by-two factorial trial. *Lancet* 2015;386:2069-77.

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Pregnancy, Primary Aldosteronism, and Somatic *CTNNB1* Mutations

TO THE EDITOR: Teo et al. (Oct. 8 issue)¹ describe three women with aldosterone-producing adenomas. Each adenoma had a somatic mutation in

CTNNB1, the gene encoding β -catenin in the Wnt cell-differentiation pathway. The authors suggest that there is an association among a somat-