Viridans Group Streptococci in Febrile Neutropenic Cancer Patients: What Should We Fear?

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(See the Major Article by Shelburne III et al on pages 223–30.)

Keywords. febrile neutropenia; viridans streptococci; bloodstream infection.

In this issue of Clinical Infectious Diseases, Shelburne et al report their development and validation of a clinical prediction model for \( \beta \)-lactam resistance in viridans group streptococci (VGS) causing bloodstream infection (BSI) and offer guidance for the use of vancomycin (or gram-positive spectrum antibiotics) for empiric therapy of febrile neutropenia (FN) [1]. Although VGS cause a significant minority of BSIs in FN patients, they are associated with a shock syndrome (VGSS) and/or acute respiratory distress syndrome (ARDS) in 7%–39% of patients, with mortality rates ranging from 2% to 21% [2–9]. VGSS/ARDS was initially described in the 1990s and linked to the presence of profound neutropenia, oral mucositis, high-dose chemotherapy, and also to fluoroquinolone or trimethoprim-sulfamethoxazole prophylaxis and ceftazidime empiric therapy for FN [5, 6, 8, 10, 11]. Poor in vitro activity against Streptococcus mitis, the most common cause of VGSS/ARDS, is characteristic of these antibiotics. Later-generation expanded-spectrum \( \beta \)-lactams with more reliable activity against VGS (and other gram-positive pathogens) have largely supplanted ceftazidime for empirical antibiotic monotherapy and include cefepime, piperacillin-tazobactam, and the antipseudomonal carbapenems, imipenem and meropenem [12, 13]. Increasingly, however, VGS bearing diminished susceptibility to penicillin and to the newer \( \beta \)-lactams are being recognized [2, 6, 10, 11]. These \( \beta \)-lactam resistant isolates primarily concern Shelburne et al as potentially causing rapid and disastrous complications from VGS bacteremia in patients with FN.

Driving this study is the thought that improved outcomes (eg, lower incidence of VGSS/ARDS and mortality) will be afforded to FN patients with \( \beta \)-lactam-resistant VGS bacteremia if they receive vancomycin (or gram-positive antibiotics) as part of the empiric \( \beta \)-lactam-based regimen. In 1997, Spanik et al observed higher mortality rates in FN patients with penicillin-resistant VGS bacteremia, while in another study published in the same year, Elting et al reported increased mortality in FN patients who did not receive vancomycin initially for documented \( \alpha \)-hemolytic streptococcal BSI [8, 10]. Both studies largely included patients treated with fluoroquinolone prophylaxis and ceftazidime therapy, 2 important risks for VGSS/ARDS. Fueled by these reports, some practitioners have reflexively added vancomycin to the empiric \( \beta \)-lactam regimen for all patients with FN, presuming that it will prevent the potentially life-threatening effects of VGS BSI. Indeed, at the MD Anderson Cancer Center, where Shelburne et al conducted their study, a stunning 96% of all patients with FN in their validation cohort (2011–2013) received vancomycin as part of the empiric therapy. In contrast, the 2010 Infectious Diseases Society of America (IDSA) guidelines recommend much stricter criteria for empiric vancomycin use, suggesting it be limited to FN patients with hemodynamic instability or other evidence of severe sepsis (an indicator for possible VGSS), documented gram-positive BSI prior to identification, skin and soft tissue infection, or pneumonia, or to those with known colonization or suspected infection due to \( \beta \)-lactam-nonsusceptible organisms (eg, methicillin-resistant Staphylococcus aureus, penicillin-resistant Streptococcus pneumoniae) [12]. Although the IDSA guidelines recognize VGS BSI as a cause of shock and ARDS, there is no recommendation for broadly adding empiric vancomycin to an initial antipseudomonal
agent, in an attempt to treat VGS preemptively. Why is there such disparity, then, between clinical practice and the IDSA guidelines regarding how vancomycin should be most effectively used (or not used) in fever and neutropenia? It may reflect differences in local epidemiology and antibiogram patterns at various centers. Furthermore, no predictive tool has been available to accurately identify FN patients at greatest risk of VGSS/ARDS. A prevailing fear among some clinicians is that patients with FN will rapidly succumb to sudden and unrelenting shock due to VGS bacteremia unless vancomycin (or other gram-positive drugs such as daptomycin) is administered “up front.” Antibiotic utilization driven by fear is certainly a dilemma for antibiotic stewardship. As Shelburne et al suggest, a reevaluation of the data may help to change this pattern.

Underlying this study were several assumptions about VGS bacteremia: (1) that a penicillin minimum inhibitory concentration (MIC) ≥2 µg/mL (defined by the authors as penicillin nonsusceptibility) adequately identifies nonsusceptibility to later generation β-lactams; (2) that a penicillin MIC ≥2 µg/mL is a surrogate marker for increased risk of VGSS and mortality; and (3) that vancomycin administered at the onset of fever in neutropenic patients with VGS bacteremia will improve outcome. The authors reviewed all VGS bloodstream isolates from FN patients at their center over a 13-year period, using 569 cases (2000–2010) in a derivation set to identify factors correlating with nonsusceptible MICs for penicillin, and then prospectively assessed their predictive value using a validation cohort of 163 VGS cases (2011–2013). Three variables correlated with isolating VGS with a penicillin MIC ≥2 µg/mL: β-lactam use in the prior 30 days, β-lactam prophylaxis, and inpatient status at onset of FN. Only 1% of patients who lacked all 3 criteria were infected with a penicillin-resistant VGS. The authors concluded that the presence of 1 or more of the 3 elements was predictive for penicillin-nonsusceptible VGS with high sensitivity, but relatively low specificity and a positive predictive value of only 0.34. They further calculated that 42% of all FN patients without these risks could have been spared receipt of empiric vancomycin. This finding is clearly a step in the right direction to curb vancomycin overuse, and we applaud the authors for their evidence-based proposal of narrowed indications for empiric vancomycin. However, the key questions remain as to whether the patients identified by this analysis were truly the ones at highest risk for VGSS/ARDS—and not just high MICs to penicillin—and if so, would empiric vancomycin have made a difference in overall outcome?

The study assumes that a penicillin MIC ≥2 µg/mL serves as a good surrogate for nonsusceptibility to later-generation β-lactams among VGS isolates. However, using Etest, the authors found that all VGS with a penicillin MIC equal to 2 µg/mL remained fully susceptible to cefepime and piperacillin-tazobactam, the most commonly used empiric therapies; only a small proportion were resistant to meropenem. Thus, defining cefepime and piperacillin-tazobactam as nonsusceptible at a penicillin MIC of 2 µg/mL in the validation analysis creates a bias against their efficacy. Understandably, the authors wanted to “cast a wide net” to ensure that all resistant VGS were captured by their definition, but by doing so they may have overdrawn conclusions about the circumstances in which vancomycin would be needed, when in fact, many VGS isolates would have been covered by standard cefepime or piperacillin-tazobactam monotherapy.

The idea that a higher penicillin MIC portends a worse outcome from VGS bacteremia is not consistently supported in the literature. In contrast to the older studies mentioned earlier, there are a number of studies that have found no correlation between the VGS penicillin or β-lactam susceptibility pattern and clinical outcome [3–7]. Han et al recently reported 202 episodes of VGS bacteremia in children and adults with FN, finding only 40% susceptible to penicillin but 80% susceptibility to cefepime; rates of VGSS, ARDS, and death were independent of antibiotic susceptibility patterns [3]. Indeed, Shelburne et al also found no difference in the incidence of VGSS and ARDS among patients with VGS showing a penicillin MIC ≤1 µg/mL (susceptible) compared with those with MIC ≥2 µg/mL (resistant). These findings suggest that in vitro antibiotic susceptibility does not necessarily predict prognosis in VGS bacteremia.

Finally, there are data to suggest an advantage in outcomes when vancomycin is given early in patients with VGS with diminished susceptibility to β-lactams [9, 10]. However, abundant data exist from randomized controlled trials affirming that the empiric routine addition of anti-gran-positive treatment with glycopeptides does not improve the outcomes of FN patients with cancer [14, 15]. In a meta-analysis of 13 randomized controlled trials comparing empiric β-lactams alone or with additional anti-gran-positive antibiotic, similar rates of mortality and treatment failure were observed [15]. The authors concluded that glycopeptides can be safely deferred until documentation of a resistant gram-positive bacterial infection is made. Similarly, Shelburne et al detected no significant difference in mortality related to vancomycin use [1]. In the vast majority of cases, VGS bacteremia pursues a relatively indolent course; only in a minority will it lead to VGSS, ARDS. The preponderance of data support the addition of vancomycin to empirical β-lactam therapy for FN if clinical deterioration occurs [2, 12, 14, 15].

In conclusion, the current study provides a clinical prediction model to help clinicians focus the prescription of empirical vancomycin (and other gram-positive antimicrobial agents) more
This achievement contributes significantly to the goals of antimicrobial stewardship, seeking to limit the burden of antibiotic pressure that can lead to bacterial resistance. However, we suggest moving beyond using β-lactam MICs as surrogates for high-risk outcomes. A focus on factors correlating with the clinically relevant outcomes of shock, ARDS, and mortality should be a next step. Risk factors associated with VGS bacteremia, including profound neutropenia, oral mucositis, fluoroquinolone prophylaxis, inpatient status, and prior β-lactam use might be incorporated into a clinical model for prediction of the devastating outcomes related to VGS bacteremia. In the meantime, we urge adherence to current evidence-based guidelines in an effort to stem the rising tide of vancomycin overuse and resistance.

**Note**

**Potential conflicts of interest.** Both authors: No reported conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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