Risk factors for viridans group streptococcal bacteremia in neutropenic and non-neutropenic patients at the NIH Clinical Center, 2009-2014: A case-case-control study

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Background
- Viridans group streptococcal (VGS) bacteremia is increasingly common among neutropenic (NP) patients. These organisms, flora of the mouth and GI tract, are thought to translocate into the bloodstream when mucosal barriers are compromised during neutropenia. Known risk factors among NP patients include mucositis and fluoroquinolone prophylaxis. Gram-positive antimicrobial coverage may be protective.
- We observed, however, that almost 40% of patients with VGS bacteremia at the NIH Clinical Center were not neutropenic (non-NP). Risk factors for such patients are not well established.
- Our goal was to identify and contrast the risk factors for VGS bacteremia among NP and non-NP patients in this 240-bed clinical research hospital.

Methods
To contrast risk factors between NP and non-NP patients we performed a case-case-control study, in which two parallel case-control studies were conducted.

Identification of cases and controls
Patients with VGS bacteremia between 1/09 and 12/14 were identified using microbiology records. Cultures deemed to be contaminants by the clinical staff at the time were excluded. We divided cases into NP and non-NP case groups based on ANC ≤ 0.5 × 10^9/L. NP and non-NP patients at the time of positive culture were matched 1:1 to controls on the basis of ANC. Hospital ward at the time of case patient VGS bacteremia, and length of stay (LOS), yielding two case and two control groups (Fig 1).

We extracted clinical data from electronic medical record review, and calculated the Charlson comorbidity index for each patient. The Pitt bacteremia score, a prognostic score (0-14 points, worse prognosis at higher scores) which incorporates clinical parameters such as fever, hypotension, need for mechanical ventilation, mental status and cardiac arrest, was also calculated for both case groups.

Statistical analysis
Analyses were conducted separately for each case-control study, and the results of the final models were then described. Data were analyzed using McNemar's test and Wilcoxon signed-rank test for between group comparisons. Odds ratios (OR) were calculated using univariable and multivariable conditional logistic regression modeling.

Results

Study population
We identified 63 NP case patients and 38 non-NP case patients (Fig 1). No patient was found to have endocarditis.

114 unique patients with first positive blood cultures for VGS in 2009-2014 were screened
13 (11%) excluded, deemed as contaminants by treating medical team
101 patients were included in the analysis

Identification of potential risk factors
Cases and controls are described in Table 1. Table 2 describes the multivariable models of potential risk factors for VGS bacteremia in NP and non-NP patients.

Univariable analysis
No clinical factor was found to be associated with development of VGS bacteremia among non-NP cases. Among NP patients, receipt of cyclophosphamide or fluoraburine, duration of radiation therapy, mucositis or other oral diagnosis, and ANC nadir in the three weeks prior to positive culture were all significantly associated with VGS bacteremia. Duration of neutropenia prior to bacteremia was not significantly associated with VGS bacteremia. Cephalosporins, carbapenems and vancomycin were protective in this group.

Other variables that were not associated with VGS bacteremia in either group included hospital ward, LOS, protein pump inhibitors or H2 blockers, other chemotherapeutic agents, dental symptoms, abnormal sinus CT, lymphitis, C. difficile infection, and intestinal graft-versus-host disease.

Multivariable analysis
Variables with p<0.1 in univariate analysis were included in the multivariate model (Table 2). No variable met this criteria in the non-NP group, but the analysis was also tested for informational purposes.

Lower ANC nadir was the sole predictor of VGS bacteremia in the NP group (OR=0.008; 95% CI <0.001-0.03). The risk of VGS bacteremia decreased by 0.4% per each 1 cell/mm^3 increase in ANC nadir. After testing the multivariate model by iteratively removing least influential variables, exposure to vancomycin in the previous three weeks was also found to be protective (OR = 0.19; 95% CI 0.06-0.63) when ANC was the only other covariate.

In the non-NP group, no factor was found to increase risk for VGS bacteremia.

Conclusions
- Among NP patients, lower ANC nadir increased risk of VGS bacteremia, and vancomycin was protective. Other potential associations (chemotherapy, radiation, oral conditions) were not related to neutropenia. Known risk factors in NP patients, such as mucositis and fluoroquinolone prophylaxis, did not predict VGS bacteremia in this study.
- No tested clinical factors predicted infection in the non-NP group.
- Limitations include matching only one control per case (a higher ratio was not possible with our matching criteria in a small hospital) and possible misclassification by medical teams of VGS cultures as contaminants or true bacteremias.
- Non-neutropenic patients may be such a heterogeneous group that there are not necessarily unifying antecedent factors that can be modified to prevent infection.
- The results of this case-case control study suggest that VGS bacteremia in neutropenic patients should continue to be considered a distinct entity that can be anticipated in profoundly neutropenic patients and managed preemptively by selective, prompt administration of vancomycin.