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# Ceftriaxone-resistant viridans streptococci bacteraemia among patients treated at a large comprehensive cancer care centre: a retrospective eighteen-year study

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**Objectives:** Viridans streptococci (VS) are opportunistic oral commensals and a common cause of bacteraemia in neutropenic patients. In this retrospective single centre cohort study, we investigated the prevalence of ceftriaxone resistance in VS (CRO-R VS) blood isolates between January 2005 and December 2022 from patients treated at a tertiary care hospital.

**Methods:** Blood culture isolates were identified using biochemicals and mass spectrometry. Susceptibility testing was performed by Kirby–Bauer and Epsilometer tests. Demographic data, clinical outcomes and antimicrobial use were assessed through electronic medical record review.

**Results:** Among 791 patients with VS bacteraemia, 31 (4%) had confirmed CRO-R VS bacteraemia over the 18-year period; 20/31 (65%) were patients also treated at the Fred Hutchinson Cancer Center and were the focus of this study. Of these 20 patients, 18 (90%) had a known haematologic malignancy; 14 (70%) had undergone haematopoietic cell transplant (HCT); 18 (90%) were neutropenic at the time of culture. Two (10%) patients died within 30 days of CRO-R VS bacteraemia. All the CRO-R isolates (20/20) were members of the *Streptococcus mitis* group, 12 were multi-drug resistant; all were susceptible to vancomycin. Most patients received vancomycin once blood cultures were positive for a Gram-positive organism.

**Conclusions:** During the study period, the frequency of VS isolate susceptibility testing increased; however, there was no concomitant increase in the percentage of CRO-R isolates at our facility. These data are important in an era where cefepime monotherapy is often used and reinforces the importance of routine resistance testing among VS bacteraemia.

## Introduction

Viridans streptococci (VS) are a group of Gram-positive commensal organisms, including the *Streptococcus mitis* group (SMG), which are found in the oropharynx, genitourinary and gastrointestinal tracts. While generally considered of lower virulence, VS may cause significant illness and mortality, especially in immunocompromised patients.[1] Up to 27% of the patients with neutropenic fever (defined as an absolute neutrophil count (ANC) < 500 cells/microlitre) are found to have bacteraemia, with VS identified as the most common cause of blood stream infections in cancer patients outside of coagulase-

negative staph.[2–5] VS bacteraemia may lead to serious complications in high-risk patients, such as acute respiratory distress syndrome and septic shock, with mortality reaching 21%–30%.[1,4,6,7]

Antimicrobial resistance is increasing globally and a particular concern in cancer patients, as most receive multiple courses of antibiotic treatment or long-term prophylaxis, increasing the risk of selecting resistant organisms. VS isolates from neutropenic cancer patients have shown penicillin resistance up to 37%.[5,8] SMG, containing >15 species of streptococci, is the most identified VS species in bloodstream infections, and has demonstrated higher levels of penicillin resistance (not including intermediate resistant isolates) compared to many other VS strains in neutropenic patients.[3,9–11] In this highly vulnerable cancer population, SMG can lead to severe disease including septic shock, acute respiratory distress syndrome, skin and soft tissue infection and endocarditis.[12,13]

Ceftriaxone, a third-generation cephalosporin with broad spectrum Gram-positive and -negative coverage, is an appealing treatment option given its once-daily administration.[14] Streptococcal resistance to penicillin and cephalosporins is due to altered VS penicillin-binding protein (pbp). The modified *pbp* genes have been shown to pass vertically within VS. Species such as *Streptococcus pneumoniae* are known to be horizontal recipients from other VS species such as SMG through natural transformation, and there is ongoing research to further characterize transmission of *pbp* genes to SMG.[1,15–17] VS strains resistant to penicillin often have a lower susceptibility to ceftriaxone and other antimicrobials.[18,19] SMG penicillin-resistant isolates specifically have shown ceftriaxone resistance levels as high as 69% [van Prehn *et al.* Supplementary data (available at *JAC-AMR* Online)].[10] Reported community VS ceftriaxone resistance rates range from 6% to 11% whereas resistance rates in cancer patients range from 4% to 23%.[5,7,10,12,16,18,20]

Given the significant impact of VS bacteraemia on neutropenic patients, we investigated the prevalence of ceftriaxone-resistant (CRO-R) VS blood isolates among VS isolates from patients undergoing treatment at a comprehensive cancer care centre in Seattle, WA, USA, between January 2005 and December 2022. We focused our study on the cancer patients at our centre because of the known risk of VS bacteraemia in these patients, common use of ceftriaxone and other cephalosporins for empiric therapy, and the potential risk of emerging resistance for this population.[3,5,6] The additional aims of this project were to determine whether the resistance profiles differ between isolates collected from cancer care centre patients and from the community. Finally, we assessed treatment regimens and hospital outcomes among cancer patients with CRO-R VS bacteraemia.

## Methods

### Patient population

We conducted a retrospective review of all blood cultures with VS isolated at the University of Washington (UW) Clinical Microbiology Laboratory between January 2005 and December 2022. The UW Clinical Microbiology Laboratory processes specimens from the University of Washington Medical Center (UWMC), a 570-bed tertiary care centre, and the Fred Hutchinson Cancer Center (Fred Hutch). Reference laboratory isolates and those without susceptibilities were excluded. VS isolated from blood culture were then categorized as either CRO-R or CRO susceptible based on antimicrobial susceptibility results. CRO-intermediate isolates were not included in the total number resistant. Electronic medical record (EMR) review of all patients with CRO-R VS bacteraemia was performed to determine patients who received evaluation or treatment (e.g. haematopoietic cell transplant-HCT) at Fred Hutch. All Fred Hutch patients underwent further analysis as described next (Figure 1). Patients <18 years of age were excluded. This study was approved by the Fred Hutch Institutional Review Board.

### Determination of VS bacteraemia and susceptibility testing

Local guidelines recommend that initial evaluation of fever in a patient undergoing chemotherapy or who is neutropenic include two sets of blood cultures; however, decisions on primary and repeat cultures at the UWMC and Fred Hutch are made by the primary clinical team. Blood cultures were incubated in automated blood culture systems (2005–2011 BACTEC 9240, Becton Dickinson Diagnostic Instrument Systems, Sparks, MD, USA; 2011-present VersaTREK™ Automated Microbial Detection System, ThermoFisher Scientific, Waltham, MA, USA) for 5 days. Microorganisms recovered from positive blood cultures were identified using standard biochemical testing and MALDI-TOF mass spectrometry (MS, Bruker Daltonics). Before 2014, a commercial biochemical-based identification system (Vitek Gram-positive Identification test, Biomerieux) was used in conjunction with optochin testing, bile solubility and, if necessary, 16S sequencing to identify SMG. In 2014, the Vitek system was replaced with MALDI-TOF MS and was used in conjunction with optochin and bile solubility to identify SMG organisms. If isolates were from cultures before introduction of MALDI-TOF MS, isolates were retrieved from frozen stocks and the original identification was confirmed by MALDI-TOF MS. VS includes *Streptococcus pneumoniae* (excluded from this study), *S. bovis* group, *S. mutans* group, *S.salivarius* group and SMG. Members of SMG included in this study are listed separately (Table S1, available as Supplementary data at *JAC-AMR* Online).

Susceptibility testing was performed using Kirby–Bauer disc diffusion and the Etest; CLSI interpretative criteria were applied (Table S2). Before 2016, susceptibility testing was performed on VS isolated from blood culture when two or more sets of blood cultures were positive or by provider request. Susceptibility testing was routinely performed on all VS isolated from blood culture regardless of the number of sets positive after 2016. Of the CRO-R isolates identified, duplicate cultures from the same patient with the same resistance pattern were counted only once. Penicillin by the CLSI standard is considered an appropriate test and resistance to penicillin is treated as resistance to ampicillin or amoxicillin.

### Data collection

Demographic data, clinical course and outcomes, and antibiotic therapy choices were collected by review of the EMR for all cancer patients. Clinical data included underlying malignancy, treatment, CRO exposure documented in the facility EMR any time before diagnosis, as well as ANC at the time of blood culture draw; neutropenia was defined as ANC $\leq$ 500 cells/microlitre. The clinical outcomes of interest were death and/or need for ICU-level care within 30 days of CRO-R VS bacteraemia. Antimicrobial prophylaxis was identified from the medication administration record and clinical notes at the time just before VS bacteraemia. Standard antibacterial prophylaxis practice at Fred Hutch is levofloxacin when neutropenic (alternatives include ceftazidime, cefpodoxime or amoxicillin/clavulanate). Empiric treatment included two time points: first, the initial antimicrobial option chosen at the time of fever before culture positivity, and the second time point when Gram-positive cocci were reported. Definitive therapy was defined as the antibiotic administered after species-level identification of VS and antimicrobial susceptibility results were reported. While VS may sometimes be considered a contaminant in the community, the standard practice at the centre is to consider all

blood stream infections with cultures positive for VS as true infections regardless of the susceptibility pattern or the number of bottles positive and to treat with antibiotics.

## Results

From 2005 to 2022 at the UWMC/Fred Hutch there were 1069 VS positive blood cultures with susceptibility results, representing 791 individual patients. Of those, 31 patients (31/791, 4%) had CRO-R VS (20/31, 65%) of whom were Fred Hutch patients. A total of 31 isolates were CRO-R VS (31/1069, 3%) (Figure 1), and every resistant isolate (31/31) was identified as members of the SMG. Before 2011 and the regular use of MALDI-TOF, isolates were identified as VS. As part of this study, the species of the resistant isolates were determined, except CRO-S isolates from 2005 to 2011. No clustering of isolates was seen based on timing of culture positivity nor location of patients within the hospital (data not shown).

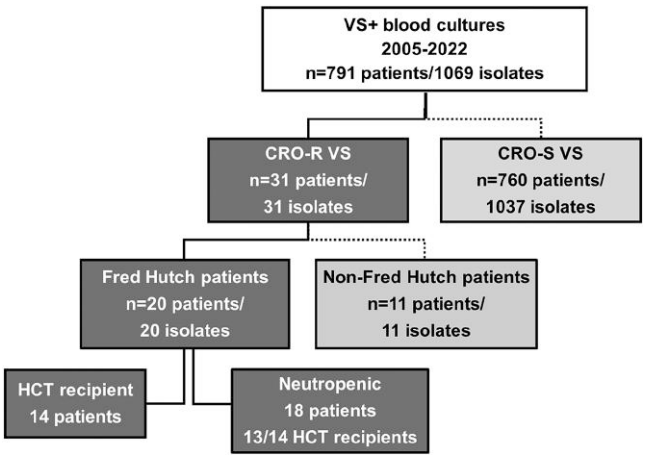


**Figure 1.** Patient/isolate selection flowchart. VS+ = viridans streptococci positive; CRO-R VS = ceftriaxone-resistant viridans streptococci; CRO-S VS = ceftriaxone-susceptible viridans streptococci; Fred Hutch = Fred Hutchinson Cancer Center.

Ceftriaxone-resistant VS prevalence at our institution varied throughout the 18 years evaluated without a clear trend (Figure 2), even as the number of VS identified increased. Before 2016 susceptibility testing was only performed if two sets of blood cultures were positive with VS or if requested by the provider. As requests became more frequent, susceptibility testing on all VS positive cultures became routine in 2016. Even with increased susceptibility testing, the percentage of VS resistant to ceftriaxone remained at or below 7% per year in all years except 2009, which was an outlier (4/12 VS isolates were CRO-R); however, the annual number of CRO-R VS positive samples did not increase significantly year-to-year (Figure 2).

Review of patient demographics for the 20 Fred Hutch patients with CRO-R VS bacteraemia revealed a population predominantly male (55%) with a median age of 43.9 years (Interquartile range (IQR) 33.3, 56.9) (Table 1). The most common underlying condition was leukaemia (35% acute myeloid leukaemia, 20% acute lymphoid leukaemia). The median inpatient stay duration for the 20 Fred Hutch patients investigated was 5.5 days (IQR 0.0, 12.3) at the time a CRO-R VS positive blood culture was collected, and most were neutropenic (90%) at the time of collection. Of the patients, 70% had a HCT before the positive culture with a median 6.5 day-time to culture positivity post-transplant (IQR 5.0, 8.3), excluding two patients who had HCT >3.5 years before CRO-R VS bacteraemia. Of the 14 HCT recipients, all but one were neutropenic at the time of culture positivity.

We next investigated whether previous exposure to ceftriaxone would increase the likelihood of developing a CRO-resistant bacterial infection. Of the 20 patients with CRO-R VS isolates, 75% had no previous CRO exposure documented in our EMR. Of the five with previously documented exposure, one patient with sickle cell disease had received multiple courses of CRO (19 documented courses between 2005 and 2022), while three of the four remaining patients received only one course of CRO before their CRO-R VS bacteraemia; two of whom received CRO within a

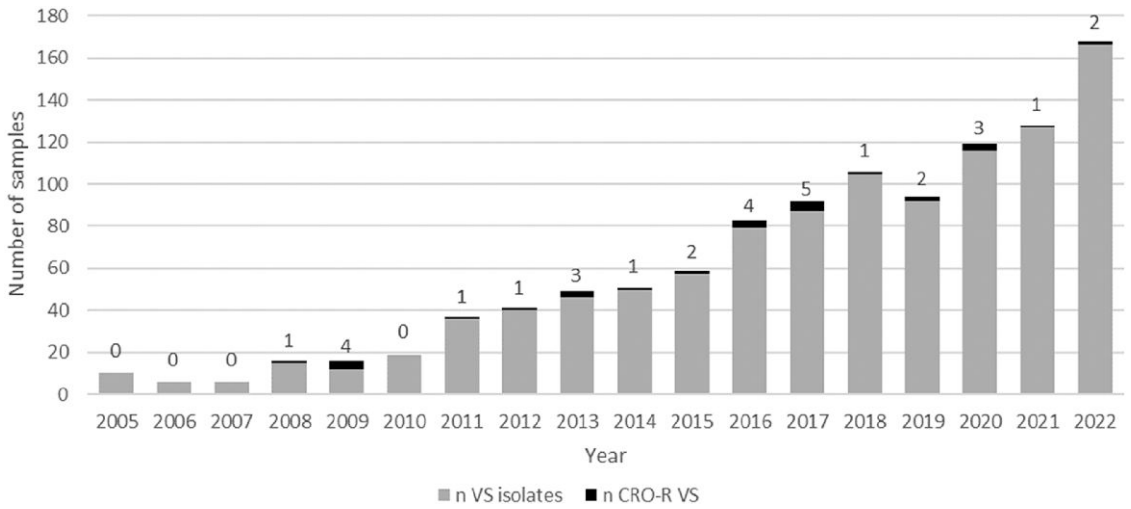


**Figure 2.** Total VS and number of ceftriaxone-resistant bacteraemia isolates identified between January 2005 and December 2022. CRO-R = ceftriaxone resistant.

**Table 1.** Patient demographics of Fred Hutch patients with ceftriaxone-resistant viridans strep positive blood cultures ($n = 20$)

| Demographics | |
|---|---|
| Age | Median 43.9 years (IQR 33.3, 56.9) |
| Sex assigned at birth | Female 9/20 (45%)<br>Male 11/20 (55%) |
| Time (days) inpatient when culture positive | Median 5.5 (IQR 0.0, 12.3) |
| Number outpatient at time of sampling | 4/20 (20%) |
| Underlying diagnosis | *N* (%) |
| Acute myeloblastic leukaemia | 7 (35) |
| Acute lymphoblastic leukaemia | 4 (20) |
| Diffuse large B cell lymphoma | 4 (20) |
| Follicular lymphoma | 1 (5) |
| Hodgkin lymphoma | 1 (5) |
| Myelodysplastic syndrome | 1 (5) |
| Multiple sclerosis | 1 (5) |
| Sickle cell disease | 1 (5) |
| HCT | 14 (70) |
| Time (days) since transplant | Median 6.5 (IQR 5.0, 8.3)[a] |
| Neutropenic at time of culture positive | 18 (90) |

IQR, interquartile range.
[a]Two out of 14 patients underwent HCT greater than 3.5 years before resistant bacteraemia and were not included in this calculation

month before the CRO-R VS bacteraemia. Twelve of the patients had previous exposure to other cephalosporins but neither ceftriaxone nor any penicillins. Three out of the 20 patients had no documented treatment with either penicillins or cephalosporins in our EMR; however, whether they received these antibiotics from other treatment facilities is unknown.

When comparing resistance to additional antibiotics in the CRO-R isolates, more Fred Hutch patient isolates were resistant to other antimicrobials than isolates recovered from non-Fred Hutch patients, across all antibiotics tested (Figure 3). This was particularly true regarding levofloxacin, the most frequently prescribed neutropenic prophylaxis among Fred Hutch patients. In 2005, prophylaxis of HCT patients undergoing myeloablative conditioning was changed from ceftazidime to levofloxacin, based on data demonstrating lower rates of bacteraemia and lower costs with no additional morbidity.[21] Our data show 70% (14/20) of Fred Hutch CRO-R VS isolates were resistant to levofloxacin (no intermediates identified). Penicillin resistance was highest at 90% (18/20), and the other two isolates showed intermediate susceptibility. No isolates were resistant to vancomycin. Since cefepime resistance testing is not standard, vancomycin is the preferred agent in practice for patients with CRO-R bacteraemia. The antibiotics we test are in Tier 1/Tier2, which are, per CLSI, 'Antimicrobial agents that are appropriate for routine, primary testing and reporting'. It is worth noting that all isolates not resistant to penicillin showed intermediate susceptibility from both Fred Hutch and non-Fred Hutch patients (Figure 3). None of the CRO-R isolates were susceptible to penicillin. All the 20 Fred Hutch CRO-R isolates were resistant to more than one antibiotic; 12 were multi-drug resistant, defined as resistant (per CLSI guidelines at the time of isolate identification) to three or more different drug classes such as penicillin (beta-lactam), clindamycin (lincosamide), levofloxacin (fluoroquinolone) or erythromycin (macrolide), not including intermediate susceptibility.

Levofloxacin was the most common prophylactic antibiotic patients were on at the time of neutropenic fever (13/20 instances), consistent with current centre treatment guidelines. The other seven patients were either on no prophylaxis (three patients) or other antibiotics including ceftazidime, cefpodoxime, amoxicillin-clavulanate and TMP-SMX (one patient on each). Empiric treatment began as soon as the patient presented with neutropenic fever before a positive blood culture, most often (13/20) with a third- or fourth-generation cephalosporin such as cefepime or ceftazidime. Only one patient was started on vancomycin empirically in addition to ceftazidime.

Once the blood culture was positive, most patients (18/20 instances) were switched to or had vancomycin added before susceptibility results. One of the remaining patients was on ceftriaxone monotherapy as the patient had a CRO susceptible VS blood culture from 5 days before. A separate patient was transitioned from vancomycin to CRO for discharge before the availability of susceptibility results. The patient was readmitted the next day due to return of symptoms, and the CRO-resistant VS was noted. Once susceptibility testing results were available, most patients (17/20 instances) continued tailored therapy with vancomycin ± additional antibiotics, depending on their clinical state. Of the remaining three instances, one patient was placed on levofloxacin (isolate was susceptible), another was discharged on linezolid with cefepime and the last, who had been on empiric vancomycin, died before susceptibility determination. We do not routinely test for cefepime resistance, but our practice has been to prioritize vancomycin over cefepime if a blood culture isolate is CRO-R.

Two of the 20 Fred Hutch patients (10%) died within 30 days of blood culture positivity. One patient quickly developed septic shock and died from, most probably, VS bacteraemia. The patient had AML and had received a HCT 6 days before death. The patient was neutropenic at the time of culture positivity, which was 1 day before death. This patient was started on ceftazidime and imipenem empirically, then vancomycin was added immediately following culture positivity. The other patient was admitted directly from home. At an outpatient visit the day before the patient endorsed fatigue and was neutropenic but afebrile. After the blood culture was positive for GPC in pairs and chains the patient was called for direct admission and empirically started on vancomycin. The patient completed 2 weeks of therapy with vancomycin. The patient's course was complicated by an invasive fungal infection, which was thought to be the most likely attributable cause of death. After completing vancomycin therapy, no additional blood cultures were positive for VS. The patient died 18 days after the VS positive culture. These two patients were the only patients requiring ICU-level care during the 30 days following diagnosis and treatment of their VS bacteraemia.

## Discussion

We investigated ceftriaxone resistance in viridans streptococci bloodstream isolates at a tertiary medical centre/comprehensive cancer centre from 2005 to 2022, and found the prevalence of

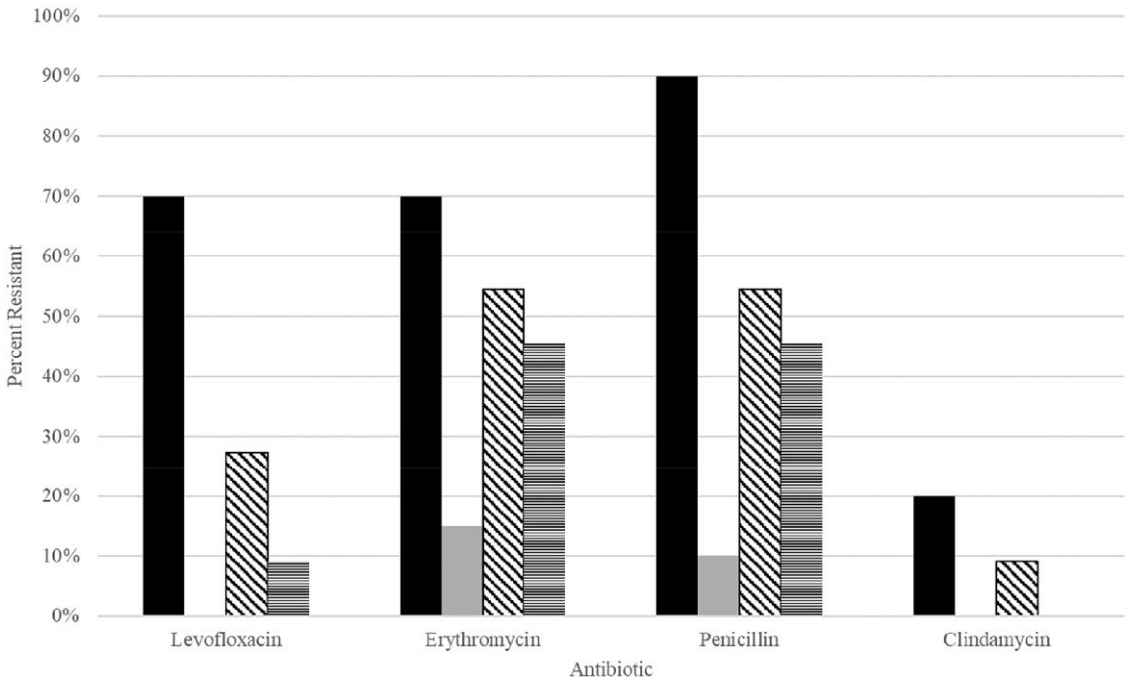


**Figure 3.** Antibiotic resistance in CRO-R VS Fred Hutch patient isolates versus non-Fred Hutch patient isolates. Solid bars = Fred Hutch patient isolates. Black bars = resistant, solid grey bar = intermediate. Stripe bars = non-Fred Hutch patient isolates. Diagonal stripe bars = resistant, horizontal stripe bars = intermediate. CRO-R VS = ceftriaxone-resistant viridans streptococci; Fred Hutch = Fred Hutchinson Cancer Center.

CRO-R VS to be low with stable prevalence over the years reviewed. Our data from stable number of CRO-R cases over time were contrary to other reports, such as Chun *et al.*, which noted increasing third-generation cephalosporin resistance over time (3.9% up to 9.7%) from the late 1990s to the early 2010s.[16] More cases were found in cancer patients including those receiving HCT when compared to the general hospitalized community, consistent with the increased use of antibiotics in this immunocompromised population. Although all samples were SMG, we found no epidemiologic evidence of nosocomial spread or clustering, suggesting these isolated cases were the result of random selection for resistant species rather than institution-wide contamination or patient-to-patient spread; however, genome sequencing analysis has not been completed. Low likelihood of nosocomial spread is also supported by the low average CRO-R VS prevalence (3%), which is below the documented CRO-R prevalence often reported in community studies of 6%–11%.[7,16,18,22] Possible reasons include successful antimicrobial stewardship, differences in CRO or other cephalosporin prescribing in these patients, or that institutional prevalence is lower than what has been reported by others.

All the CRO-R VS isolates from this cohort were resistant to more than one antibiotic class, including a high number of levofloxacin and PCN resistant isolates; 12 were considered multidrug resistant (defined as resistant to three or more drug classes). Only one patient had documented receipt of multiple courses of ceftriaxone before developing CRO-R VS bacteraemia; however, 17/20 had previous beta-lactam exposure, increasing the risk of selection for resistant isolates. It is notable that several CRO-R VS isolates (two Fred Hutch and five non-Fred Hutch) showed intermediate resistance to penicillin while being resistant to CRO. In a study by Shelburne *et al.* looking at susceptibility to beta-lactams in VS blood culture isolates in neutropenic patients, they found all isolates resistant to CRO had a penicillin MIC $\geq$ 4 mg/L, indicating all isolates were resistant to penicillin; however, in the study by Diekema *et al.*, they reported 25% of samples with intermediate resistance to penicillin were resistant to CRO ($MIC_{90}$ 1 mg/L).[8,19]

Five of the 20 Fred Hutch patients were outpatient at the time of blood draw, and one patient was in the emergency department. Of these six, all but one were admitted with neutropenic fever before culture positivity. The other patient was a direct admission after the culture became positive. Most often, we found empiric treatment for neutropenic fever did not cover for CRO-R infections. Once the blood cultures turned positive, empiric therapy (primarily vancomycin) was adequate, but this was frequently greater than 12 h after the start of the fever and collection of blood cultures, including the two patients who passed. Our guidelines up until 2018 recommended empiric vancomycin if a patient has febrile neutropenia with evidence of mucositis. After 2018, mucositis was no longer a reason to use vancomycin and the primary empiric treatment for neutropenic fever was changed to cefepime. At least nine patients (9/20, 45%) were noted to have mucositis at the time of their bacteraemia, however, this is a common symptom seen in pre-engraftment and induction patients, and along with the relatively low CRO-R VS prevalence, it would not make sense to alter the treatment recommendations. Vancomycin is currently reserved for those patients presenting other symptoms such as hemodynamic instability or sepsis.

VS bacteraemia carries high mortality; however, in our data only one patient died due to septic shock related to their bacteraemia. Other facilities have shown higher rates of mortality among patients with VS bloodstream infections, including Guerro-Del-Cueto *et al.* (30-day mortality 10% up to 43% due to SMG or *S. sanguinis* bacteraemia, respectively, in 43 neutropenic patients) and Radocha *et al.*, who reported 5.9% mortality due to VS bacteraemia up to 28 days in neutropenic cancer patients.[1,3] Han *et al.*, however, found lower mortality rates of 1.6%–2.1% when comparing paediatric to adult VS bacteraemia in neutropenic patients.[2] Bochud *et al.* published a review of 13 clinical studies from the 1970s to the early 1990s showing a range of 4%–18% of deaths in neutropenic patients due to VS bacteraemia (timeframe not clarified).[23] In Marron's study of cephalosporin resistance in VS, the rates of overall and attributable mortality to CRO-S and CRO-R VS were found to not significantly differ, suggesting that it is the intrinsic virulence of VS in general or species' specific virulence factors rather than the multi-drug resistant strains affecting outcomes.[20]

Our study was limited in that it is a single centre, treating a specific population of patients. It does not appear that any cases were linked; however, our number of cases was small, making it challenging to assess relatedness. Furthermore, we did not sequence samples to assess for clusters or molecular evidence of transmission events. Additionally, resistance testing was not always completed in the earlier years, leaving a gap in the data. We did not have access to treatment provided at outside facilities, therefore previous exposure to CRO may not be accounted for, nor do we have access to all medical records for each patient to accurately document previous exposure to any cephalosporin or penicillin use, which may also drive resistance to CRO. Finally, the same level of EMR investigation of the community cases of CRO-R VS for comparison to the cancer patients was not performed.

In summary, antibiotic resistance is an increasing global threat and should be considered when determining treatment, particularly in populations who have received multiple courses of antibiotics, such as cancer patients. Resistance to cefepime, a commonly prescribed empiric antibiotic in the immunocompromised population, is thought to be linked to CRO resistance and is extrapolated from CRO resistance patterns.[5] CRO-R VS is present in our facility and the community. Our results indicate CRO-R VS bacteraemia in immunocompromised patients at our facility is infrequent and not increasing. These data do not suggest modifications to primary treatment recommendations for neutropenic fever. Importantly, however, we recommend continued resistance testing for all VS isolates. Centres should routinely evaluate rates of resistance to assess whether changes in empiric therapy should be modified within their highly vulnerable cancer populations.

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## Transparency declarations

The following authors have financial interests associated with this work to declare: Dr Catherine Liu is a site investigator for a clinical trial sponsored by Pfizer and has served on an advisory board for SNIPR BIOME. Dr Steven Pergam receives research support from Global Life Technologies and participates in clinical trials with Cidara, F2G and Symbio.

## Supplementary data

Supplemental Tables S1 and S2 are available as Supplementary data at *JAC-AMR* Online.

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