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ORIGINAL ARTICLE

Outcomes of neutropenic hemato-oncological patients with *viridans group streptococci* (VGS) bloodstream infection based on penicillin susceptibility

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Abstract

Viridans group streptococci (VGS) bloodstream infection (BSI) in neutropenic patients can be a severe complication. A higher prevalence of vancomycin use has been reported due to reduced susceptibility to penicillin. We aimed to assess the impact on mortality of both penicillin minimal inhibitory concentration (MIC) and the use of vancomycin. We conducted a retrospective multicenter study including consecutive neutropenic patients with VGS BSI between 2007 and 2019. Univariable and multivariable analyses were conducted to evaluate risk factors for mortality, including penicillin susceptibility as an independent variable. Non-susceptibility to penicillin was defined as MIC ≥ 0.25. We included 125 neutropenic patients with VGS BSI. Mean age was 53 years and ~ 50% were women. Overall, 30-day mortality rate was 25/125 (20%), and 41 patients (33%) had a VGS isolate non-susceptible to penicillin. In univariable analysis, no significant association was demonstrated between penicillin non-susceptibility and mortality (9/25, 26% vs. 32/100, 32%, $p = 0.81$). Among patients with a non-susceptible strain, the use of vancomycin was not significantly associated with mortality (empirical, $p = 0.103$, or definitive therapy, $p = 0.491$). Factors significantly associated with increased mortality in multivariable analysis included functional status (ECOG > 1, adjusted odds ratio [aOR] 12.53, 95% CI 3.64–43.14; $p < 0.0001$); allogeneic transplantation (aOR 6.33, 95% CI 1.96–20.46; $p = 0.002$); and co-pathogen in blood cultures (aOR 3.99, 95% CI 1.34–11.89; $p = 0.013$). Among neutropenic hemato-oncological patients with VGS BSI, penicillin non-susceptibility and the use of vancomycin were not associated with mortality. Thus, vancomycin should not be used routinely as empirical therapy in neutropenic patients with suspected VGS BSI.

Keywords Strep viridans · Bloodstream infection · Neutropenic fever

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Introduction

Viridans group streptococci (VGS) are the cause of a small but significant proportion of bloodstream infections (BSIs) in febrile neutropenic (FN) patients, reported in ~ 5% and up to 18–29% of BSIs in different studies [1, 2]. These BSIs are associated with VGS shock syndrome (VGSS) and/or acute respiratory distress syndrome (ARDS) in 7–39% of patients, with high mortality reported between 2 and 21% [3].

Considering the severity of the infection and data from older studies showing improved outcomes when vancomycin is added to the initial regimen [4, 5], some centers use vancomycin as part of the empirical therapy of FN. In addition, increasing reports on reduced susceptibility to penicillin and other beta-lactams probably contribute to the continued practice of using empirical vancomycin in FN [2, 4, 5]. A recent study from Australia demonstrated VGS to be the second most common pathogen in bacteremic FN patients, with 20% reported not susceptible to penicillin (6.5% resistant) [6]. An additional study demonstrated 37% penicillin resistance among VGS isolates, and 4% were also ceftriaxone resistant [7]. In a study by Shelburne et al., 96% of 163 patients with VGS bacteremia between 2011 and 2013 received vancomycin as part of the empirical regimen [8]. This is in spite of evidence-based data and Infectious Diseases Society of America (IDSA) guidelines, recommending vancomycin empirical therapy only for specific indications [9, 10].

A controversy exists on whether higher penicillin minimal inhibitory concentration (MIC) is associated with worse outcomes, including mortality, VGSS, and/or ARDS [3]. Most studies demonstrating no association between penicillin susceptibility and poor outcomes were conducted in children. Shelburne et al. found no association in adults; however, the comparison was between patients with penicillin MIC ≤ 1 µg/mL and those with MIC ≥ 2 µg/mL, with no data on patients with MIC between these values. Risk factors for an isolate with penicillin MIC ≥ 2 µg/mL were evaluated in this large cohort. These included the use of beta-lactams during the previous 30 days, the use of beta-lactam prophylaxis, and the nosocomial onset of the BSI [8].

We aimed to compare outcomes of FN patients with VGS BSI of penicillin-susceptible vs. penicillin non-susceptible isolates. We also aimed to evaluate whether the use of vancomycin, either as empirical or as definitive therapy, impacts mortality.

Methods

This is a retrospective cohort study conducted in two medical centers in Israel (Rabin Medical Center, Beilinson Hospital, and Rambam Health Care Campus). These centers are both university-affiliated, tertiary referral center, with 23–30 hemato-oncology/bone marrow transplantation beds. In both centers, Gram negatives predominate in blood cultures from hemato-oncology units, with the most common being *E. coli*, followed by *Klebsiella* spp. and *Pseudomonas aeruginosa*.

Consecutive adult hemato-oncology patients with VGS BSI during neutropenia between 1/1/2007 and 31/12/2019 were included. Patients were identified by using the computerized medical records of the microbiology laboratory in each participating center. Patients with VGS BSI who were neutropenic during blood culture collection were included once (first BSI). Patients with neutropenia due to therapy of solid tumors were not included.

The primary outcome was 30-day mortality. Secondary outcomes included VGSS, ARDS, need for vasopressors and ventilation, recurrent VGS BSI, and ICU admission.

Definitions

VGS BSI was defined as any positive blood culture for VGS during neutropenia that was accompanied by signs of infection (fever ≥ 38.0, chills, or hypotension). This definition was preferred over the CDC surveillance definition of mucosal barrier injury–laboratory confirmed bloodstream infection (MBI–LCBI) since, in clinical practice, most of these patients are treated as true bacteremia [11].

Neutropenia was defined as an absolute neutrophil count of < 500 cells/µL.

VGSS was defined as hypotension (systolic blood pressure < 90 mm/Hg) despite adequate fluid resuscitation or need for vasopressors and/or development of ARDS [12, 13].

ARDS was defined as acute hypoxemia, accompanied by bilateral lung infiltrates, that was not of cardiac origin.

Antibiotic coverage for Gram-positive cocci was considered either vancomycin, daptomycin, or linezolid [10].

Penicillin-resistant VGS was defined as MIC ≥ 2 µg/mL, and penicillin sensitivity as MIC ≤ 0.25 µg/mL (i.e., non-susceptible VGS was defined as MIC > 0.25 µg/mL) [14].

VGS isolates were identified by the Bruker Biotyper MALDI-TOF MS system (Bruker Daltonik GmbH) as previously described [15]. Measurements were performed with the Bruker Biotyper MALDI-TOF MS system using the FlexControl software with the Compass Flex Series version 1.3 software and a 60-Hz nitrogen laser (337 nm wavelength). Spectra were analyzed using the MALDI Biotyper system's automation control and the Bruker Biotyper 3.4 software and library. Identification scores of ≥ 2.000 indicated species-level identification, scores of 1.700 to 1.999 indicated genus-level identification, and scores of < 1.700 indicated no reliable identification [15, 16].

Antimicrobial susceptibility testing of these isolates was performed using the VITEK 2 system, Etest, or disk diffusion method, according to the CLSI guidelines [17].

The empirical antibiotic regimen recommended by local guidelines for cases of hemodynamically stable FN was piperacillin-tazobactam in both participating centers during the study years. Meropenem was started in cases of septic shock. Vancomycin (or other Gram-positive coverage) was started according to the IDSA guidelines [10]. The accepted prophylactic regimen was ciprofloxacin 500 mg twice daily during neutropenia.

Statistical analysis

Dichotomous variables were compared using chi-square test. Continuous data were expressed as mean ± standard deviation or as median and interquartile range (25–75 percentiles), as appropriate, and compared using *t*-test for normal distributing variables and Mann–Whitney *U*-test for non-normal distribution. Univariable and multivariable analyses were conducted to evaluate risk factors for mortality, including penicillin susceptibility as a variable in the analysis. Variables considered significant in univariable analysis ($p < 0.05$) were introduced into the multivariable analysis. Analyses were performed using SAS. Sensitivity analyses according to the number of positive cultures (defining MBI–LCBI) and the presence of co-pathogens were planned.

Results

Overall, 125 hemato-oncological patients, who had VGS BSI during neutropenia, were included. These patients represented 66 patients from Rambam Health Care Campus, and 59 from Rabin Medical Center. Mean age was 53 years and ~ 50% (61/125) were women. Most patients (87%) had an active hematological disease at the time of BSI; however, most (85%) were independent in their functional capacity (ECOG 0). Most common malignancy was acute leukemia, followed by multiple myeloma and lymphoma; almost half of the patients had a previous stem cell transplant (allogeneic or autologous) (see Table 1 for baseline characteristics of patients). In 41 patients (33%), the isolate was penicillin non-susceptible; and in 8 patients (6.4%), it was penicillin resistant. Empirical therapy included in most cases a beta-lactam (111/125, 89%, piperacillin-tazobactam was used in 91/111 patients, meropenem in 15/111, and ceftazidime 5/111), and vancomycin was added in 62% of patients (78/125) (Table 1). Univariable analysis of risk factors for 30-day mortality is presented in Table 1.

No significant association was demonstrated between penicillin non-susceptibility and mortality (9/25, 26% of patients with a non-susceptible strain died, compared to 32/100, 32% who remained alive, $p = 0.81$) (Table 1). The use of vancomycin as either empirical or definitive therapy was also not associated with mortality; however, a trend towards lower mortality was demonstrated with the use of beta-lactams as definitive therapy (Table 1). Among patients with a non-susceptible strain, the use of vancomycin was not significantly associated with mortality (as either empirical, $p = 0.103$, or definitive therapy, $p = 0.491$).

In multivariable analysis, the following variables remained significantly associated with mortality: ECOG > 1 (aOR 12.53, 95% CI 3.64, 43.14; $p < 0.0001$); allogeneic transplantation (aOR 6.33, 95% CI 1.96, 20.46; $p = 0.002$); and co-pathogen in blood culture (aOR 3.99, 95% CI 1.34, 11.89; $p = 0.013$). No significant association was demonstrated between penicillin non-susceptibility and mortality (Table 2). Only 40 patients fulfilled the criteria for MBI–LCBI; among them, five patients died. Due to these small numbers, we did not perform a separate analysis. An analysis excluding 23 patients with a virulent co-pathogen in the index blood culture (mostly Gram negatives) showed no association between either penicillin non-susceptibility or vancomycin use and mortality.

In addition, penicillin non-susceptibility was not associated with other poor outcomes, including VGSS, ARDS, need for vasopressors or mechanical ventilation, ICU admission, or recurrence of bacteremia (Table 3).

Among the included patients, 30 (24%) underwent echocardiography within 14 days since the first positive culture. None of them had evidence of infective endocarditis.

Discussion

In this cohort of 125 hemato-oncology patients with *viridans group streptococci* BSI during neutropenia, non-susceptibility to penicillin was not associated with increased mortality. Moreover, the use of vancomycin as either empirical or definitive therapy did not have association with mortality. Outcomes of these adults with VGS BSI were poor, with mortality rate of 20% at 30 days, shock in 25%, and ARDS in 17%. Risk factors for mortality included reduced functional capacity, allogeneic transplantation, and a co-pathogen in blood cultures.

Our findings of no association between penicillin non-susceptibility and poor outcomes were also demonstrated by Shelburne et al. In this study, the non-susceptibility cut-off was MIC ≥ 2 µg/mL, while we used MIC ≥ 0.25 µg/mL; however, in both studies, the isolation of a "non-susceptible" VSG was not associated with increased mortality, shock, or ARDS. This is supported by additional studies demonstrating no association [2, 3].

We found that empirical as well as definitive use of vancomycin was not associated with improved outcomes. This is supported in general in febrile neutropenia by a meta-analysis of randomized controlled trials demonstrating no mortality

Table 1 Univariable analysis of risk factors for 30-day mortality among neutropenic patients with VGS BSI

Variable	Entire cohort ($N=125$)	Alive ($N=100$)	Dead ($N=25$)	OR (95% CI)	p-value
Age (mean ± SD)	53.9 ± 15.8	55.1 ± 16.8	51.5 ± 13.1		0.32
Gender (female) (*N* (%))	61 (48.8)	47 (47)	14 (56)	1.44 (0.59–3.47)	0.5
Hematologic diseases (*N* (%))					0.15
AML	63 (50.4)	50 (50)	13 (52)		
ALL	12 (9.6)	8 (8)	4 (16)		
MDS	6 (4.8)	4 (4)	2 (8)		
Lymphoma	16 (12.8)	11 (11)	5 (20)		
Multiple myeloma	26 (20.8)	25 (25)	1 (4)		
Transplant type (*N* (%))					0.005
Autologous*	36 (28.8)	33 (33)	3 (12)		
Allogeneic*	27 (21.6)	16 (16)	11 (44)		
No transplantation	62 (49.6)	51 (51)	11 (44)		
Prior to the BSI					
Oral mucositis (*N* (%))	63 (50.4)	52 (52)	11 (44)	0.73 (0.3–1.75)	0.51
Diarrhea (*N* (%))	44 (35.2)	36 (36)	8 (32)	0.84 (0.33–2.13)	0.82
Presence of central venous catheter (*N* (%))	109 (87.2)	91 (91)	18 (72)	0.25 (0.08–0.77)	0.02
Abx prophylaxis at least 48 h prior (N (%))	88 (70.4)	78 (78)	10 (40)	0.19 (0.07–0.48)	< 0.001
Beta-lactam treatment within 30 days prior to infection (*N* (%))	40 (32)	26 (26)	14 (56)	3.62 (1.46–8.98)	0.007
Characteristics of infection					
Fever at infection onset (*N* (%))	107 (85.6)	88 (88)	19 (76)	0.43 (0.14–1.29)	0.19
Diastolic BP (mean ± SD)	52.5 ± 3.5	59.8	63.3		0.41
Systolic BP (mean ± SD)	120 ± 9.9	108.2	108.9		0.91
Lowest neutrophil count (IQR 25%, 50%, 75%)	0.01, 0.06, 0.11	0.07	0.18		0.22
Any co-pathogen (*N* (%))	35 (28.0)	22 (22.0)	13 (52.0)	3.84 (1.54–9.60)	0.005
Enterobacterales (*E. coli*, *Klebsiella pneumoniae*) (*N* (%))	16 (12.8)	9 (9.0)	7 (28.0)		
Coagulase-negative staphylococci (*N* (%))	12 (9.6)	10 (10.0)	2 (8.0)		
Other** (*N* (%))	6 (4.8)	2 (2.0)	4 (16.0)		
Type of *Streptococcus viridans* (*N* (%))					0.75
S. mutans	9 (7.2)	6 (6.0)	3 (12.0)		
S. mitis	52 (41.6)	42 (42.0)	10 (40.0)		
S. salivarius	6 (4.80)	5 (5.0)	1 (4.0)		
S. viridans spp.	39 (31.2)	33 (33)	6 (24.0)		
Other	19 (15.2)	14 (14.0)	5 (20.0)		
Penicillin non-susceptible (MIC > 0.25) (*N* (%))	41 (32.8)	32 (32)	9 (36)	1.19 (0.48–2.99)	0.81
Treatment with in vitro covering antibiotic within 48 h (*N* (%))	108 (87.1)	86 (86)	11 (91.67)	1.79 (0.38–8.47)	0.74
Definitive beta-lactam treatment (*N* (%))	117 (93)	96 (96)	21 (84)	0.22 (0.05–0.96)	0.0503
Definitive vancomycin treatment (*N* (%))	96 (78)	77 (77)	19 (76)	0.95 (0.34–2.65)	1
Empiric beta-lactam treatment (*N* (%))	111 (88.8)	91 (91)	20 (80)	0.4 (0.12–1.31)	0.15
Empiric vancomycin treatment (*N* (%))	78 (62.4)	60 (60)	18 (72)	1.71 (0.66–4.48)	0.36

AML, acute myeloid leukemia; *ALL*, acute lymphoid leukemia; *MDS*, myelodysplastic syndrome; *Abx*, antibiotics; *BSI*, bloodstream infection; *CI*, confidence interval; *SD*, standard deviation; *BP*, blood pressure; *IQR*, interquartile; *WBC*, white blood cell; *MIC*, minimum inhibitory concentration

Odds ratio > 1 correlates with higher risk for mortality

*Median time from transplant to positive culture was 12 (interquartile range 10.75–15 days)

**_Enterococcus_ spp. = 2; _S. aureus_ = 1; _Streptococcus pneumoniae_ = 1; _Rothia mucilaginosa_ = 1; _Acinetobacter_ spp. = 1; _Candida_ spp. = 1

Table 2 Multivariable analysis of risk factors for 30-day mortality among neutropenic patients with VGS BSI

Variable	Adjusted odds ratio	95% confidence interval	*p*-value
ECOG performance status > 1	12.53	3.64, 43.14	< 0.0001
Allogeneic SCT (compared to auto or none)	6.33	1.96, 20.46	0.002
Co-pathogen	3.99	1.34, 11.89	0.013
Penicillin non-susceptible (MIC > 0.25)	0.7	0.22, 2.18	0.54

VGS, *viridans group streptococci*; *ECOG*, Eastern Cooperative Oncology Group; *SCT*, stem cell transplantation; *MIC*, minimum inhibitory concentration

Odds ratio > 1 correlates with higher risk for mortality

Table 3 Secondary outcomes by susceptibility status of the VGS isolate

Variable	Entire cohort (*N* = 125)	Susceptible *Streptococcus viridans* (*N* = 84)	Non-susceptible *Streptococcus viridans* (*N* = 41)	*p*-value
Shock	30 (24.8)	22 (27.5)	8 (19.5)	0.46
ARDS	21 (17.4)	15 (18.8)	6 (14.6)	0.76
Need for mechanical ventilation	13 (10.7)	11 (13.8)	2 (4.9)	0.24
Need for vasopressors	20 (16.5)	14 (17.5)	4 (14.6)	0.89
ICU	6 (5)	5 (6.2)	1 (2.4)	NA
Recurrent VGS BSI within 30 days	6 (5)	5 (6.2)	1 (2.4)	NA

VGS, *viridans group streptococci*; *ARDS*, acute respiratory distress syndrome; *ICU*, intensive care unit; *BSI*, bloodstream infection

benefit with the addition of anti-Gram-positive coverage to beta-lactam empirical therapy [9]. Moreover, in a study evaluating 257 cases of bacteremia septic shock in FN, only 9% of cases were caused by any streptococcal species, and empirical coverage for Gram positives did not impact mortality [18]. Specifically for VGS BSI, Shelburne et al. also did not demonstrate mortality difference following the use of vancomycin [8]. In the subgroup of patients with non-susceptible VGS in our cohort, vancomycin, as part of the definitive therapy, was not associated with mortality benefit either.

Risk factors for mortality included reduced functional capacity, allogeneic transplantation, and a co-pathogen in blood cultures. Previous studies on VGS BSI in neutropenic patients did not address predictors of mortality other than bacterial susceptibility and treatment.

Older studies reported increased mortality among neutropenic patients with VGS BSI who had a non-susceptible isolate and/or were not treated with vancomycin [13, 19]. Following this, vancomycin has become an integral part of the empiric therapy for neutropenic fever in some centers [8], although the IDSA guidelines do not recommend its routine use [3, 10]. Our study supports the recommendation to avoid the use of vancomycin as routine empiric treatment for neutropenic fever. Regarding definitive therapy for VGS BSI, we did not demonstrate an association between vancomycin definitive therapy and mortality. Moreover, even among patients with a non-susceptible strain, the use of vancomycin did not reduce mortality. This may be explained by susceptibility of the VGS to other beta-lactam antibiotics. In the study by Shelburne et al., all penicillin non-susceptible isolates were found to be susceptible to both cefepime and piperacillin-tazobactam, and most to meropenem [8].

Our study has several limitations. The study period was 12 years and variations in treatment may have occurred during this time. In fact, in the first 3 years, only 6 patients were included. However, patients were included from two of the main referral hemato-oncology centers in our country, where hematological practices were similar and following international guidelines. Both centers used ciprofloxacin as prophylaxis among neutropenic patients, and vancomycin was used empirically in specific situations, according to the IDSA guidelines [10]. Infection control practices are guided by a national infection control center and are similar in both centers [20].

We used the clinical practical definition of at least one positive blood culture and symptoms to diagnose VGS BSI. Though we believe this is the optimal definition, since clinically such patients are almost always treated as true BSI, we acknowledge that some of these cases may be contamination only. In addition, our analysis includes cultures growing a co-pathogen. This situation is similarly usually treated as true infection, but some cases may represent true BSI of the co-pathogen only. We considered in an additional analysis excluding patients with a virulent co-pathogen which showed similar results to the original analysis. Although mortality was higher among patients with VSG and co-pathogens, there was no association between penicillin

non-susceptibility or vancomycin use and mortality in the subgroup of patients who had only VGS BSI.

In summary, among neutropenic patients with VGS BSI, we found that non-susceptibility to penicillin was not associated with increased mortality. The addition of vancomycin, as empirical or definitive therapy, was not associated with improved outcomes. Therefore, we recommend not to use vancomycin routinely for this infection. Further studies should assess the association between penicillin non-susceptibility and susceptibility to other beta-lactams.

Data availability All data can be provided by the corresponding author upon request.

Code availability Not applicable.

Declarations

Ethics approval This study was approved by the local ethical committee of both Rabin Medical Center and Rambam Health Care Campus.

Consent to participate Informed consent was waived by both ethical committees due to the retrospective design.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

References

1. Cordonnier C, Buzyn A, Leverger G, Herbrecht R, Hunault M, Leclercq R et al (2003) Epidemiology and risk factors for gram-positive coccal infections in neutropenia: toward a more targeted antibiotic strategy. Clin Infect Dis 15(36):149–158. https://doi.org/10.1086/345435
2. Han SB, Bae EY, Lee JW, Lee DG, Chung NG, Jeong DC et al (2013) Clinical characteristics and antibiotic susceptibility of viridans streptococcal bacteremia in children with febrile neutropenia. Infection 41:917–924. https://doi.org/10.1007/s15010-013-0470-7
3. Freifeld AG, Razonable RR (2014) Viridans group streptococci in febrile neutropenic cancer patients: what should we fear? Clin Infect Dis 15(59):231–233. https://doi.org/10.1093/cid/ciu264
4. Dulanto Chiang A, Sinaii N, Palmore TN (2018) Risk factors for viridans group streptococcal bacteremia in neutropenic and non-neutropenic patients: a single center case-case-control study. Open Forum Infect Dis 5:ofx260. https://doi.org/10.1093/ofid/ofx260
5. Marron A, Carratalà J, Alcaide F, Fernández-Sevilla A, Gudiol F (2001) High rates of resistance to cephalosporins among viridans-group streptococci causing bacteraemia in neutropenic cancer patients. J Antimicrob Chemother 47:87–91. https://doi.org/10.1093/jac/47.1.87
6. Carvalho AS, Lagana D, Catford J, Shaw D, Bak N (2020) Bloodstream infections in neutropenic patients with haematological malignancies. Infect Dis Health 25:22–29. https://doi.org/10.1016/j.idh.2019.08.006
7. Zimmer AJ, Stohs E, Meza J, Arnold C, Baddley JW, Chandrasekar P et al (2022) Bloodstream infections in hematologic malignancy patients with fever and neutropenia: are empirical antibiotic therapies in the United States still effective? Open Forum Infect Dis 9:ofac240. https://doi.org/10.1093/ofid/ofac240
8. Shelburne SA, Lasky RE, Sahasrabhojane P, Tarrand JT, Rolston KVI (2014) Development and validation of a clinical model to predict the presence of β-lactam resistance in viridans group streptococci causing bacteremia in neutropenic cancer patients. Clin Infect Dis 15(59):223–230. https://doi.org/10.1093/cid/ciu260
9. Paul M, Dickstein Y, Borok S, Vidal L, Leibovici L (2014) Empirical antibiotics targeting gram-positive bacteria for the treatment of febrile neutropenic patients with cancer. Cochrane Database Syst Rev 14:003914. https://doi.org/10.1002/14651858.CD003914.pub3
10. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA et al (2011) Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clin Infect Dis 15(52):e56-93. https://doi.org/10.1093/cid/cir073
11. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA et al (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 101:1644–55. https://doi.org/10.1378/chest.101.6.1644
12. The ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E et al (2012) Acute respiratory distress syndrome: the Berlin definition. JAMA 20(307):2526–33. https://doi.org/10.1001/jama.2012.5669
13. Elting LS, Rubenstein EB, Rolston KV, Bodey GP (1997) Outcomes of bacteremia in patients with cancer and neutropenia: observations from two decades of epidemiological and clinical trials. Clin Infect Dis 25:247–259. https://doi.org/10.1086/514550
14. EUCAST: Clinical breakpoints and dosing of antibiotics [Internet]. [cited 2021 19]; https://www.eucast.org/clinical_breakpoints/
15. Chen P-L, Lee T-F, Wu C-J, Teng S-H, Teng L-J, Ko W-C et al (2014) Matrix-assisted laser desorption ionization-time of flight mass spectrometry can accurately differentiate Aeromonas dhakensis from A. hydrophila, A. caviae, and A. veronii. J Clin Microbiol 52:2625–8. https://doi.org/10.1128/JCM.01025-14
16. Hsueh P-R, Kuo L-C, Chang T-C, Lee T-F, Teng S-H, Chuang Y-C et al (2014) Evaluation of the Bruker Biotyper matrix-assisted laser desorption ionization-time of flight mass spectrometry system for identification of blood isolates of Acinetobacter species. J Clin Microbiol 52:3095–3100. https://doi.org/10.1128/JCM.01233-14
17. CLSI & Antimicrobial Susceptibility Testing (AST) [Internet]. Clinical & Laboratory Standards Institute [cited 2022 5]; https://clsi.org/meetings/susceptibility-testing-subcommittees/clsi-and-ast/
18. Chumbita M, Puerta-Alcalde P, Gudiol C, Garcia-Pouton N, Laporte-Amargós J, Ladino A et al (2022) Impact of empirical antibiotic regimens on mortality in neutropenic patients with bloodstream infection presenting with septic shock. Antimicrob Agents Chemother 15(66):e0174421. https://doi.org/10.1128/AAC.01744-21
19. Spanik S, Trupl J, Kunova A, Botek R, Sorkovska D, Grey E et al (1997) Viridans streptococcal bacteraemia due to penicillin-resistant and penicillin-sensitive streptococci: analysis of risk factors and outcome in 60 patients from a single cancer centre before and after penicillin is used for prophylaxis. Scand J Infect Dis 29:245–249. https://doi.org/10.3109/00365549709019036
20. The Israeli national center for infection prevention and control [Internet]. www.gov.il [cited 2022 5];https://www.gov.il/he/departments/units/infection_control_center/govil-landing-page