Infectious Risks and Complications in Adult Leukemic Patients Receiving Blinatumomab

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Abstract. Background: Blinatumomab is an anti-CD19 immunotherapy approved for relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) with significantly increased survival rate. While blinatumomab showed lower rates of infection, neutropenia and mucosal barrier injury versus chemotherapy, its infection risks are not well described.

Methods: All patients who received blinatumomab for ≥ seven days at an academic cancer center from May 2015 to April 2017 were included. Patient characteristics pertinent to infectious risks and complications were examined.

Results: Twenty patients with refractory (25%), relapsed (70%), or remitted (5%) B-ALL who received a total of 35 cycles were included. Ten of the 35 cycles were interrupted, none of which were due to infections. Twenty-six infections (n) were observed with lower respiratory (9), gastrointestinal (6) and bacteremia (5) being most common. Compared to patients without nodular, possible mold pneumonia (n=16), patients with nodular pneumonia (n=4) had significantly lower baseline absolute neutrophil count (ANC) (2319 v. 208/µL, p=0.011). There were no differences in baseline characteristics including ANC between bacteremic and non-bacteremic patients. One patient was discharged with no antibacterial prophylaxis since ANC recovered to >500cells/µL, but developed Pseudomonal bacteremia within a week with ANC ~100cells/µL.

Conclusion: Despite blinatumomab’s relatively modest myelosuppression and the lack of mucotoxicity, host factors (e.g., duration and degree of neutropenia/lymphopenia) play a key role and should be considered when choosing anti-microbial prophylaxis. In relapsed/refractory disease, the ANC should be monitored closely post blinatumomab since neutropenia can unexpectedly develop after treatment which may be compounded by the underlying disease and recent chemotherapy effects.

Keywords: Blinatumomab, Infection, Prophylaxis, Neutropenia.

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Introduction. Blinatumomab is a bispecific monoclonal antibody that enables CD3-positive T-cells to identify and eradicate CD19 expressed on B-cells in acute lymphoblastic leukemia (ALL).1 It activates endogenous T-cells by connecting CD3 in the T-cell receptor complex with CD19 on either malignant or benign B-cells, thus forming a cytolytic synapse between a cytotoxic T-cell and
the cancer target B-cell. Blinatumomab was approved for use in patients with relapsed or refractory B-cell precursor ALL based on a phase 2 trial which showed a 43% complete remission rate with complete or partial hematologic recovery and 6.1 months of the median overall survival.²

More recently, a multi-institutional phase 3 trial by Kantarjian and colleagues showed blinatumomab group with a significantly increased overall survival as compared to chemotherapy group, which led to an early termination of the study; the median overall survival was 7.7 months in the blinatumomab group v. 4.0 months in the chemotherapy group (hazard ratio for death blinatumomab vs. chemotherapy, 0.71, p=0.01).³

Interestingly, in the phase 3 trial, blinatumomab group had numerically lower rates of infection (34.1% v. 52.3%), neutropenia (37.8% v. 57.8%), lymphopenia (1.5% v. 3.7%) and stomatitis (6.7% v. 12.8%) as compared to chemotherapy group.¹,³ However, complications from blinatumomab also included cytokine release syndrome (4.9% v. 0%), which mimics infection by mediating the production of cytotolytic proteins, release of inflammatory cytokines, and proliferation of T-cells, then ultimately lysis of CD19-positive cells. Furthermore, numerically higher rates of hypogammaglobulinemia (6.0% v. 0.9%),³ upper respiratory tract infection (7.1% v. 0.9%) and serious pneumonia (3.7% v. 1.8%) were observed with blinatumomab, which rose concerns for its infectious risks and complications.¹ Of note, the phase 3 trial required antifungal prophylaxis primarily using posaconazole for the patients who previously underwent allogeneic hematopoietic stem-cell transplantation (HSCT) and presented with a medical history of graft-versus-host disease (GVHD), but the protocol does not discuss antibacterial prophylaxis.⁴ In the phase 2 trial, institutional guidelines for infections were followed when patients became neutropenic, but no details about antimicrobial prophylaxis were provided.²

Currently, antiviral prophylaxis with acyclovir and anti-Pneumocystis jiroveci pneumonia prophylaxis with sulfamethoxazole-trimethoprim are recommended as per National Comprehensive Cancer Network (NCCN) guidelines⁵ for patients with active ALL. However, guidelines for anti-bacterial and anti-fungal prophylaxis are not well established in patients receiving blinatumomab. In this retrospective review, we intended to describe infectious risks and complications in these patients to assist in the supportive care from an Infectious Diseases standpoint including determination of appropriate antimicrobial prophylaxis regimen.

**Patients and Methods.**

**Study Subjects and Design.** A single-center, retrospective, non-interventional study was conducted among adult patients who received blinatumomab for the treatment of ALL between May 1, 2015 and April 1, 2017 at Moffitt Cancer Center (Tampa, FL, USA). All patients who underwent blinatumomab treatment during the study period were identified from Moffitt Cancer Center Cerner’s PowerChart. Among these, patients with less than seven days of the blinatumomab treatment were excluded.

The study was approved by the Institutional Review Board of University of South Florida. For this type of study formal consent is not required; an informed consent waiver was granted as all data were currently in existence and no patient-specific interventions were conducted for the study. The collection of data was in compliance with the Health Insurance Portability and Accountability Act of 1996.

**Patient Characteristics and Infectious Risks.** Once patients were identified, the following characteristics were extracted from the medical records: age; gender; treatment phase (refractory to primary or salvage therapy, first relapse with remission <12 months, first relapse with remission >12 months, untreated second or greater relapse, relapse after HSCT or treatment with chimeric antigen receptor modified T-cells (CART), remission, or unspecified); prior chemotherapy regimens; other immunosuppressive comorbid conditions or treatment; recent infections within 7 days prior to initiation of blinatumomab; recent use of intravenous antimicrobials within 90 days prior to initiation of blinatumomab; days between prior cytotoxic chemotherapy and blinatumomab; total number of blinatumomab cycles and reasons for interrupted blinatumomab treatment if any; baseline absolute neutrophils (ANC) and lymphocyte (ALC) count; incidence, severity and duration of neutropenia and lymphopenia and whether there was a growth factor support or not.

**Infectious Complications.** Microbiological culture-proven infections and clinically diagnosed
infections by imaging and physical exams were recorded. Nodular pneumonia defined as an opaque macronodule of \( \geq 1 \text{cm} \) in diameter, which is by far the most common CT finding in invasive aspergillosis and present in \( > 90\% \) of patients,\(^6\) is assessed at baseline and every two weeks during the duration of neutropenia using CT thorax without contrast. Mortalities at 30 and 60 days after the end of the first cycle of blinatumomab were assessed.

Statistical Analysis. For bacteremia and nodular pneumonia suspicious for mold infection, the following characteristics were compared between the case and control groups using Mann-Whitney U test for the ordinal or non-normally distributed continuous variables and chi-square test for nominal variables: immunosuppressing conditions or treatments, cytotoxic chemotherapy prior to blinatumomab within 21 days, baseline neutrophil and lymphocyte counts, and incidence, severity and duration of neutropenia and lymphopenia. Multinomial logistic regression tests were performed after univariate analyses to evaluate risk factors associated with nodular pneumonia and bacteremia. A two-tailed \( P \) value of \(< 0.05 \) was considered to be statistically significant. All data were analyzed using SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0., Armonk, NY, USA).

Results.

Patient Characteristics and Infectious Risks. Twenty patients who received a total of 35 cycles of blinatumomab between May 1, 2015 and April 1, 2017 were included in analyses after excluding two patients who received blinatumomab for less than seven days. Baseline characteristics are summarized in Table 1. Ten of the 35 cycles were interrupted for the following reasons: 4 cytokine release syndrome (CRS), 3 liver function test abnormalities (1 transaminitis, 2 hyperbilirubinemia) and 3 patients with disease progression while on blinatumomab. None of the interruptions were deemed due to infections although a patient with CRS also had mild ground glass pneumonia. Most patients had refractory (25\%) or relapsed (70\%) disease with a median of two previous chemotherapies. Four patients had recent infections within 7 days prior to initiation of blinatumomab: \textit{C. difficile} colitis (n=1), viral upper respiratory infection (n=1), Pseudomonal bacteremia (n=1) and one patient with both sinusitis and nodular,\(^6\) possible\(^7\) mold pneumonia per CT scan. Twelve of 20 patients received intravenous antimicrobials within 90 days prior to blinatumomab treatment. Only two patients received growth factor support. Mean durations of neutropenia (ANC \(< 500 \text{ cells/µL} \)) and severe neutropenia (ANC \(< 100 \text{ cells/µL} \)) were 11.1 \( \pm 3.9 \) and 2.7 \( \pm 1.5 \) days, respectively, and the corresponding durations for lymphopenia were 12.6 \( \pm 11.3 \) (ALC \(< 500 \text{ cells/µL} \)) and 1.4 \( \pm 1.5 \) (ALC \(< 100 \text{ cells/µL} \)) days.

Irrs. \( ^{6} \)If a patient had more than one immunosuppressing conditions or treatment, it was counted multiple times.

\( ^{b} \)Hydroxyurea+cyclophosphamide (n=1), FLAD+idarubicin (n=1), cyclophosphamide (n=3), cyclophosphamide+ VXL (n=1) \textit{ANC} or ALC on day 1 of the first blinatumomab cycle received at our institution; HSCT=Hematopoietic stem cell transplantation; CART=Chimeric.

\begin{table}[ht]
\centering
\caption{Patient Characteristics.}
\begin{tabular}{|l|c|}
\hline
\textbf{Characteristic} & \textbf{BLINATUMOMAB (n=20)} \\
\hline
\hline
Age, y, mean ± SD & 46.1 ± 15.7 \\
\hline
Female gender, n & 11 \\
\hline
Treatment phase, n (%) & \\
\hline
Refactory to primary or salvage therapy & 5 (25) \\
First relapse with remission <12 months & 3 (15) \\
First relapse with remission >12 months & 1 (5) \\
Untreated second or greater relapse & 4 (20) \\
Relapse after allo-HSCT or treatment with CART cells & 6 (30) \\
Remission & 1 (5) \\
\hline
Previous chemotherapy, n, median & \\
1 & 2 \\
2 & 7 \\
3 & 3 \\
\geq 4 & 6 \\
\hline
Other immunosuppressive comorbid conditions or treatment & \\
Other cancer & 3 \\
Diabetes mellitus & 2 \\
HSCT or CART & 3 \\
Cytotoxic chemotherapy < 21 days & 6 \\
Immunosuppressants for GVHD & 2 \\
Consecutive steroid ≥ 7 days & 3 \\
Baseline ANC\(^{a}\), mean ± SD & 1897 ± 1997 \\
Baseline ALC\(^{a}\), mean ± SD & 942 ± 1058 \\
\hline
\end{tabular}
\end{table}

Infectious Complications. While six patients did not experience infections, 14 patients had a total of 26 infections, of which lower respiratory (n=9), gastrointestinal (n=6) and bacteremia (n=5) were
most common during or 30 days after the blinatumomab treatment. Four patients had nodular, possible invasive mold pneumonia, three of which were newly developed on blinatumomab with normal baseline CT thorax. None of the four patients had met direct (i.e., cytology, direct microscopy, or culture-proven) nor indirect [i.e., Aspergillus galactomannan antigen (GM) or β-D-glucan test (BDG)] microbiological criteria for proven or probable invasive fungal infection, but had host factors and radiologic evidence of invasive mold pneumonia (i.e. nodular consolidation with halo signs). One patient who already had possible mold pneumonia prior to blinatumomab received isavuconazole throughout blinatumomab treatment. Two patients were on micafungin and the last patient was on voriconazole followed by posaconazole as antifungal prophylaxis before the CT findings of possible mold pneumonia. Compared to patients without nodular, possible mold pneumonia, patients with nodular pneumonia had significantly lower ANC on the first day of blinatumomab (2319 v. 208/µL, p=0.011). In multinomial logistic regression, ANC on the first day of blinatumomab remained significantly associated with nodular pneumonia (p= 0.020) when controlled for other immunosuppressing conditions and cytotoxic chemotherapy within 21 days prior to blinatumomab.

There were 5 episodes of bacteremia from 4 patients, two of which were polymicrobial (Table 2). Three of the 4 patients received cytotoxic chemotherapy within 21 days of blinatumomab, and the timelines between the onset of bacteremia and cytotoxic chemotherapy are listed in the footnote (Table 2). One patient was discharged with no antibacterial prophylaxis since ANC recovered to >500 cells/µL, but developed Pseudomonal bacteremia on day 35 of blinatumomab and days to become severely neutropenic (ANC < 100 cells/µL) were significantly correlated to nodular pneumonia (Table 3), but the duration of lymphopenia nor the severity of lymphopenia were not related (data not shown). The similar analysis for bacteremia found no significantly associated factors.

| Site of infection                  | Number of cases |
|-----------------------------------|----------------|
| Head, eyes, ears, nose, throat    | 1              |
| Herpes libialis                   | 1              |
| Tonsilitis                        | 1              |
| Sinusitis                         | 1              |
| Otitis media                      | 1              |
| Lower respiratory                 | 2              |
| Bronchitis                        | 3              |
| Ground glass pneumonia            | 4              |
| Nodular, possible mold pneumonia  | 5              |
| Blood                             |                |
| Leptotrichia + Bacteroides fragilis | 1            |
| Enterococcus faecium              | 1              |
| Streptococcus mitis/oralis        | 1              |
| Pseudomonas aeruginosa            | 1              |
| Escherichia coli + S. mitis/oralis | 1            |
| Skin                              | 3              |
| Cellulitis                        |                |
| Vulvovaginitis                    | 1              |
| Gastrointestinal                  | 1              |
| Cholecystitis                     | 1              |
| Liver abscess                     | 1              |
| Proctitis, appendicitis vs. typhilitis | 1          |
| Clostridium difficile colitis     | 3              |

*Two episodes of bacteremia in a patient on day 7 and day 9 of blinatumomab, the patient had hemorrhoids and received hydroxyurea on day -3 to -1 and cyclophosphamide on day 13 to 17. Bacteremia on day 9 of blinatumomab, the patient had mucositis, and did not receive cytotoxic chemotherapy < 21 days; Bacteremia on day 35 of blinatumomab, the patient received cyclophosphamide day -7 to -3, and was discharged with no antibacterial prophylaxis since the ANC recovered to >500 cells/µL, but developed Pseudomonal bacteremia in a week with ANC~ 100/µL; Bacteremia on day 35 of blinatumomab, cyclophosphamide -1 to -3, then VXL on day 18 of blinatumomab.

Two patients were sent to hospice care by 30 days post blinatumomab with progressive disease, one of whom also had nodular, possible mold pneumonia and bacteremia. There were two other patients who expired in the 30 to 60-day range, one of whom experienced multiple infectious complications (i.e., pansinusitis, possible mold pneumonia, P. aeruginosa bacteremia and C. difficile colitis). Additional two patients were sent to hospice care by 60 days post blinatumomab with progressive disease.
Discussion. Blinatumomab is an anti-CD19 immunotherapy, newly approved for relapsed or refractory B-cell ALL with significantly increased survival rate. While it showed lower rates of infection, myelosuppression and mucosal barrier injury as compared to conventional chemotherapy in phase 3 clinical trial, there are yet concerns about its infectious risks due to hypogammaglobulinemia, severe pneumonia as well as infection-mimicking complications such as cytokine release syndrome. In our small retrospective chart review of 20 patients who received blinatumomab, lower respiratory infections were most commonly observed followed by intra-abdominal infections and bacteremia. We report a relatively high incidence rate of 15% for nodular, possible mold pneumonia newly developed on blinatumomab treatment, which was associated with duration and degree of neutropenia.

Host factors in hematologic malignancies, i.e., impaired antifungal defenses, have been recognized as important risks for invasive fungal disease which have accounted for a disproportionate number of fungal pneumonia in North America and Europe. While we did not find statistical differences in other host factors such as receipt of immunosuppressive agents or other immunosuppressing conditions including history of HSCT between the patients with and without nodular pneumonia, we found the differences in baseline ANC, which is a well-known risk factor for fungal pneumonia. Historically, the incidence of invasive fungal infection in hematologic malignancy or HSCT ranges from 0.8-11.3%. The high incidence rates of 15% (i.e., 3 of 20 patients excluding one patient who already had possible mold pneumonia prior to blinatumomab) for possible mold pneumonia in our patient echoed the role of the compromised host factors in the patients with relapsed or refractory ALL for whom blinatumomab is approved. This is well reflected in our patients’ treatment phase and numbers of previous chemotherapies, 50% of which were comprised of untreated second or greater relapse or post HSCT and who received ≥ three previous chemotherapies, respectively. Although blinatumomab itself causes less myelosuppression than conventional chemotherapy, when designing antimicrobial prophylaxis in these patients with relapsed or refractory ALL, compromised host factors should be considered, and we advocate for anti-mold coverage when the baseline ANC is < 500 cells/µL.

On the other hand, the incidence of bacteremia was not significantly associated with the baseline ANC. Since chemotherapy-induced mucositis is associated with early onset of bacteremia and blinatumomab causes less stomatitis than conventional chemotherapy (6.7% v. 12.8%), we investigated the timing between the onset of bacteremia and other cytotoxic chemotherapy given pre and post blinatumomab (Table 2). While hydroxyurea is not considered conventional chemotherapy, it could cause severe mucositis, thus was counted as cytotoxic chemotherapy. Although 3 of the 4 bacteremic patients received cytotoxic chemotherapy prior to initiation of blinatumomab within 21 days, 2 of those 3 patients had bacteremia on day 35 of blinatumomab, which makes it less likely that the episodes of bacteremia were related to the cytotoxic chemotherapy that was received prior to  

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Table 3. Factors associated with nodular, possible mold pneumonia and bacteremia.

| Variable | Nodular pneumonia (N=4) | No nodular pneumonia (N=16) | P value | Bacteremia (N=4) | No bacteremia (N=16) | P value |
|----------|-------------------------|-----------------------------|---------|------------------|----------------------|---------|
| Other Immunosuppressing conditions, n, % | 4, 100 | 8, 50 | 0.4 | 2, 50 | 8, 50 | 1.0 |
| Immunosuppressants other than blinatumomab, n, % | 3, 75 | 5, 31 | 0.4 | 3, 75 | 5, 31 | 0.4 |
| Cytotoxic chemotherapy within 21 days prior to blinatumomab, n, % | 3, 75 | 3, 19 | 0.07 | 3, 75 | 3, 19 | 0.1 |
| Numbers of chemotherapy regimens prior to blinatumomab, median | 2 | 2 | 0.9 | 2 | 2 | 1.0 |
| ANC on day 1 of blinatumomab, mean ± SD | 208 ± 362 | 2319 ± 2083 | **0.01** | 1997 ± 2617 | 1872 ± 1986 | 0.6 |
| ALC on day 1 of blinatumomab, mean ± SD | 443 ± 284 | 1067 ± 1180 | 0.1 | 1578 ± 2359 | 783 ± 495 | 0.6 |
| Days to ANC <500, mean ± SD | 0.3 ± 0.5 | 4.6 ± 5 | 0.1 | 2.3 ± 2.6 | 4 ± 5 | 0.8 |
| Days to ANC <100, mean ± SD | 0.5 ± 1 | 17 ± 18 | **0.02** | 4 ± 7 | 14 ± 18 | 0.2 |

ANC= absolute neutrophil counts, ALC= absolute lymphocyte counts, SD=standard deviation.
blinatumomab. Furthermore, one of these two patients who had bacteremia on day 35 of blinatumomab, also received VXLD (dexamethasone, doxorubicin, vincristine, bortezomib and peg-asparaginase) on day 18 of blinatumomab, which is known to induce mucositis and bacterial translocation from the gut. Nonetheless, compared to non-bacteremic patients, numerically higher number of patients with bacteremia received cytotoxic chemotherapy ≤21 days of blinatumomab (Table 3). Other than mucositis, chemotherapy dose gram/m², severe neutropenia of ANC <100 cell/µL, or previous use of antibacterial prophylaxis for neutropenia have been identified as risks for bacteremia. Understandably, one of our patients had hemorrhoids and developed two episodes of polymicrobial bacteremia. Another patient developed pseudomonal bacteremia when ANC dropped to around 100 cells/µL after being discharged post count recovery, i.e. ANC>500 cell/µL without antibacterial prophylaxis. Fluctuation in ANC is not uncommon in relapsed or refractory disease, and ANC should be monitored closely during both inpatient and outpatient stays as neutropenia can unexpectedly develop after blinatumomab which may be compounded by the underlying disease and recent chemotherapy effects. While we did not identify specific risk factors associated with breakthrough bacteremia, we propose antibacterial prophylaxis to be individualized based on the degree of neutropenia, other recent cytotoxic chemotherapy, mucositis, previous bacterial infections and other risk factors such as hemorrhoids. For example, antibacterial prophylaxis may be initiated when ANC < 100 cell/µL for most patients receiving blinatumomab treatment, but the ANC cut-off may be changed to <500 cell/µL if other risk factors coexist.

Conclusions. Based on the findings herein, we advocate for anti-mold coverage when ANC < 500/µL in this patient population considering compromised host factors. While we need more data to support our recommendation for anti-bacterial prophylaxis in this population, it may be prudent to individualize based on well-known risk factors. In relapsed or refractory disease, the ANC should be monitored closely post blinatumomab since neutropenia can unexpectedly develop after treatment.

References:

1. Kantarjian H, Stein A, Golubet N, Fielding AK, Schuh AC, Ribera JM, Wei A, Dombret H, Foa R, Bassan R, Arslan O, Sanz MA, Bergeron, Demirkan F, Lech-Maranda E, Rambaldi A, Thomas X, Horst HA, Bruggemann M, Klapper W, Wood BL, Fleishman A, Nagorsen D, Holland C, Zimmerman Z, Topp MS. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med 2017;376:836-47. https://doi.org/10.1056/NEJMoa1609783

2. Topp MS, Golubet N, Stein AS, Zugmaier G, O'Brien S, Bargou RC, Dombret H, Fielding AK, Helftter L, Larson RA, Neumann S, Foa R, Litzow M, Ribera JM, Rambaldi A, Schiller g, Bruggemann M, Hoest HA, Holland C, Jia C, Maniar T, Huber B, NagorsenD, Forman SJ, Kantarjian HM. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicenter, single-arm, phase 2 study. Lancet Oncol 2015;16:57-66. https://doi.org/10.1016/S1470-2045(14)71170-2

3. Supplement to: Kantarjian H, Stein A, Golubet N, Fielding AK, Schuh AC, Ribera JM, Wei A, Dombret H, Foa R, Bassan R, Arslan O, Sanz MA, BergeronJ, Demirkan F, Lech-Maranda E, Rambaldi A, Thomas X, Horst HA, Bruggemann M, Klapper W, Wood BL, Fleishman A, Nagorsen D, Holland C, Zimmerman Z, Topp MS. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med 2017;376:836-47. https://doi.org/10.1056/NEJMoa1609783

4. Protocol Kantarjian H, Stein A, Golubet N, Fielding AK, Schuh AC, Ribera JM, Wei A, Dombret H, Foa R, Bassan R, Arslan O, Sanz MA, BergeronJ, Demirkan F, Lech-Maranda E, Rambaldi A, Thomas X, Horst HA, Bruggemann M, Klapper W, Wood BL, Fleishman A, Nagorsen D, Holland C, Zimmerman Z, Topp MS. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med 2017;376:836-47. https://doi.org/10.1056/NEJMoa1609783

5. National Comprehensive Cancer Network. Prevention and treatment of cancer-related infections. https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf, Accessed Nov 2, 2017.

6. Greene R. The radiological spectrum of pulmonary aspergillosis. Med Mycol 2005;43 Suppl 1:S1-47-54.

7. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, Pappas PG, Maertens J, Lorholtay O, Kaufman CA, Denning DW, Patterson TF, Maschmeyer G, Bille J, Dismukes WE, Herbrecht R, Hope WW, Kibbler CC, Kullberg BJ, Marr KA, Mu-oz P, Odds FC, Perfect JR, Restrepo A, Ruhnke M, Segal BH, Sobei JD, Sorrell TC, Viscoli C, Wingard JR, Zauitis T, Bennett JE. European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group; National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008;46:1813-21. https://doi.org/10.1086/588660

PMid:18462102 PMCID:PMC2671227

8. Bitar D, Lorholtay O, Le Stray Y, Nicolau J, Coignard B, Tattevin P, Che D, Dromer F. Population-based analysis of invasive fungal infections. France, 2001-2010. Emerg Infect Dis 2014;20:1149-55. https://doi.org/10.3201/eid2007.140087

P MID:24960357 PMCID:PMC4073874

9. Aziz N, Neovyes D, Pfüller M, Meier-Kriesche HU, Quan SP, Horn D. The PATH (Prospective antifungal therapy) Alliance© registry and invasive fungal infections: update 2012. Diagn Microbiol Infect Dis 2012;73:293-300. https://doi.org/10.1016/j.diagmicrobio.2012.06.012

PMID:22738487

10. Gerson SL, Talbot GH, Hurwitz S, Strom BL, Lusk EJ, Cassileth PA. Prolonged granulocytopoenia: the major risk factor for invasive
10. Kurosawa M, Yonezumi M, Hashino S, Tanaka J, Nishio M, Kaneda M, Ota S, Koda K, Suzuki N, Yoshida M, Hirayama Y, Takimoto R, Torimoto Y, Morii A, Takahashi T, Iizuka S, Ishida T, Kobayashi R, Oda T, Sakai H, Yamamoto S, Takahashi F, Fukuhara T. Epidemiology and treatment outcome of invasive fungal infections in patients with hematological malignancies. Int J Hematol 2012;96:748-57. https://doi.org/10.7326/0003-4819-100-3-345

11. Sun Y, Huang H, Chen J, Li J, Ma J, Li J, Liang Y, Wang J, Li Y, Yu K, Hu J, Jin J, Wang C, Wu D, Xiao Y, Huang X. Invasive fungal infection in patients receiving chemotherapy for hematological malignancy: a multicenter, prospective, observational study in China. Tumour Biol 2015;36:757-67. https://doi.org/10.1007/s13277-014-2649-7. PMid:25293517

12. Pagano L, Carra M, Candoni A, Offidani M, Fianchi L, Martino B, Pastore D, Picardi M, Bonini A, Chierichini A, Fanci R, Caramatti C, Invernizzi R, Mattei D, Mitra ME, Melillo L, Aversa F, Van Lint MT, Falciucci P, Valentinii CG, Girmenia C, Nosari A. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. Haematologica 2006;91:1068-75. PMid:16885047

13. Auberger J, Lass-Fleor C, Ulmer H, Nogler-Semenitz E, Clausen J, Gunsilius E, Emsele H, Gastl G, Nachbaur D. Significant alterations in the epidemiology and treatment outcome of invasive fungal infections in patients with hematological malignancies. Int J Hematol 2008;88:508-15. https://doi.org/10.1007/s12185-008-0184-2. PMid:18982251

15. Van der Velden WJ, Herbers AH, Netea MG, Blijlevens NM. Mucosal barrier injury, fever and infection in neutropenic patients with cancer: introducing the paradigm febrile mucositis. Br J Haematol 2014;167:441-52. https://doi.org/10.1111/bjh.13113 PMid:25196917

16. Lewis V, Yanofsky R, Mitchell D, Dix D, Ehther MC, Gillmeister B, Johnston D, Michon B, Stobart K, Portwine C, Silva M, Cellot S, Price V, Bowes L, Zekeer S, Brossard J, Beyene J, Sun J, Predictors and outcomes of viridans group streptococcal infections in pediatric acute myeloid leukemia: from the Canadian infections in AML research group. Pediatr Infect Dis J. 2014;33:126-9. https://doi.org/10.1097/INF.0000000000000058 PMid:24064558

17. Girmenia C, Bertaina A, Pioecchi A, Perrucio K, Algarotti A, Busca A, Cattaneo C, Raiola AM, Guidi S, Iori AP, Candoni A, Ierena G, Milone G, Marcacci C, Scimè R, Musso M, Cadillo L, Sica S, Castagna L, Corradini P, Marchesi F, Pastore D21, Alessandri EP, Annalong C, Ciciri F, Santarone S, Nasti L, Farina C, Viscosi C, Rossolfini GM, Bonifazi F, Rambaldi A; Gruppo Italiano Trapianto di Midollo Osseo (GITMO) and Associazione Microbiologi Clinici Italiani (AMCLI). Incidence, risk factors and outcome of pre-engraftment Gram-negative bacteremia after allogeneic and autologous hematopoietic stem cell transplantation: an Italian prospective multicenter survey. Clin Infect Dis 2017; 65:1884-96. https://doi.org/10.1093/cid/cix690

18. De Rosa FG, Motta I, Audisio E, Frairia C, Busca A, Di Perri G, Marmont F. Epidemiology of bloodstream infections in patients with acute myeloid leukemia undergoing levofloxacin prophylaxis. BMC Infect Dis 2013;13:563-7. https://doi.org/10.1186/1471-2334-13-563 PMid:24289496 PMCid:PMC4219399.