Factors and outcomes related to the use of guideline-recommended antibiotics in patients with neutropenic fever at the Uganda Cancer Institute

Elizabeth A. Gulleen, MD¹², Scott V. Adams, MPH, PhD¹, Bickey Chang, MPH, MD³, Lauren Falk, MD⁴, Riley Hazard, BS⁵, Johnblack Kabukye, MBChB, MS⁶, Jackie Scala, MD⁷, Catherine Liu, MD¹², Warren Phipps, MD, MPH¹², Omoding Abrahams, MBChB, MMed⁶, Christopher C. Moore, MD⁸

1. Vaccine and Infectious Diseases Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA
2. Allergy and Infectious Diseases Division, Department of Medicine, University of Washington, Seattle, Washington, USA
3. Department of Internal Medicine, University of Minnesota, Minneapolis, Minnesota, USA
4. Department of Obstetrics and Gynecology, Rush University, Chicago, Illinois, USA
5. School of Population and Global Health, University of Melbourne, Melbourne, Australia
6. Uganda Cancer Institute, Kampala, Uganda
7. Department of Internal Medicine, University of Texas San Antonio, San Antonio, Texas, USA
8. Division of Infectious Diseases and International Health, Department of Medicine, University of Virginia, Charlottesville, Virginia, USA

Corresponding author/request for reprints:
Christopher C Moore, MD
University of Virginia Health System
Division of Infectious Diseases & International Health

© The Author(s) 2021. Published by Oxford University Press on behalf of Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Summary: We examined adherence to guideline-recommended antibiotics in 49 neutropenic fever episodes among adults with acute leukemia at the Uganda Cancer Institute. Guideline-recommended antibiotics were ordered in 37 (75%) events, but median time to guideline-recommended antibiotic order was 3 days.
ABSTRACT

Background
Neutropenic fever (NF) is associated with significant morbidity and mortality for patients receiving cancer treatment in sub-Saharan Africa (sSA). However, the antibiotic management of NF in sSA has not been well described. We evaluated the timing and selection of antibiotics for patients with NF at the Uganda Cancer Institute (UCI).

Methods
We conducted a retrospective chart review of adults with acute leukemia admitted to UCI from January 1, 2016, to May 31, 2017, who developed NF. For each NF event, we evaluated the association of clinical presentation and demographics with antibiotic selection as well as time to both initial and guideline-recommended antibiotics. We also evaluated the association between ordered antibiotics and the in-hospital case fatality ratio (CFR).

Results
Forty-nine NF events occurred among 39 patients. The time to initial antibiotic order was <1 day. Guideline-recommended antibiotics were ordered for 37 (75%) NF events. The median time to guideline-recommended antibiotics was 3 days. Fever at admission, a documented physical examination, and abdominal abnormalities were associated with a shorter time to initial and guideline-recommended antibiotics. The in-hospital CFR was 43%. There was no difference in in-hospital mortality when guideline-recommended antibiotics were ordered as compared to when non-guideline or no antibiotics were ordered. (HR: 0.51, 95%CI: [0.10, 2.64] and 0.78, 95%CI: [0.20, 2.96], respectively).
Conclusions

Patients with acute leukemia and NF had delayed initiation of guideline-recommended antibiotics and a high CFR. Prospective studies are needed to determine optimal NF management in sSA, including choice of antibiotics and timing of antibiotic initiation.

**Key Words:** neutropenic fever, antimicrobial stewardship, hematologic malignancy, guideline-adherence, sub-Saharan Africa
INTRODUCTION

Cancer is a growing cause of morbidity and mortality in sub-Saharan Africa (sSA). By 2030 more than 1.28 million new cancer cases and 970,000 cancer-related deaths are expected in sSA annually.\(^1\) As cancer detection and treatment has improved, treatment-related infections are a growing concern.\(^2\)-\(^7\) Chemotherapy-associated neutropenic fever (NF) is an oncologic emergency requiring rapid initiation of empiric broad-spectrum antibiotics to avoid early death.\(^8\),\(^9\) Consensus guidelines for NF management have been developed and validated in high-income countries (HICs).\(^8\),\(^9\) According to these guidelines, patients should receive empiric broad-spectrum antibiotics that have anti-pseudomonal activity.\(^8\),\(^9\) The time from NF onset to guideline-recommended antibiotic administration is an important predictor of outcomes.\(^10\),\(^11\) Accordingly, antibiotic administration within one hour of NF onset is a key clinical care metric.\(^12\) In HICs where NF guidelines are well-established, case fatality ratios (CFRs) range from <5% in patients with solid tumors to 15-20% in patients with hematologic malignancies.\(^13\)

Several small retrospective studies from sSA suggest that NF is associated with high CFRs.\(^14\)-\(^20\) We recently showed that up to 46% of Ugandan patients with hematologic malignancies died within 30 days of NF onset.\(^3\) The reasons for these high CFRs are not clear. Providers may have incomplete knowledge of the NF guidelines, there may be inconsistent access to guideline-recommended antibiotics, and international guidelines may not adequately account for the antimicrobial resistance patterns found in sSA.\(^20\),\(^21\) Identifying the unique factors that influence timely initiation of guideline-recommended antibiotics is key to improving antibiotic delivery and decreasing CFRs among patients with NF in sSA. While several studies from sSA describe the antibiotics prescribed to treat NF, few have evaluated provider adherence to guideline recommendations.\(^20\)-\(^22\)

Our primary objective was to evaluate baseline adherence to guideline-recommended antibiotics for patients with NF at a national cancer referral center in sSA before the initiation
of antimicrobial stewardship interventions. Accordingly, we completed a retrospective chart review of adult patients with acute leukemia and NF at the Uganda Cancer Institute (UCI) in Kampala, Uganda to evaluate provider adherence to guideline-recommended antibiotics and to identify factors associated with timely antibiotic orders. Our secondary objective was to explore associations between clinical outcomes and the time from NF onset to the order for guideline-recommended antibiotics.

METHODS

Study design

We conducted a single-center retrospective cohort study of adults with acute leukemia admitted to the UCI from January 1, 2016, to May 31, 2017, and developed NF during their hospital admission. The study period occurred after the release of the updated 2016 UCI Neutropenic Fever Guidelines and before the launch of our prospective cohort study regarding the microbiology of NF in patients with acute leukemia at UCI.3

Study setting and population

The UCI is a national cancer referral hospital located in Kampala, Uganda and is the African Development Bank designated East African Center of Excellence in Oncology. More than 5,000 patients are treated at the UCI annually. Adults with acute leukemia receive treatment at the inpatient Liquid Tumor Centre (LTC). Daily patient care is conducted by medical officers. They are supervised by fellowship-trained oncologists who oversee the cancer treatment plan. All medical documentation occurs in paper charts that are stored in the UCI Medical Records Department when they are not in clinical use.

We used the LTC Admission Logbook to identify patients ≥18 years with acute leukemia who were hospitalized during the study period. We obtained the medical charts from the UCI Medical Records Department and reviewed each chart for inclusion criteria. We included
only patients with histopathologically confirmed leukemia who experienced at least one NF event during a hospital admission.

The Uganda Cancer Institute neutropenic fever guidelines

The “UCI Guidelines for NF Management” were established in 2014 and updated just before our study period (Table 1). The UCI NF Guidelines include recommendations for the a) clinical identification, b) microbiologic evaluation, and c) choice of empiric antibiotics for patients with NF (Table 1). To create these guidelines, a group of UCI clinicians and pharmacists collaborated with infectious diseases specialists from the Fred Hutchinson Cancer Research Center (Seattle, WA, USA). The group adapted the “Infectious Diseases Society of America Clinical Practice Guidelines for the Management of Fever in Neutropenia” to account for locally available microbiologic tests and antibiotics.

Neutropenic fever (NF)

We defined neutropenia as an absolute neutrophil count (ANC) of <500 cells/µL. When a temperature was recorded, we defined fever as a single axillary temperature of ≥37.5°C. When a temperature was not recorded, we defined fever as any use of the word “fever” or “febrile” to describe the patient in the medical record. We considered a febrile patient to have NF if they had documented neutropenia within 2 days before fever onset or within 2 days after NF occurred. We defined a NF event as the first neutropenic fever that occurred during that hospital admission. For patients who had more than one hospital admission during the study period, each admission was evaluated independently. Thus, each patient could have up to one NF event per hospital admission (Supplemental Table 1).
Antibiotic treatment

For each NF event, we evaluated the time from NF onset to the first antibiotic ordered (time to initial antibiotics) regardless of whether the antibiotic was guideline-recommended. We also evaluated the time from NF onset to the first order for guideline-recommended antibiotics (time to guideline-recommended antibiotics). We considered an antibiotic to be guideline-recommended if it was a first- or second-line antibiotic in the UCI NF Guidelines (Table 1).

Data collection, management, and quality assurance

We provided standardized training for all data collectors. We used EpiInfo (Centers for Disease Control, Atlanta, Georgia) to abstract data into case report forms. Abstracted data included patient demographics, clinical presentation, and laboratory findings. To evaluate NF management, we abstracted all blood cultures and antibiotics ordered throughout the hospitalization. We used a checklist to record physical examination abnormalities documented within 2 days of NF onset. Finally, we recorded the date of hospital discharge or in-hospital death. We analyzed the data using R (R Foundation for Statistical Computing, Vienna, Austria) and STATA16 (StataCorp, College Station, TX, USA).

Statistical analysis

We used descriptive statistics to summarize categorical variables as frequencies and percentages and continuous variables as medians with interquartile ranges (IQRs). We conducted Kaplan-Meier analyses of the a) time to initial and b) time to guideline-recommended antibiotic orders. We measured time in days and classified orders written on the date of NF onset as 0.1 days to ensure inclusion in the survival analyses. We excluded the NF episodes in which patients already had guideline-recommended antibiotics ordered at the time of NF onset. For the time to initial antibiotics analyses, we followed patients from NF onset to the first new antibiotic order or until they were censored due to death or hospital discharge.
discharge. For the time to guideline-recommended antibiotics analyses, we followed patients from NF onset to the first guideline-recommended antibiotic order or until they were censored due to death or hospital discharge. We then estimated the percentage with 95% confidence intervals (95%CIs) of NF episodes for which a) any antibiotics and b) guideline-recommended antibiotics were ordered within one day of NF onset. We used Cox proportional hazards regression to estimate hazard ratios (HRs) with 95%CIs to describe associations between the time to a) initial and b) guideline-recommended antibiotics with patient characteristics including age, sex, reason for hospital admission, time from admission to NF onset, and physical examination findings at the time of NF. We used clustered standard error estimation to account for correlation between repeated NF episodes in the same patient.

For the mortality analyses, we included the first hospitalization with a NF event. We followed patients from NF onset to death or until they were censored due to hospital discharge. We treated orders for antibiotics as a time-varying categorical exposure with three possible values: 0 from NF onset to any antibiotic order; 1 following the order of non-guideline recommended antibiotics and prior to the order of guideline-recommended antibiotics; or 2 following the order of guideline-recommended antibiotics. We analyzed participant demographics and clinical characteristics as potential confounders of the association between antibiotics with in-hospital mortality. We considered p <0.05 as statistically significant for all analyses.

Ethical considerations

The University of Virginia Institutional Review Board (IRB), the Fred Hutchinson Cancer Research Center IRB, the Uganda Cancer Institute Research and Ethics Committee, and the Uganda National Council on Science and Technology approved the study with a waiver of consent.
RESULTS

Study population and demographics

Of the 95 patients with acute leukemia, we located 66 (69%) charts for review (Supplemental Figure 1). Of these, 39 (59%) patients had at least one NF event. Among these 39 unique patients, there were 49 hospitalizations with a NF event. Nine of 49 (18%) NF events occurred at admission or within one day of hospitalization. For the remaining 40 NF events, the median (IQR) time from hospital admission to documented fever-onset was 15 (9, 18) days. In 44 of 49 (90%) NF events, the measured temperature was documented at NF onset.

Among the 39 patients, the median age at the time of first hospitalization was 31 years, and approximately half were female (Table 2). The most frequently encountered cancers were acute lymphocytic leukemia (n=22, 56%) and acute myelogenous leukemia (n=14, 36%). Most patients had newly diagnosed cancer at the time of first hospitalization (n = 32, 82%). There were 9 (23%) patients who had documented comorbidities, which included hypertension, diabetes, and renal disease. One patient was living with HIV.

Clinical presentation

A review of systems was documented within two days of fever onset in 36 of 49 (73%) NF events (Supplemental Table 1). Among these 36 NF events, the most frequent complaints were subjective fever (n=14, 39%), nosebleed (n=6, 17%), headache (n=6, 17%), diarrhea (n=6, 17%), and abdominal pain (n=5, 13%). A physical examination was documented within 2 days of fever onset in 34 (69%) NF events. Among these 34 NF events, the most frequently documented abnormalities were abdominal tenderness (n=12, 35%), hepatosplenomegaly (n=7, 20%), and skin rashes or lesions (n=7, 20%). All patients had at least one ANC obtained during their hospitalization. The median (IQR) ANC at the time of NF onset was 50 (10, 120) cells/µL.
Microbiologic evaluation

Blood cultures were ordered in 9 of 49 (18%) NF events. In 1 NF event, cultures were ordered twice for a total of 10 blood cultures. The median (IQR) days from fever onset to first culture order was 9 (2, 21) days. Only 4 of 10 (40%) cultures had results documented in the chart: 3 had no growth and 1 had growth of Gram-negative cocci, which were susceptible to meropenem.

Antimicrobial management

In 8 (16%) of 49 NF events, patients already had guideline-recommended antibiotics ordered at the time of fever onset (Figure 1). In the remaining 41 NF events, antibiotics were ordered in 39 (95%). In these 39 NF events, guideline-recommended antibiotics were ordered for initial treatment in 18 (46%), and non-guideline-recommended antibiotics were ordered for initial treatment in 21 (54%). In 11 (52%) of these 21 NF events, guideline-recommended antibiotics were subsequently ordered. Thus, guideline-recommended antibiotics were ordered in 37 of 49 (75%) NF events. Among the 2 NF events in which no antibiotics were ordered, 1 patient died in the hospital and 1 was discharged alive. The antibiotics ordered for initial NF treatment are shown in Figure 2.

Time to initial antibiotic therapy

Among 32 of 41 NF events, antibiotics were ordered within one day of fever onset (78%, 95%CI: [65%, 89%]) (Figure 3A); the median time from NF onset to the first antibiotic order was <1 day (95%CI, 0 to 3 days). We found no association between sex or type of malignancy and time to initial antibiotics. For all 9 events in which NF was documented at admission, antibiotics were ordered within one day, compared to 23 of 32 (72%, 95%CI: [56%, 86%]) when NF was not documented at admission (HR [95%CI]: 1.50 [1.12, 2.00]). When a physical examination was documented at NF onset, antibiotics were ordered within one day in 25 of 30 NF events (83%; 95%CI: [68%, 94%]) compared with 7 of 11 (64%; 95%CI: [37%, 89%]) when no physical examination was documented (HR [95%CI], 1.66
[0.98, 2.81]). In the 30 NF events in which a physical examination was documented, antibiotics were ordered within one day for all 7 events in which there was an abnormal abdominal examination finding, compared with 18 of 23 NF events (78%; 95%CI: [60%, 92%]) with no documented abdominal findings (HR [95%CI]: 1.53 [1.15, 2.03]).

**Time to guideline-recommended antibiotic therapy**

Among 15 of 41 NF events, guideline-recommended antibiotics were ordered within one day of fever onset (37%; 95%CI: [24%, 53%]). The median time from NF onset to the first order for guideline-recommended antibiotics was 3 days (95%CI, 1 to 11 days) (Figure 3B). We found no association between sex or type of malignancy and time to guideline-recommended antibiotics. When NF was documented at admission, guideline-recommended antibiotics were ordered within one day in 6 of 9 NF events (67%, 95%CI: [38%, 92%]), compared to 9 of 32 (28%, 95%CI: [16%, 47%]) when NF was not present on admission (HR [95%CI]: 2.42 [1.12, 5.22]). When a physical examination was documented at NF onset, guideline-recommended antibiotics were ordered within one day for 14 of 30 NF events (47%, 95%CI: [31%, 66%]), compared to 1 of 11 (9%, 95%CI: [1%, 49%]) in which no physical examination was documented (HR [95%CI]: 1.96 [0.94, 4.09]). Among the 30 NF events in which a physical examination was documented, antibiotics were ordered within one day for 5 of 7 NF events (71%, 95%CI: [39%, 96%]) in which there was an abnormal abdominal examination finding, compared with 3 of 23 (10%; 95%CI: [23%, 62%]) with no documented abdominal findings (HR [95%CI]: 1.84 [0.87, 3.90]).
Mortality

Of the 39 patients with NF included in the study, 20 (51%) were known to have died during the study period. Seventeen patients died during their initial hospitalization for a CFR of 43%. An order for non-guideline-recommended antibiotics or guideline-recommended antibiotics was associated with a non-significant lower hazard of in-hospital mortality (HR: 0.51, 95%CI: [0.10, 2.64] and 0.78, 95%CI: [0.20, 2.96], respectively). This relationship did not change with adjustment for participant characteristics.

DISCUSSION

In this study, we retrospectively evaluated the antibiotic management of adult inpatients with acute leukemia and NF at a single national cancer center in sSA. In most NF events, antibiotics were ordered on the day of NF onset. However, only about one-third had guideline-recommended antibiotics ordered on the day that NF occurred, and it took a median of 3 days for guideline-recommended antibiotics to be ordered. The in-hospital CFR of 43% was high, and we did not find a significant association between mortality and an order for guideline-recommended antibiotics.

Since most NF events had at least one antibiotic ordered on the day of NF onset, there seemed to be general recognition that NF requires rapid antibiotic initiation. However, most patients had non-guideline-recommended antibiotics ordered for initial NF treatment. Understanding why guideline-recommended antibiotics were not routinely ordered is key to improving NF management at UCI and in similar cancer centers throughout sSA. Lack of guideline knowledge is frequently identified as a barrier to guideline adherence.23,24 Since our goal was to assess baseline adherence to guideline-recommendations, our study started shortly after the UCI NF Guidelines were updated and before the launch of our ongoing prospective cohort study investigating the microbiology of NF at UCI. Thus, lack of
knowledge may have contributed to low guideline implementation. Since this was a retrospective study, we were unable to assess provider knowledge as a contributing factor. We are currently evaluating the knowledge and attitudes regarding the NF guidelines among UCI clinicians. We will use these findings to determine whether targeted educational interventions (e.g., lectures, online modules), could improve knowledge and increase guideline adherence. 21,25

The unique management of patients with neutropenia could also have affected antibiotic selection. The Uganda Ministry of Health has created the Uganda Clinical Guidelines for Management of Common Conditions to provide standardized, evidence-based recommendations for managing priority health conditions. These guidelines recommend using relatively narrow spectrum antibiotics (e.g., cloxacillin) to treat febrile patients if they do not appear critically ill. 26 Since patients with neutropenia have attenuated neutrophil-mediated inflammation, they may lack the traditional signs and symptoms of severe infection. 27 In our study, patients with a documented physical examination abnormality had a shorter time to guideline-recommended antibiotic order. A previous study from Uganda showed that increased frequency of vital sign documentation was associated with higher illness acuity and increased mortality in patients with sepsis. 28 Similarly, a documented physical examination abnormality may be a surrogate marker for illness severity, indicating that those who appeared clinically unwell were more likely to receive the broad-spectrum antibiotics (e.g., piperacillin-tazobactam, ceftriaxone) recommended by the UCI NF Guidelines. 29 We also found that patients who were febrile at the time of hospital admission were more likely to have guideline-recommended antibiotics ordered on the day of NF onset than those who developed fever later during hospitalization. Since it is standard UCI practice to document a full history and physical examination when a patient is admitted to the hospital, those with severe illness may be more quickly recognized and guideline-recommended antibiotics more rapidly ordered. These findings suggest that educating
clinicians about the need to initiate broad-spectrum antibiotics (e.g., piperacillin-tazobactam) regardless of illness severity could improve guideline adherence among patients with NF.

Antibiotic stockouts (lack of product in the pharmacy) are another key barrier to guideline implementation in low-resource settings. Stockouts are associated with the use of alternative antibiotics that are less effective, have increased rates of adverse events, and can drive antimicrobial resistance. While we do not have records of the available antibiotics during the study period, stockouts due to local or national shortages occur periodically at the UCI. During these times, clinicians must prescribe non-guideline antibiotics or ask patients to purchase the preferred antibiotic at a local pharmacy, which may not be feasible. This reliance on antibiotic self-procurement from local pharmacies is associated with the use of substandard or falsified medications, which can result in increased mortality and drive antimicrobial resistance. The extent to which stockouts resulted in the prescription of non-guideline antibiotics could not be determined in our study but should be prospectively evaluated.

We found an in-hospital CFR of 43% for the first hospitalization of patients with NF. This is consistent with findings from our ongoing prospective cohort study among patients with NF at UCI. However, it is significantly higher than the 7-22% CFR among patients who are hospitalized for sepsis in Uganda and the 5-20% CFR for patients with NF who live in HICs. NF studies from HICs show that decreasing the time to guideline-recommended antibiotics reduces mortality. In our study, we found no difference in CFRs among those who received an order for guideline-recommended antibiotics compared to those who received an order for non-guideline-recommended or no antibiotics. This may reflect our relatively small sample size. It is also possible that the antibiotics that were ordered were not administered. Alternatively, it may reflect the presence of antibiotic resistance, which resulted in treatment failure even among those who received guideline-recommended antibiotics. Given the increasing prevalence of multi-drug-resistant bacteria in sSA, it is
possible that the UCI NF guidelines provide evidence-based recommendations in accordance with international guidelines but do not adequately address local antimicrobial resistance patterns. Prospective studies are currently underway to investigate the presence of multi-drug resistant bacteria at UCI and to evaluate patient outcomes in relation to antibiotic administration.

Our study had other limitations, including the retrospective chart review study design. Although we identified 95 patients hospitalized with acute leukemia during our study period, only 69% of patient charts were available for review. However, there is no reason to believe that patients with missing charts experienced different antibiotic prescription patterns than those whose charts were available. Consequently, we believe that our findings can be extrapolated to other patients at the UCI. The use of paper medical records and incomplete medical documentation also posed a challenge since all microbiology results were handwritten, and antibiotic administration was inconsistently documented. As noted, we did not have a list of antibiotics available at the UCI pharmacy during the time of our study. Thus, it is possible that some patients did not receive the prescribed antibiotics.
In conclusion, most patients at the UCI who had acute leukemia and developed NF had antibiotics ordered on the day that fever occurred, but experienced delayed prescription of guideline-recommended antibiotics. These findings emphasize the need for prospective studies to understand why providers do not always adhere to the NF guidelines. Given the high CFRs among this patient population, it is also vital to understand the microbiologic causes of NF in sSA in order to determine whether international guidelines adequately address local antimicrobial resistance patterns. Meanwhile, clinicians in sSA should continue to treat neutropenic fever as an emergency that requires rapid procurement of blood cultures and empiric administration of broad-spectrum guideline-recommended antibiotics when they are available. Further studies are needed to develop implementation strategies to facilitate rapid initiation of guideline-recommended antibiotics among patients with cancer and NF in sSA.
ACKNOWLEDGEMENTS

We gratefully acknowledge the clinicians and patients of the UCI. The authors thank Dr. Rhoda Morrow for critical examination of the manuscript.

CONFLICT OF INTEREST

The authors report no potential conflicts.

PATIENT CONSENT STATEMENT

The University of Virginia Institutional Review Board (IRB), the Fred Hutchinson Cancer Research Center IRB, the Uganda Cancer Institute Research and Ethics Committee, and the Uganda National Council on Science and Technology approved the study with a waiver of consent.

SOURCES OF FUNDING

EAG received funding from the University of Virginia Department of Infectious Diseases Internal Seed Grant and the Fred Hutchinson Cancer Research Center NIH T32 Training Program in Infectious Diseases in the Immunocompromised Host. BC received funding through the ASTMH Benjamin K. Kean Travel Fellowship, the IDSA Medical Scholars Program, and the University of Virginia School of Medicine. BC, RH, and LF received funding through the University of Virginia Center for Global Health.
AUTHOR CONTRIBUTIONS

EAG, JK, AO, and CCM contributed to conceptualization. EAG, BC, RH, JK, AO, and CCM contributed to the methodology. EAG, BC, LF, and JS abstracted the data. SA and EAG performed the data analysis. EAG and SA drafted the manuscript, which was edited by all authors. All authors have read and agreed with the published version of the manuscript. EAG takes responsibility for the integrity of the work as a whole.

DATA AVAILABILITY

Data available upon request
Figure Legends

Figure 1. Antibiotic orders for neutropenic fever events among adult inpatients with acute leukemia at the Uganda Cancer Institute from January 1, 2016, to May 31, 2017.

Figure 2. First antibiotic ordered for after fever onset for adult inpatients with acute leukemia and neutropenic fever at the Uganda Cancer Institute from January 1, 2016, to May 31, 2017 (n=39). *

*Among the 39 neutropenic fever events, 16 (41%) had 1 antibiotic ordered, 17 (44%) had 2 antibiotics ordered, and 6 (15%) had 3 antibiotics ordered.

Figure 3. Kaplan-Meier estimates of the time from onset of neutropenic fever to (A) initial antibiotic order and (B) first guideline-recommended antibiotic order for adult inpatients with acute leukemia at the Uganda Cancer Institute from January 1, 2016, to May 31, 2017. The Y-axis indicates percentage of neutropenic episodes.
REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International journal of cancer 2010;127:2893-917.
2. Arega B, Woldeamanuel Y, Adane K, Sherif AA, Asrat D. Microbial spectrum and drug-resistance profile of isolates causing bloodstream infections in febrile cancer patients at a referral hospital in Addis Ababa, Ethiopia. Infection and drug resistance 2018;11:1511.
3. Lubwama M, Adams S, Muwonge C, et al. Multidrug-Resistant Bacteria Are Common Cause of Neutropenic Fever and Increase Mortality Among Patients with Hematologic Malignancies in Uganda. Open Forum Infectious Diseases; 2019: Oxford University Press US. p. S108-S9.
4. Lubwama M, Phipps W, Najjuka CF, et al. Bacteremia in febrile cancer patients in Uganda. BMC research notes 2019;12:464.
5. Mohammed HB, Yismaw MB, Fentie AM, Tadesse TA. Febrile neutropenia management in pediatric cancer patients at Ethiopian Tertiary Care Teaching Hospital. BMC research notes 2019;12:528.
6. Mvalo T, Eley B, Bamford C, et al. Bloodstream infections in oncology patients at Red Cross War Memorial Children’s Hospital, Cape Town, from 2012 to 2014. International Journal of Infectious Diseases 2018;77:40-7.
7. von Knorring N, Nana T, Chibabhai V. Cumulative antimicrobial susceptibility data for a tertiary-level paediatric oncology unit in Johannesburg, South Africa. South African Journal of Oncology 2019;3:8.
8. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. 2011;52:e56-e93.
9. Averbuch D, Orasch C, Cordonnier C, et al. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance:
summary of the 2011 4th European Conference on Infections in Leukemia. Haematologica 2013;98:1826-35.

10. Butts AR, Bachmeier CC, Dressler EV, et al. Association of time to antibiotics and clinical outcomes in adult hematologic malignancy patients with febrile neutropenia. Journal of Oncology Pharmacy Practice 2017;23:278-83.

11. Faye Anderson D, Lisa Rioux B. Implementation of an evidence-based order set to impact initial antibiotic time intervals in adult febrile neutropenia. Oncology nursing forum; 2011: Oncology Nursing Society. p. 661.

12. Flowers CR, Seidenfeld J, Bow EJ, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2013;31:794-810.

13. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer 2006;106:2258-66.

14. Buys H. Klebsiella pneumoniae bloodstream infections in hospitalised children at Red Cross War Memorial Children's Hospital: 2006 - 2011: University of Cape Town; 2015.

15. Malande OO, Nuttall J, Pillay V, Bamford C, Eley B. A ten-year review of ESBL and non-ESBL Escherichia coli bloodstream infections among children at a tertiary referral hospital in South Africa. PloS one 2019;14:e0222675.

16. Naidu G. Infectious complications in the South African Black child with cancer [PhD]. Johannesburg: University of Witwatersrand; 2017.

17. Steinhaus N, Al-Talib M, Ive P, et al. The management and outcomes of Staphylococcus aureus bacteraemia at a South African referral hospital: A prospective observational study. International Journal of Infectious Diseases 2018;73:78-84.

18. Fentie A, Wondimeneh Y, Balcha A, Amsalu A, Adankie BT. Bacterial profile, antibiotic resistance pattern and associated factors among cancer patients at University of Gondar Hospital, Northwest Ethiopia. Infection and drug resistance 2018;11:2169.
19. Mvalo T, Eley B, Bamford C, et al. Bloodstream infections in oncology patients at Red Cross War Memorial Children's Hospital, Cape Town, from 2012 to 2014. Int J Infect Dis 2018;77:40-7.

20. Mohammed HB, Yismaw MB, Fentie AM, Tadesse TA. Febrile neutropenia management in pediatric cancer patients at Ethiopian Tertiary Care Teaching Hospital. BMC research notes 2019;12:1-6.

21. Muchela MA. Patterns of antibiotic prescription during febrile episodes in pediatric patients with cancer at the Kenyatta National Hospital [Master of Medicine]. Nairobi, Kenya: University of Nairobi; 2020.

22. Vanderpuye V, Yarney J, Beecham K. Management of febrile neutropenia in patients receiving chemotherapy for solid tumors: a retrospective study of twenty cases from the radiotherapy centre, Accra, Ghana. West Afr J Med 2010;29:303-8.

23. Hooft AM, Ripp K, Ndenga B, et al. Principles, practices and knowledge of clinicians when assessing febrile children: a qualitative study in Kenya. Malaria Journal 2017;16:381.

24. Mula CT, Middleton L, Human N, Varga C. Assessment of factors that influence timely administration of initial antibiotic dose using collaborative process mapping at a referral hospital in Malawi: a case study of pneumonia patients. BMC Infectious Diseases 2018;18:697.

25. Knowles R, Sharland M, Hsia Y, et al. Measuring antibiotic availability and use in 20 low- and middle-income countries. Bulletin of the World Health Organization 2020;98:177-87C.

26. Authority MoHatUND. National Guidelines on Management of Common Disease Conditions. 2016. Kisubi, Uganda: Marianum Press Ltd; 2016.

27. Sickles EA, Greene WH, Wiernik PH. Clinical presentation of infection in granulocytopenic patients. Archives of Internal Medicine 1975;135:715-9.

28. Asiimwe SB, Okello S, Moore CC. Frequency of vital signs monitoring and its association with mortality among adults with severe sepsis admitted to a general medical ward in Uganda. PLoS One 2014;9:e89879.
29. Ndabarora E, Chipps JA, Uys L. Systematic review of health data quality management and best practices at community and district levels in LMIC. Information Development 2014;30:103-20.

30. Tickell KD, Mangale DI, Tornberg-Belanger SN, et al. A mixed method multi-country assessment of barriers to implementing pediatric inpatient care guidelines. PLoS One 2019;14:e0212395.

31. Lewis JM, Abouyannis M, Katha G, et al. Population Incidence and Mortality of Sepsis in an Urban African Setting, 2013-2016. Clin Infect Dis 2020;71:2547-52.

32. Jacob ST, Moore CC, Banura P, et al. Severe sepsis in two Ugandan hospitals: a prospective observational study of management and outcomes in a predominantly HIV-1 infected population. PloS one 2009;4:e7782.

33. Kalyesubula R, Mutyaba I, Rabin T, et al. Trends of admissions and case fatality rates among medical in-patients at a tertiary hospital in Uganda; A four-year retrospective study. PloS one 2019;14:e0216060-e.

34. Madney Y, Elkady W, Elmahalawy H, Ebeid E. Infection related complications during maintenance phase treatment for children with acute lymphoblastic leukemia in developing countries: Single center experience, egypt. Pediatric Blood and Cancer 2018;65:S136-S7.

35. Saravanan M, Ramachandran B, Barabadi H. The prevalence and drug resistance pattern of extended spectrum β-lactamases (ESBLs) producing Enterobacteriaceae in Africa. Microbial pathogenesis 2018;114:180-92
Table 1. Summary of microbiologic evaluation and antibiotic recommendations for adult inpatients with neutropenic fever per the 2016 Uganda Cancer Institute Neutropenic Fever Guidelines.

| Microbiologic Evaluation of Neutropenic Fever |
|-----------------------------------------------|
| Blood cultures obtained within 30 minutes of fever detection. |
| Blood cultures obtained prior to antibiotic initiation. |

| Empiric Antibiotic Regimens for Neutropenic Fever |
|-----------------------------------------------|
| **First-line: If no suspicion for multi-drug resistant organism** |
| Piperacillin-tazobactam. |
| If evidence of sepsis/shock: add gentamicin |
| **First-line: If high suspicion for multi-drug resistant organism** |
| Chloramphenicol, meropenem, or imipenem |
| **Second-line: if first line regimens unavailable** |
| Ceftriaxone +/- ciprofloxacin +/- gentamicin |
| If suspected abdominal source: add metronidazole |

*Ceftriaxone only recommended in cases where no first-line antibiotics are available due to drug shortages; fluoroquinolones and gentamicin are not considered guideline-recommended unless ordered in conjunction with ceftriaxone.*
Table 2. Characteristics of adult inpatients with acute leukemia and neutropenic fever at time of first hospital admission to the Uganda Cancer Institute from January 1, 2016, to May 31, 2017.

| Characteristics               | Total (n=39) |
|-------------------------------|-------------|
| **Demographics**              |             |
| Age, year, median (IQR)       | 31 (25, 49) |
| Male sex, n (%)               | 20 (51)     |
| **Cancer History**            |             |
| Cancer Type, n (%)            |             |
| Acute Lymphomatous Leukemia   | 22 (56)     |
| Acute Myelogenous Leukemia    | 14 (36)     |
| Other*                        | 3 (8)       |
| Stage of Malignancy, n (%)    |             |
| Initial Diagnosis             | 32 (82)     |
| Relapsed Disease              | 4 (10)      |
| Other                         | 3 (8)       |
| **HIV**                       |             |
| Positive                      | 1 (3)       |
| Negative                      | 25 (64)     |
| Unknown                       | 13 (33)     |

*Two with undifferentiated acute leukemia and one with a history of myelodysplastic syndrome with blast crisis which was managed like AML.
Figure 1

Neutropenic fever episodes
(n = 49)

Guideline-recommended antibiotics already ordered at fever onset
(n = 8)

Neutropenic fever episodes for analysis
(n = 41)

Antibiotics never ordered
(n = 2)

Antibiotics ordered
(n = 39)

First ordered antibiotic guideline-recommended
(n = 18)

First ordered antibiotic non-guideline recommended
(n = 21)

Guideline-recommended antibiotic ordered later
(n = 11)

Guideline-recommended antibiotics not ordered later
(n = 10)
Figure 3

A

Empiric Antibiotics Ordered (%)

Days from Neutropenic Fever Onset

Number Remaining

41 14 8 6 3 3 2 1 1 1 1 1 1 1

Median <1 day

B

Guideline-Recommended Empiric Antibiotics Ordered (%)

Days from Neutropenic Fever Onset

Number Remaining

41 22 14 13 11 10 6 4 4 3 3 1 0

Median 3 days