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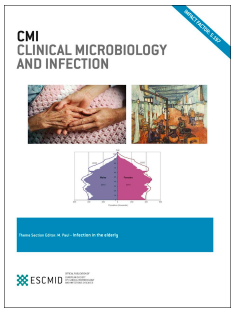

Prevention and treatment of bacterial infections in patients with haematological cancers and hematopoietic stem cell transplantation: headways and shortcomings

Ahmet Görkem Er, MD, Abdullah Tarik Aslan, MD, Malgorzata Mikulska, MD, Murat Akova, MD

PII: S1198-743X(24)00447-6

DOI: https://doi.org/10.1016/j.cmi.2024.09.015

Reference: CMI 3751

To appear in: *Clinical Microbiology and Infection*

Received Date: 12 June 2024

Revised Date: 20 August 2024

Accepted Date: 19 September 2024

Please cite this article as: Er AG, Aslan AT, Mikulska M, Akova M, Prevention and treatment of bacterial infections in patients with haematological cancers and hematopoietic stem cell transplantation: headways and shortcomings, *Clinical Microbiology and Infection*, https://doi.org/10.1016/j.cmi.2024.09.015.

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Ahmet Görkem Er, Abdullah Tarik Aslan, Malgorzata Mikulska, Murat Akova

Intended Category: Narrative review

This paper is submitted as one of the papers to be considered in the Theme Section entitled "State of the Art Review of Infectious Complications in Immunocompromised Patients" edited by Roy Chemaly, MD

Authors and affiliations:

1) Ahmet Görkem Er, MD

Hacettepe University School of Medicine

Department of Infectious Diseases and Clinical Microbiology

Ankara, Turkiye.

2) Abdullah Tarik Aslan, MD

Faculty of Medicine, UQ Centre for Clinical Research,

University of Queensland, Brisbane, QLD, Australia.

3) Malgorzata Mikulska, MD

Department of Health Sciences, Division of Infectious Diseases, University of Genova,

Division of Infectious Diseases, IRCCS Ospedale Policlinico San Martino, Genova, Italy

4) Murat Akova, MD (Corresponding author)

Hacettepe University School of Medicine

Department of Infectious Diseases and Clinical Microbiology

Ankara, Turkiye.

Postal address: Hacettepe Tip Fakultesi

Enfeksiyon Hastaliklari ve Klinik Mikrobiyoloji Anabilim Dali

Sihhiye, Ankara, Turkiye 06230.

Telephone (Office): +90-312 311 1271

Fax: +90-312 310 4179

E-mail: makova@hacettepe.edu.tr

Abstract

Background: There has been an unprecedented increase of immunocompromised (IC) patients in clinical practice due to various reasons. Bacterial infections are a major cause of morbidity and mortality in this population. Emerging antibacterial resistance poses a significant challenge for prophylaxis and treatment.

Objectives: We aim to provide an update on antibacterial prophylaxis and management, particularly in high-risk IC patients, including those with acute leukaemia and haematopoietic stem cell transplantation.

Sources: We reviewed original articles, systematic reviews, metanalyses and guidelines using PubMed, Scopus and Web of Science.

Content: We discussed the pros and cons of fluoroquinolone (FQ) prophylaxis in neutropenic patients in the context of personalized medicine. We also attempted to give an outline of

empirical treatment of presumed bacterial infections and targeted therapy options for documented bacterial infections considering the recent surge of multiresistant bacteria in haematological cancer patients and local epidemiology. The shortcomings of the current strategies and future needs are discussed in detail.

Implications: Antibacterial prophylaxis with FQs may still have a role in preventing bacterial infections in carefully selected high-risk haematology patients. Empirical treatment algorithms still need to be adjusted according to host and local factors. Use of rapid diagnostic methods may lessen the need of broad spectrum empirical antibiotic usage. However, these tests may not be easily available due to budget constraints in countries with limited resources but high rate of the bacterial resistance. Although new antimicrobials provide opportunities for effective and less toxic treatment of highly resistant bacterial infections, large-scale data from IC patients are very limited. Using data-driven approaches with AI tools may guide the selection of appropriate patients who would benefit most from such prophylactic and treatment regimens.

Keywords: Multidrug resistance, bacterial infection, immunosuppression, neutropenia, haematological cancer, stem cell transplantation, prophylaxis, targeted therapy, machine learning, artificial intelligence.

Introduction

Patients receiving chemotherapy and haematopoietic stem cell transplantation (HSCT) are at particularly high-risk for bacterial infections which can lead to life-threatening complications. Very limited antibiotic options are available for drug-resistant pathogens, and using broad-spectrum antibiotics can also cause selective pressure, favouring the emergence of resistance (1).

The following sections address the current strategies for prophylactic, empirical and targeted use of antibiotics, particularly in patients with acute leukaemia (AL) and/or allogeneic HSCT (allo-HSCT) who are at the highest risk of developing severe bacterial infections among the larger group of immunocompromised (IC) patient population. We also attempt to describe the future needs and the questions which have not been adequately addressed in the current clinical trials.

Sources

We conducted searches on PubMed, Scopus, and Web of Science for articles published using the queries in Supplementary Note 1.

Antimicrobial strategies to prevent bacterial infections in patients with AL and allo-HSCT

Earlier studies and guidelines recommended the use of either oral non-absorbable antibiotics or those with good oral bioavailability, such as fluoroquinolones (FQs) as prophylactic agents in afebrile neutropenic patients to decrease the incidence of febrile neutropenia (FN), bacterial infections and both overall and infection-related mortality (2). However, more recent data have contradictory recommendations in different guidelines regarding antibiotic

prophylaxis (AP) (3-5). The protective effect of antibiotics used in prophylaxis against bacteraemia was shown in a systemic meta-analysis of 113 studies while addressing the increasing resistance to FQ (6). The European Conference on Infections in Leukaemia (ECIL) also critically appraised data dated between 2006 and 2014, and found that FQ prophylaxis did not affect mortality but was associated with a lower rate of bloodstream infections and episodes of FN. The drawbacks were no impact on mortality, selection of resistance, damage to microbiota and side effects. Thus, a tailored approach considering emerging antimicrobial resistance (AMR) and toxicity at the local level was recommended (7). A similar approach was advocated in the recently updated national German guidelines (8). The concept of discouraged universal FQ prophylaxis was recently reviewed in detail (9).

It is highly challenging to generalize recommendations for AP since numerous parameters and other risk factors such as older age, history of poor nutrition, indwelling catheters or mucositis, and prior chemotherapy-induced FN are involved in the decision-making process (10). In addition, inferences based on existing data sources are debatable, and it is difficult to draw conclusions even for high-risk patients, as most meta-analyses report results for a mixed population, including children, adults, AL, and HCST recipients, and evaluate various FQ drugs (9). Consistent with the heterogeneity of patients, a recent two-stage cluster analysis of 372 episodes of FN identified four distinct clinical phenotype patterns: three groups of acute leukaemia patients either with bacterial infection, fungal infection and no infection, and one group of lymphoma patients with no infection, with differences in medical complications but no differences in AP. This observation raises the question of whether there was an inappropriate use of AP, as the patients' microbiological characteristics and clinical outcomes differed among these groups (11).

Furthermore, two main changes that have occurred over the last decades should be considered in the decision-making process. First, there is a clear trend of improving medical treatments, accessing health care, and sanitation, which has reduced overall mortality and morbidity from infectious diseases worldwide (12). Among IC patients, the mortality rates of control groups in studies evaluating the efficacy of FQ prophylaxis during the historical timeline varied between 36% and, most recently, <6% (9). This shift probably led to a further reduction of the previously observed impact of FQs on mortality in recent studies. Second, the evolution of microorganisms is ongoing, and the burden of AMR disproportionately affects countries based on income levels (13). This causes drastic paradigm changes in decisions. Although different studies show discordant results about the frequency of FQ-resistant strains after discontinuation of prophylaxis at the centre level, it is necessary to reduce the antibiotic burden from a global perspective (14, 15). In colonized patients, FQ exposure might increase the prevalence of colonizing with FQ-resistant Enterobacterales [17]. Such exposure may also be related with increased risk of infection or colonization with multi-drug resistant (MDR) strains including vancomycin-resistant *Enterococci* (VRE) and extended-spectrum β-lactamase (ESBL) producing Gram-negatives (7).

Although FQs are generally well tolerated, safety concerns restrict their use to specific indications (16-18). Particular caution should be taken when prescribing FQs in patients with renal impairment, solid organ transplantation, or on systemic corticosteroids for the increased risk of adverse effects (AEs). Immunocompromised patients are also vulnerable to disruption of the microbiome, which can increase the risk of *Clostridioides difficile* infection, not only due to FQ usage but also as a result of chemo- and immuno-therapeutics, antimicrobial treatment of existing infections and graft-versus-host disease (19, 20).

In summary, AP with FQs may still have a role in preventing bacterial infections in carefully selected high-risk haematology patients. However, considering the wide heterogeneity of the IC population, novel approaches are required to identify potential candidates for AP.

Current strategies for empirical and targeted therapies in immunocompromised patients with a haematological malignancy

Prompt administration of empirical antimicrobial therapy (EAT) in patients with FN (i.e., <0.5 x 10^9/L neutrophils and body temperature > 38°C) has been the standard practice for decades (3-5, 8). However, the current millennial approach recognizes a heterogeneous population of IC patients with varying risk factors for offending microorganisms and mortality due to infection (21). Thus, a risk-based EAT in FN has become the standard practice tailoring EAT based on (I) the local epidemiology of AMR, (II) patients' risk factors for resistant bacteria, and (III) a complicated clinical course (22). Currently, two different strategies have been employed: An 'escalation' strategy is recommended in patients without any risk factors for MDR Gram-negative bacteria (MDR-GNB) infections. In this approach, initial EAT typically includes monotherapy with an anti-pseudomonal cephalosporin or piperacillin-tazobactam (22). If the patient deteriorates or initial EAT is not active against the causative pathogen isolated later, therapy is then escalated to a broader spectrum (e.g., carbapenems or novel β-lactam/β-lactamase inhibitors [BLBLIs] covering carbapenem-resistant pathogens or combination regimens including aminoglycosides). A 'de-escalation' approach is considered in patients with one or more risk factors for MDR-GNB infection (23-26). In this strategy, the empirical therapy should be active against the most probable resistant GNB, with, for instance, early use of carbapenems (if ESBL-producing GNBs are frequent) or novel BLBLIs (if carbapenem resistance is suspected) with or without an aminoglycoside (24, 27, 28). Furthermore, an

escalation strategy should be employed in patients who are presented with a stable condition. For critically ill patients (e.g., patients presented with septic shock), a de-escalation approach is typically used. Anti-Gram-positive antibiotics are not empirically recommended upfront unless certain predisposing conditions are present since such practice has not been associated with better patient outcomes (29). Upon availability of microbiological results, antimicrobial therapy can be de-escalated to a narrower-spectrum antibiotic regiment. There is insufficient data for an iv to oral switch in neutropenic patients with documented bloodstream infections (BSIs) as most studies excluded these patients from clinical trials (30-32).

Targeted treatment recommendations for various highly resistant GNB infections of clinical importance are outlined in Supplementary Figure 1. The list of antibiotics currently approved and those being evaluated in phase III trials for these bacterial infections are also shown in Supplementary Table 1. Treatment alternatives for methicillin-resistant *Staphylococcus aureus* (MRSA) and VRE are depicted in Supplementary Figure 2.

Antibiotic therapies should be discontinued in patients with non-severe fever of unknown origin after three days and 48 hours of apyrexia, regardless of the absolute neutrophil count (22). A landmark RCT also reinforced that cessation of antibiotic therapy after three days of apyrexia in patients with fever of unknown origin was safe and even beneficial in high-risk neutropenic patients without AP (33). With the widespread availability of rapid diagnostic tests (RDTs) and artificial intelligence (AI) tools, antimicrobial stewardship practices would be upscaled in many countries.

Shortcomings and future needs

The following considerations may require attention to improve AP strategies and the therapy of severe infections in IC patients:

i- Reliable tools to identify the risk of infections with MDR-GNB in colonized patients are missing. There is no strong evidence to recommend the routine use of selective digestive decontamination and faecal microbiota transplantation when MDR-GNB colonization occurs in IC hosts (34). It is not yet clear whether empiric regimens covering colonizing MDR pathogens should be universally employed in the presence of systemic infection, especially in patients who do not have a serious clinical presentation (35-39). Furthermore, as accurate prediction of whether a patient is infected with MDR-GNB is difficult and requires accounting for many environmental and patient-specific risk factors; clinicians typically recommend empirical regimens that cover all potential causative pathogens. Although rapid diagnostic tests (RDTs) to identify some resistance genes are commercially available, these tests do not contain a comprehensive list of known antimicrobial resistance determinants, which is particularly important in case of *Pseudomonas aeruginosa* which can have different non-enzyme-based resistance mechanisms. These tests may also be resource-intensive for settings where the prevalence of drug-resistant organisms is low and may be cost-prohibitive for countries where the prevalence of these organisms is high (35).

ii- **Monotherapy *vs* combination empirical regimens.** Although the widespread use of combination therapy for empirical treatment of patients with a haematological malignancy is not needed, these regimens can be considered in patients with septic shock, Gram-negative bacteraemia, breakthrough fever during monotherapy, and in patients with profound

neutropenia and intestinal mucositis due to cytotoxic chemotherapy (22, 24). A retrospective study in neutropenic patients with bactaeremia mainly caused by *E. coli* and *P. aeruginosa* showed that empirical combination therapy with a beta-lactam and an aminoglycoside was related with reduced 7-day mortality with no increased toxicity (22, 24). A properly designed prospective, randomised controlled trial (RCT) should confirm these observations.

iii- **Difficulty in performing randomized controlled trials.** Target trial emulation framework as a method for casual inference from observational data can provide an alternative where RCTs are difficult to perform for various reasons. Causal inference is needed to understand which intervention works or harms the treatment of investigated diseases. The most evidence-based method for making causal inference between an intervention and outcome(s) is RCTs. Nevertheless, RCTs are difficult to perform due to reasons such as high costs, lack of incentives, under-recruitment, and infeasibility. Additionally, RCTs may not be suitable for finding answers to some questions, such as appreciation of the benefit of early over late appropriate therapy for the treatment of Gram-negative bacteraemia. In such a hypothetical trial, it would not be ethical to assign a group of patients to a late appropriate therapy arm. In order to figure out what intervention works or harms in these cases, there is a very specific technique called target trial emulation (TTE) (40). This method basically offers to make causal inferences from observational data by emulating a hypothetical pragmatic RCT as closely as possible. However, it would not be possible to emulate a double-blind RCT with this methodology; only a pragmatic trial design can be emulated (41). Another important point to emphasize is that TTE methodology cannot replace RCTs since the impact of unmeasured confounders cannot be eliminated due to the absence of randomization (40). However, TTE studies are collaborators (not competitors) of RCTs. As an example, TTE studies can be used

to extend the results of RCTs to specific patient subgroups (e.g., HSCT recipients) and to understand the effect of interventions over long follow-up periods.

iv- **Determination of a cut-off for prevalence of resistance at which a de-escalation approach should be adopted.** AMR is continuously monitored at regional or national level to verify whether EAT regimens for specific infectious diseases recommended by local or national guidelines are still valid. These recommendations are usually created by looking at following criteria: epidemiology of AMR, disease severity, efficacy of antibiotic treatment, previous antimicrobial exposures, AEs, costs, and *C. difficile* infection (42). Nevertheless, the criteria used for selecting EAT are quite heterogeneous and require standardization (42). Given the increasing trend in AMR, there is a clear need for rigorous tools to establish thresholds for EAT recommendations to support guideline recommendations with the best and most timely evidence. Randomized controlled trials and cost-effectiveness modelling studies are well needed to define optimal thresholds for EAT of infectious syndromes in IC hosts.

v- **Antimicrobial pipeline for MDR-GNB infections:** Almost 50 new antimicrobial agents with in vitro activity against GNB are currently in Phase I, II, or III clinical trials (43). Although some of these agents may not reach clinical use, they could potentially strengthen the antimicrobial armamentarium against MDR-GNB infections. Concrete plans should be made during clinical development to ensure that these agents reach the regions of the world where resistance to GNB is most prevalent. In order to understand the efficacy and safety of newer antimicrobials in the treatment of MDR-GNB infections in hematologic malignancy patients, large-scale, pragmatic and personalized medicine-based clinical trial designs should be implemented in future clinical trials.

vi – **Vast differences in the risk of bacterial infections and lethal bacterial infection among IC patients.** While almost all the above-discussed issues are fundamental in neutropenic patients, mainly with haematological malignancies, the risk profile might be completely different than in all other IC subjects. In these populations, early and accurate diagnosis is more important than antibiotic prophylaxis or early empirical treatment.

vii- **Leveraging data-driven approaches for precision medicine.** In line with precision medicine approaches, novel data-driven algorithms should be developed for decision-making processes that digest large amounts of heterogeneous and multimodal data, such as patient health records and regional antibiotic resistance rates (44). Recently, AI algorithms have been increasingly applied to detect and predict AMR and used for antibiotic prescriptions (monotherapy *vs* combination empirical regimens), establishing clinical decision support systems, and even predicting AMR in the environment, such as soil and wastewater (45). In addition, risk scoring tools can provide rapid prediction of MDR-GNB infections in settings where RDTs are unavailable or are resource-prohibitive or can be used to triage when expensive RDTs should be employed (46, 47).

Trained algorithms need to be validated, and randomized clinical trials should be conducted on these patients to understand AI's true effects and limitations more comprehensively and to implement these algorithms into clinical practice (48). Significant challenges will undoubtedly arise in storage, analysis, and interpretation, but advances in big data management and establishing and leveraging standardized, publicly available large datasets have the potential to better predict the risk of infections at the individual level to guide the choice of AP and treatment regimens, as seen in oncological studies (49, 50).

288

289 **Conclusions:** A pre-determined, AI-aided, personalized approach may help to identify high-
290 risk IC patients as candidates for AP. Strategies should include host risk factors and local
291 resistance patterns to implement effective empirical and targeted therapies. We still need to
292 use the available tools effectively for early identification of offending bacterial pathogens
293 with their resistance patterns to avoid empirical therapy as much as possible. Data from
294 randomized trials with new antimicrobials in this group of patients are urgently needed.

295

296 **Authors' contributions:** AGE and ATA reviewed the literature and drafted the initial text. All
297 authors contributed to the article's conception, writing and critical review.

298

299 **Transparency declaration:** ATA declares having honorarium from Pfizer for writing a
300 manuscript not related with the current one. Other authors declared no conflicts of interest.
301 No external funding was received for preparing this manuscript.

302

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