HMC RESEARCH PROTOCOL

Study Title:	Middle East Study of Infections in Patients with Hematological Malignancies (MESI–HM)
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Contents

1) Synopsis 2
2) Abbreviations, Acronyms, and Definitions 3
3) Background 5
4) Objectives 6
5) Study Methodology 6
6) Study Population and Study Setting/Location 7
7) Study Procedures 8
8) Statistical Considerations and Data Analysis 10
9) Adverse Events Reporting 10
10) Ethical Considerations 10
11) Funding 10
12) Dissemination of Results 11
13) References 11

Institutional Review Board Hamad Medical Corporation Doha - Qatar
MRC-01-23-912 Validity: 07 02 2024 - 05 02 2025 E-stamped 07 Feb 2024

HMC RESEARCH PROTOCOL

Table of amendments

		1.	

MRC-01-23-912 Validity: 07 02 2024 - 05 02 2025 E-stamped 07 Feb 2024

HMC RESEARCH PROTOCOL

Synopsis

Bloodstream infections (BSI) are documented in up to 40% of patients undergoing chemotherapy for hematological malignancies (HM), including those receiving hematopoietic stem cell transplants (HSCT). In this setting, early appropriate antimicrobial therapy is important to improve clinical outcomes, including survival. The global increase in antimicrobial resistance has been matched by an increase in multi-resistant infections in HM and HSCT patients, with higher rates of inappropriate antimicrobial therapy and treatment failure. The aim of this project is to prospectively study the epidemiology of BSI in HM and HSCT patients across the Middle East. The objectives are to describe the epidemiological trends, identify risk factors for inappropriate antimicrobial therapy, and predictors of persistent BSI, microbiological relapse, and all-cause mortality.

The proposed is a prospective, multi-center, multi-national observational study including hematology and HSCT centers in countries in the Arabian Peninsula. Eligibility criteria include active underlying HM or receipt of an HSCT, age ≥18 years, and ≥1 blood culture yielding the growth of ≥1 clinically significant microorganism(s). Data collection will include demographic details, clinical and microbiological characteristics, clinical management, and 30-day outcomes.

This will be an observational study without hypothesis testing, and therefore no formal sample size estimation. Each participating center will enroll 100 consecutive eligible BSI episodes. The prospective data collection would minimize data missingness and enable more reliable statistical analyses.

The study is entirely observational without any direct or indirect interference with standard clinical care. Being included in this study is not anticipated to be associated with more than minimal risk. Each site will code their subjects' data and enter de-identified data into a secure electronic data capture tool (Castor, Amsterdam, the Netherlands). A waiver of informed consent will be sought from research review boards in the participating centers. The study will be funded by Hamad Medical Corporation's Medical Research Center.

Study Timeline

January 1, 2024 to December 31, 2028 (5 years)

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MRC-01-23-912 Validity: 07 02 2024 - 05 02 2025 E-stamped 07 Feb 2024

2. Abbreviations, Acronyms and Definitions

ANC	absolute neutrophil count
BSI	bloodstream infection
ESBL	extended-spectrum beta-lactamase
HM	hematological malignancies
HSCT	hematopoietic stem cell transplantation
KPC	*Klebsiella pneumoniae* carbapenemase
MBL	metallo-beta-lactamases
MDR	multi-drug resistant
NDM	New Delhi metallo-beta-lactamase
OXA	oxacillinase

Bloodstream infection (BSI) episode

A blood culture yielding a growth of a microorganism that is thought to be clinically significant, unless occurs within 14 days of an already enrolled BSI, or at any time before resolution of active signs of infections associated with an already enrolled episode.

Polymicrobial bloodstream infection

The isolation of ≥2 clinically significant microorganisms from ≥1 blood culture within ≤48 hours. Microorganisms from the same species are counted once, regardless of any differences in their antimicrobial susceptibility patterns.

Persistent bloodstream infection

The isolation of the same clinically significant microorganism(s) from blood cultures collected ≥7 days after the index blood culture.

Primary (endogenous) bloodstream infection

A laboratory confirmed bloodstream infection that is not secondary to an infection at another body site.

Secondary bloodstream infection

A bloodstream infection that is thought to have originated from a site-specific infection at another body site.

Breakthrough bloodstream infection

MRC-01-23-912 Validity: 07 02 2024 - 05 02 2025 E-stamped 07 Feb 2024

Bloodstream infection onset while the patient is receiving systemic antimicrobials, including antibacterial or antifungal prophylaxis.

Central line-associated bloodstream infection

A laboratory confirmed bloodstream infection where an eligible organism is identified, and an eligible central line is present.

Pneumonia

≥1 of fever (>38°C), leukopenia (WBC <4,000/mm) and for adults ≥70 years old, altered mental status with no other recognized cause PLUS ≥2 of New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements, new onset or worsening cough, or dyspnea, or tachypnea, rales or bronchial breath sounds, and worsening gas exchange (e.g., O_2 desaturations (e.g., PaO_2/FiO_2 ≤240), increased oxygen requirements or increased ventilator demand) PLUS ≥2 serial chest radiographs with ≥1 new or progressive and persistent infiltrate, Consolidation or cavitation.

Intra-abdominal infection

Peritoneal inflammation in response to microorganisms, resulting in purulence in the peritoneal cavity. Complicated intra-abdominal infection extends beyond the hollow viscus of origin into the peritoneal space and is associated with either abscess formation or peritonitis.

Urinary tract infection

≥1 of fever (>38°C) in a patient that is ≤ 65 years of age, suprapubic tenderness, costovertebral angle pain or tenderness, urinary frequency, urinary urgency and/or dysuria PLUS a urine culture with ≤2 species of organisms identified, at least one of which is a bacterium of ≥10^5 CFU/ml.

Skin and soft tissue infection

Clinical entities that involve microbial invasion of the layers of the skin and underlying soft tissues. They may be purulent (e.g., furuncles, carbuncles, abscesses) or non-purulent (e.g., erysipelas, cellulitis, necrotizing fasciitis).

Study Day 0

The date on which the index blood culture was drawn.

Microbiological relapse

Recovery of the same species as that isolated from the index blood culture from a blood culture drawn anytime between discontinuation of active therapy for the index culture and the end of follow up.

MRC-01-23-912 Validity: 07 02 2024 - 05 02 2025 E-stamped 07 Feb 2024

Neutropenia

Absolute neutrophil count of $<0.5x10^9$ cells/L.

Prolonged neutropenia

Neutropenia for ≥7 consecutive days.

Corticosteroid therapy

Receipt of ≥20 mg of prednisolone, or equivalent, for ≥4 weeks within the 90 days prior to the index BSI.

Empiric antimicrobial therapy

The administration of systemic antimicrobial therapy for suspected infection, whether based on fever or any other clinical or laboratory markers.

Targeted therapy

The administration of systemic antimicrobial to specifically target a microbiological isolate that is thought to be the etiologic agent of the clinical infection. Continuation of an empiric agent after the availability of microbiological results to support its appropriate is considered, from that timepoint onwards, targeted therapy.

Appropriate antimicrobial therapy

The administration of ≥1 in vitro active antimicrobial agent within 24 hours after obtaining the index blood culture.

Difficult to treat resistance

Gram-negative bacteria with in vitro nonsusceptibility to all the available beta-lactams and fluoroquinolones.

MRC-01-23-912 Validity: 07 02 2024 - 05 02 2025 E-stamped 07 Feb 2024

3. Background

Blood stream infections (BSI) are relatively common in hospitalized patients and are associated with considerable morbidity and mortality.[1,2] Global epidemiology trends have consistently shown growing detrimental clinical impact in associated with multi-resistant Gram-negative infections, especially extended-spectrum beta-lactamase (ESBL)-producers and carbapenem-resistant organisms.[3,4] Considerable epidemiological differences exist in the distribution of carbapenemases in different parts of the world. For example, serine carbapenemases, such as *Klebsiella pneumoniae* carbapenemase (KPC), predominate in North America and China, whereas metallo-beta-lactamases (MBL), such as New Delhi metallo-beta-lactamase (NDM) are most frequent in the Indian subcontinent.[5,6] On the other hand, MBLs and oxacillinases (OXA) with carbapenemase activity, such as OXA-48-like enzymes, are the most common carbapenemases encountered in the Middle East.[7-9] Preferred treatment options for Gram-negative bacteria depend on the underlying resistance determinants, including the spectra and types of beta-lactamases and carbapenemases.[5,6] Therefore an understanding of the local and regional epidemiology of resistance determinants is essential for earlier appropriate antimicrobial therapy, especially in serious infections in vulnerable patients, such as those with hematological malignancies (HM) and recipients of hematopoietic stem cell transplants (HSCT).[10-12]

BSIs are documented in up to 40% of patients undergoing chemotherapy for HM, including those receiving HSCT.[13,14] In this setting, early appropriate antimicrobial therapy is important to improve clinical outcomes, including survival.[12,15-17] The global increase in antimicrobial resistance has been matched by an increase in multi-resistant infections in HM and HSCT patients, with higher rates of inappropriate therapy and treatment failure.[11] For example, in 1,164 BSIs over a 25-year period in HM and HSCT patients in Spain, there was a significant decrease in Gram-positive infections, and an increase in Gram-negative infections, especially multi-drug resistant (MDR) *Pseudomonas aeruginosa*, *E. coli* and *Klebsiella pneumoniae*. All-cause mortality increased over the study period, along with inappropriate empiric antimicrobial therapy, especially in BSIs caused by MDR Gram-negative bacteria.[18] In another study, inappropriate antimicrobial therapy was reported in 18% of BSI caused by ESBL-producing *E. coli*, 51% of those caused by MDR-*P. aeruginosa*, and more than 80% of *Stenotrophomonas maltophilia* BSIs.[19] Similar patterns of increasing resistance and resulting inappropriate therapy in HM and HSCT patients have been reported from the United States,[20,21] Italy,[22] the Netherlands,[23] Turkey,[24] China,[25] Australia,[26]

MRC-01-23-912 Validity: 07 02 2024 - 05 02 2025 E-stamped 07 Feb 2024

Advanced chemotherapy and HSCT services have evolved significantly across countries of the Middle East. While improving survival and offering opportunities for better quality of life, such treatment programs are inevitably associated with various degrees of immune suppression, mucosal disruption, and use of invasive devices; all of which increase the risk of invasive infections. For example, a single-center report from Saudi Arabia described 102 BSI episodes in HM patients, of which *K. pneumoniae* (33%), *P. aeruginosa* (24%) and *E. coli* (18%) were most frequent, and approximately one third (37%) were caused by MDR bacteria.[27] In a more recent 10-year study of 1,166 BSI episodes from 513 HM and HSCT patients from Qatar, more than 80% were caused by Gram-negative bacteria, of which 41% were ESBL-producers, and, worryingly, 18% were carbapenem-resistant.[28] Several studies from the Middle East have reported resistance mechanisms in bacterial infections.[7-9,29-38] However, to the best of our knowledge, no reports have focused on HM and HSCT patient populations.

The aim of this project is to prospectively study the epidemiology of BSI in HM patients across the Middle East. The objectives are to describe the incidence, identify risk factors for inappropriate empiric therapy, and predictors of poor clinical outcomes including persistent BSI, microbiological relapse, and all-cause mortality. We believe the findings will support more appropriate risk stratification and earlier administration of appropriate antimicrobial therapy for HM and HSCT patients with BSI in the Middle East, and the wider region.

4. Objectives

To characterize BSI in HM and HSCT patients from the Middle East in terms of:

1) The epidemiology including overall incidence and by type of pathogen.
2) Risk factors for inappropriate empiric therapy.
3) Rate and risk factors for persistent BSI.
4) Rate and risk factor for microbiological relapse at 30 days.
5) Rate and risk factors for all-cause mortality at 7 days, 14 days and 30 days.

5. Study Methodology

Study Design

This will be a prospective, multi-center, multi-national cohort study, to describe the epidemiology, microbiological and clinical characteristics, and outcomes of HM/HSCT patients with BSIs, and to identify risk factors for poor clinical outcome markers.

Intervention

MRC-01-23-912 Validity: 07 02 2024 - 05 02 2025 E-stamped 07 Feb 2024

None

6. Study Population and Study Setting/Location

HMC is the leading study site. Once HMC MRC and IRB approvals are secured, HM and/or HSCT centers in countries in the Middle East (i.e., Saudi Arabia, UAE, Kuwait, Oman, Bahrain, Lebanon, Egypt, Tunisia, Algeria, and Morocco) will be invited to participate in the study. Those who agree will need to seek local research approval followed by prospective data collection and entry for 100 consecutive eligible BSI episodes.

Sample Size Calculation

This will be an observational study without hypothesis testing, and therefore no formal sample size estimation. Each participating center will enroll 100 consecutive eligible bloodstream infection episodes. Prospective data collection would minimize data missingness and enable more reliable statistical analyses.

Inclusion Criteria

1) Age ≥18 years.
2) Active underlying HM, or past or imminent receipt of an HSCT.
3) A BSI episode, defined as a blood culture yielding a growth of ≥1 micro-organism that is thought to be clinically significant, unless occurs within 14 days of an already enrolled BSI, or at any time before resolution of active signs of infections associated with an already enrolled episode.

Exclusion Criteria

1) A BSI within 14 days of an already enrolled BSI, or at any time before resolution of active signs of infections associated with an already enrolled episode.

7. Study procedures

Study Duration and Timelines

Recruitment and follow-up is expected to take place over the period from September 15, 2024 to December 31, 2027 (48 months). Data analyses and the preparation of manuscripts is expected to be performed between January 1, 2028, and December 31, 2028 (12 months).

MRC-01-23-912 Validity: 07 02 2024 - 05 02 2025 E-stamped 07 Feb 2024

Informed Consent

The study is entirely observational without any direct or indirect interference with standard clinical care. Being included in this study is not anticipated to be associated with more than minimal risk. Each site will enter de-identified data into a secure electronic data capture tool (Castor, Amsterdam, the Netherlands).

The study is therefore eligible for a waiver of informed consent, subject to confirmation by the institutional review boards in the participating centers.

Screening for Eligibility and Enrollment

Site investigators will identify potential participants in collaboration with the diagnostic microbiology services. Screening for eligibility will be performed on Castor, the electronic data capture tool. Follow up data will be prospectively extracted from the site's medical records and entered in Castor.

Each center will enroll 100 consecutive eligible episodes. Should one or more centers drop out, the remaining centers will continue to screen and enroll participants until their total target sample size of 100 eligible BSI episodes is reached.

Risk

Participation in this study is associated with no more than minimal risk. Participants will receive standard clinical care for their infections, as decided by their treating physicians and according to the local clinical policies and practices.

Enrollment in the study does not imply a need for any additional testing, beyond what is considered clinically indicated, nor any modification of therapy in any specific way. No biological specimens or radiological investigations are required specifically for this study. All laboratory testing and any form of clinical investigation will be based on the clinical needs of the patients and decided by the treating physicians.

Data Collection, Management and Confidentiality

Initial data collection will include demographics, clinical characteristics of the underlying HM and/or HSCT, clinical (e.g.; Charlson Co-morbidity Score, Pitt bacteremia score, vital signs, baseline laboratory findings, suspected source of infection, the presence of any vascular lines or other prosthesis, invasive procedures, immune modulating/suppressive therapy) and microbiological (e.g.; date, species, antimicrobial susceptibility, resistance genes) characteristics of the bloodstream infection,

MRC-01-23-912 Validity: 07 02 2024 - 05 02 2025 E-stamped 07 Feb 2024

antimicrobial management (empiric and targeted), and need for ICU admission (including vasopressor support, renal replacement, and/or mechanical ventilation). Follow up will include clinical and laboratory parameters and microbiological investigations up to 30 days after the date of the index blood culture.

Study data will be retrieved from the participants' medical records and entered in Castor, the study's secure electronic data capture tool (Castor EDC, Amsterdam, Netherlands). Castor EDC is ISO 27001-certified (the technical and security standards of the International Organization for Standardization and the International Electrotechnical Commission), NEN 7510 (Dutch standard for information security in healthcare), and ISO 9001 (international standards of quality management system).

Castor EDC automatically generates codes for each enrolled subject. Only de-identified data will be entered; no identifiable data will be shared outside the enrollment site. Site PIs will maintain information linking the subjects' identifiers with their Castor EDC codes in password-protected Microsoft Excel files. These files will be stored in secure, server-backed, workplace computers. No hard copies will be made of such files, nor they will be shared or stored in full or in part in mobile memory devices, mobile phones, personal portable computers, or any other personal device.

Data will be collected de-identified, codes will be used to cover the patients' identifiers such as name, healthcare number, and date of birth. Links to the identifiers will be destroyed after data collection. The de-identified study data will be stored for at least 5 years post study completion.

The Lead PI is the administrator for the online database and will control all access to electronic data. Investigators will be granted access after completing online training on Castor EDC, in addition to virtual demonstration sessions with the Lead PI. Site PIs will in turn train their co-investigators on the system before being granted access.

The Lead PI will have access to all de-identified study data. Site PIs will have access to data for participants from their respective sites, but not from other sites. Study investigators will only have access to data relevant to their role within the study. Castor EDC system has a built-in audit system that tracks and registers all changes made, including the user details and date and time of any changes made.

The study Masterfile will include the study protocol and de-identified study documents. No identifiable data will be printed or stored in any hard copy format. The study documents will be stored by the Site PI's in lockable cabinets in secure offices within the official workplace premises. In

MRC-01-23-912 Validity: 07 02 2024 - 05 02 2025 E-stamped 07 Feb 2024

the case of HMC, this will be the Research Office, Communicable Disease Center. The specific location of storage for collaborating sites will be identified once the centers have confirmed their wish to join the study.

Subject Withdrawal/Withdrawal of Consent

Not applicable

Outcomes

1. Overall BSI incidence per 1,000 patient days.
2. BSI incidence per 1,000 patient days by type of microorganism.
3. Risk factors for inappropriate empiric therapy (logistic regression).
4. Rate and risk factors for persistent BSI (logistic regression), defined as the isolation of the same clinically significant microorganism(s) from blood cultures collected ≥7 days after the index blood culture.
5. Rate and risk factor for microbiological relapse at 90 days (Kaplan-Meier, and Cox proportional hazards), defined as the recovery of the same species as that isolated from the index blood culture from a blood culture drawn anytime between discontinuation of active therapy for the index culture and the end of follow up.
6. Rate and risk factors for all-cause mortality at 7 days, 14 days, and 30 days (Kaplan-Meier, and Cox proportional hazards).

8. Statistical Considerations and Data Analysis

Descriptive results for quantitative variables will be presented as the mean and standard deviation (SD) or median with interquartile range, depending of data distribution. Numbers (percentage) will be reported for qualitative variables. Bivariate analysis will be performed using Independent Sample t-test or Mann Whitney U-test for quantitative variables, and Chi-Square test or Fisher Exact test for qualitative variables.

BSI incidence per 1,000 patient days will be reported, with 95% confidence intervals, using the formula (number of episodes/total HM/HSCT inpatient days during the corresponding period) x 1,000.

Logistic regression models will be used to identify associations with inappropriate empiric therapy, and persistent BSI. Kaplan-Meier survival curves with log-rank P values will be used to assess time to

MRC-01-23-912 Validity: 07 02 2024 - 05 02 2025 E-stamped 07 Feb 2024

microbiological relapse and all-cause mortality. In addition, Cox proportional hazards will be used to identify independent predictors of microbiological relapse and all-cause mortality.

All statistical analyses will be performed by a Senior Biomedical Statistician using Stata Statistical Software, Release 15 (StataCorp., College Station, Texas).

9. Adverse Event Reporting

This will be an entirely observational study without any direct or indirect intervention. Therefore, there will be no provision for ascertainment or reporting of adverse events.

10. Ethical Considerations

The study will be conducted in full conformance with the principles of the "Declaration of Helsinki", Good Clinical Practice (GCP) and within the laws and regulations of the participating centers' host countries.

Participation in this study will be associated with no more than minimal risk. Participants will receive standard clinical care for their infections, as decided by their treating physicians and according to the local clinical policies and practices. Every reasonable effort will be made to protect the confidentiality of the participants' identifiable data.

Each study site will seek approval from their institutional review board (IRB), along with a waiver of informed consent before stating any enrollment.

11. Funding

Funding, which will be mostly for Castor EDC subscription and future article processing charges, will be sought from Hamad Medical Corporation's Medical Research Center. No other source of funding or sponsorship will be sought.

12. Dissemination of Results

The protocol will be registered at ClinicalTrials.gov (https://clinicaltrials.gov). Results will be presented at national, regional, and international scientific conferences. In addition, manuscripts will be prepared for publication in a peer-reviewed journals with the highest possible impact factors. The authorship of any papers will include all of the investigators who meet the International Committee of Medical Journal Editors (ICJME) criteria for authorship.[39] The order of author names on any publications will reflect their respective overall contribution. Priority will be given to those with the

MRC-01-23-912 Validity: 07 02 2024 - 05 02 2025 E-stamped 07 Feb 2024

most significant intellectual input into study conceptualization and design, study funding and administration, site administration, number of successfully enrolled subjects with complete datasets, contribution to data analysis and interpretation, and manuscript drafting. Depending on any limitation imposed by journals on the number of authors, those with the least significant contribution may be grouped under "MESI-HM Study Group" and their full names and affiliations provided elsewhere. The Lead PI will make the final decisions on all matters related to the order of authors' names on any publications.

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MRC-01-23-912 Validity: 07 02 2024 - 05 02 2025 E-stamped 07 Feb 2024

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MRC-01-23-912 Validity: 07 02 2024 - 05 02 2025 E-stamped 07 Feb 2024

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MRC-01-23-912 Validity: 07 02 2024 - 05 02 2025 E-stamped 07 Feb 2024

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