Critically Hematological Ill Patients Antimicrobial Stewardship (C.H.I.P.S) in intensive care unit: a global cross-sectional survey—an international research project within the Nine-i investigators network

Cristina Sarda[1], Alexis Tabah[2,3], Djamel Mokart[4], Emine Alp[5], Kostoula Arvaniti[6], Murat Akova[7], Jordi Rello[8]

[1]Infectious Diseases Department, Fondazione IRCCS Policlinico San Matteo Pavia, Italy; [2]Intensive Care Unit, Redcliffe and Caboolture Hospitals, Brisbane, QLD, Australia; [3]Faculty of Medicine, University of Queensland Brisbane, QLD, Australia; [4]Réanimation Polyvalente et Département d'Anesthésie et de Réanimation, Institut Paoli-Calmettes, Marseille, France; [5]Department of Infectious Diseases and Clinical Microbiology, Infection Control Committee, Erciyes University, Kayseri, Turkey; [6]Intensive Care Unit, Papageorgiou University Affiliated Hospital, Thessaloniki, Greece; [7]Department of Infectious Diseases, Hacettepe University School of Medicine, Ankara, Turkey; [8]CRIPS, Vall d'Hebron Institute of Research (VHIR), Barcelona, Spain

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Correspondence to: Cristina Sarda. Infectious Diseases Department, Fondazione IRCCS Policlinico San Matteo, University of Pavia, p. le Golgi 19, 27100 Pavia, Italy. Email: cristina.sarda@gmail.com.

Background: Critically Hematological Ill Patients Antimicrobial Stewardship (C.H.I.P.S) is a global cross-sectional survey will describe the most clinical relevant bacteria and antimicrobial pattern of resistance among hematological patients admitted to intensive care units (ICU). At the same time, a global expert challenges on infection control and treatment will be provided.

Methods: A global survey will be performed using an electronic platform (SurveyMonkey®). The survey will compile data on key aspects of the current treatment of antimicrobial-resistant bacteria infections among hematological patients admitted in ICU worldwide. All responses to survey questions will be presented as summary statistics and reporting proportions. Statistical analysis by Chi-square test or Fisher's exact test will be performed to evaluate potential associations.

Discussion: Efforts on the development of recommendations and antimicrobial stewardship (AMS) programs focused on critical hematological patients should be directed in the near future. Prevention strategies, type and, timing of antimicrobial therapy, de-escalation (ADE) approach have to be tailored to these patients.

Keywords: Multidrug-resistant (MDR) bacteria; infection difficult to treat; antimicrobial de-escalation (ADE); antimicrobial stewardship (AMS); hematological patients; febrile neutropenia (FN); intensive care unit (ICU)

Introduction

Managing of infections in hematological patients admitted in intensive care units (ICUs) represents a high-complexity challenge. In patients with hematological malignancies, including those receiving hematopoietic stem cell transplant (HSCT), bacterial and fungal infections are a frequent cause of increased morbidity and mortality, particularly

during severe and prolonged neutropenia. Bloodstream infections (BSI) represent the major cause of death in febrile neutropenic (FN) patients, with a prevalence between 10% and 38% (1-4). Crude mortality rate ranges from 12% to 42%. Severe sepsis and septic shock in these patients might occur in 20–30% and 5–10% among patient with febrile neutropenia (FN), respectively (5,6).

Gram-negative bacteria (GNB) have been reported as the main causative pathogen of BSIs in FN patients (7-9). Similarly, increasing antimicrobial resistance of GNB has been described in hematological population (10). Mortality caused by multi drug resistant (MDR) GNB was unacceptably high and has been estimated between 36% and 58% (11,12).

Regarding Gram positive bacteria, Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) have also been reported as the overriding resistant pathogens in some centers (13,14).

In the case of suspected or confirmed severe infections due to MDR bacteria, being able to choice promptly the adequate empirical and specific therapies is mandatory for prognosis (12,15). At the same time, inadequate treatment can adversely affect morbidity, mortality, health-care costs and favors the spread of MDR bacteria (16).

However, for hematological patients, lack of shared expert opinions about management including the timing of adequate treatment causes further misunderstanding in real world clinical practice. The increased risk of infections in terms of incidence in neutropenic and non-neutropenic hematological patients admitted in the ICU, along with the divergent prognosis for high- versus low-risk FN patients during infection, should be globally recognized as an important issue of those patients' care overall. As recently reported, preceding knowledge of MDR colonization in hematologic patients could serve as a determinant of appropriate empirical therapy when facing BSI (17). Considering the current guidelines (18,19), time to blood cultures positivity has been recently proposed as a tool for assisting prompt efforts of antibiotic stewardship, including de-escalation or discontinuation strategies (20-25). It is, hereby, confirmed that all these matters need to be clarified and shared universally. At least, an appropriate and personalized therapy for hematological critically ill patients should be defined and ultimately approved. Nevertheless, only a few studies on antimicrobial stewardship (AMS) programs concerns hematological patients admitted in the ICU (5).

The hypothesis is: the complexity of hematological patients admitted in the ICU requires well-defined personalized treatment protocols, aiming better patient outcomes, especially in the era of universal spread of MDR bacteria.

The primary objective of this study is to identify common core elements of the treatment of hematological patients admitted in the ICU, taking into consideration most available expert opinions.

Secondary objectives are: to evaluate clinical and epidemiological characteristics of hematological patients admitted in the ICU; to describe the pattern of bacterial infections and antimicrobial resistance profiles and their impact on outcome among hematological populations. This would be useful to identify patterns of AMS and develop recommendations for improvement in this specific ICU patient population.

Methods

Based on recent recommendations and guidelines this survey was designed (18,19,22,23). The survey will be performed using an electronic platform (SurveyMonkey®). This survey will be distributed by invitation from the members of the Steering Committee; it will be an online questionnaire requiring no specific data of patients, no intervention and no informed consent is required. Due to the observational aim of the study, qualifying as quality control assessment, research ethics board consultation was exempted. In order to develop a more realistic understanding of clinical practice, we encouraged all clinicians that care for critically ill patients, with interest and experience on critical infectious diseases to response to the survey, especially those with interest and experience on hematological patients. Paediatric (under 18 years old) and neonatal ICUs were excluded. Decisions of escalation of therapy are out of the scope of this study.

Questionnaire

The survey will compile data on key aspects of the current management of critically ill hematological patients in ICU. Details of the survey are summarized and enclosed. The information and details of the first part of the questionnaire are only to identify duplicates. Data analyses and reports will be done with anonymization of respondents. Details of the survey are summarized in Supplementary Part and include the questionnaire (Part A, B, C) and a figure (Logo of the survey). The C.H.I.P.S questionnaire will be available

online in April 2019.

Definitions

Antibiotic resistance was defined according to the current definitions and the EUCAST clinical breakpoints (26-28). Multidrug resistant (MDR) bacteria were defined as bacteria non-susceptibility to at least one agent in three or more antimicrobial categories (carbapenems, ureidopenicillins, ceftazidime and cefepime, monobactams, aminoglycosides, fluoroquinolones, fosfomycin and colistin). Extensively multidrug resistance bacteria (XDR) were defined as a bacteria non-susceptible to at least one agent in all but less than 2 antimicrobial categories. Pan-drug resistant bacteria (PDR) were defined as bacteria non-susceptible to all currently available antibacterial.

Definition of difficult to treat resistance (DTR) among Gram negative bacteria requires *in vitro* testing against ≥1 carbapenem, ≥1 extended-spectrum cephalosporin, and ≥1 fluoroquinolone, as recently proposed (28). Different mechanisms of antimicrobial resistance in GNB have been identified including target modification, efflux pumps, hydrolyzing enzymes (e.g., β-lactamases).

Alteration of bacterial membrane permeability, trough porin OprD gene mutation and/or overexpression of efflux system (MexA-MexB), can contribute to determining resistance towards several antibiotic classes including aminoglycosides, tetracycline, β-lactams and quinolones. Polymyxins resistance may be a mix of gene mutations (mcr-1), such as genes encoding proteins involved in LPS biosynthesis, metabolism, transport, and regulation.

Beta-lactamase enzymes are divided in 4 classes (29,30): class A β-lactamase: Extended-spectrum β-lactamase (ESBL) enzymes, (TEM, SHV and CTX-M enzymes), confer resistance to cephalosporins (including 3rd generation cephalosporins), penicillin-β-lactamase inhibitors combinations, aztreonam and cefepime (MIC >1). Serine carbapenemase (e.g., KPC, *Klebsiella pneumoniae carbapenemase*) confers resistance to all β-lactams.

Class B β-lactamases are bacterial enzymes including metallo-beta-lactamase (MBL). The most geographically spread MLBs include IMP, VIM, and NDM. Organisms producing MBLs usually show resistance to penicillins, cephalosporins, carbapenems, and available β-lactams. These enzymes are inhibited by aztreonam.

A class C of β-lactamases (AmpC), confer resistance to penicillins and cephalosporins (mainly 3rd generation) when overexpressed or associated with efflux and/or permeability mutations. Unlike ESBLs, AmpC enzymes are not inhibited by β-lactamase inhibitors.

Class D oxacillinases (OXA) represent a large heterogeneous group of beta-lactamase enzymes, not inhibited by currently available β-lactamase inhibitors, except Avibactam that can be active against some oxacillinases (OXA 48).

Among Gram positive resistant bacteria, VRE is defined as an *Enterococcus faecium* showing a vancomycin resistance. MRSA showing resistance to all beta lactams on the market, except Ceftaroline.

FN is defined as an oral temperature of >38.3 ℃ or two consecutive readings of >38.0 ℃ for 2 h and an absolute neutrophil count (ANC) of <0.5×10⁹/L or expected to fall below 0.5×10^9/L (31-33).

Blood-stream infection (BSI) was defined by the isolation of a bacterium in one blood culture; two positive cultures with the same antibiotic susceptibility tests are required for diagnosing coagulase-negative *staphylococci* or *Corynebacterium* spp. BSI.

Antimicrobial de-escalation (ADE) approach is defined as a switch from the initial broad spectrum of empirical therapy to a narrower spectrum of specific therapy.

Statistical analysis

All responses to survey questions are categorical variables and will be presented as summary statistics and reporting proportions (percentages). Analysis by Chi-square test (or Fisher's exact test when appropriate) will be performed to evaluate potential associations. A two-tailed P value less than 0.05 will be considered statistically significant.

Aim

To determine the most clinically important resistant pathogens among hematological patients admitted in ICU. To assess knowledge of preventability and infection control measures taken into account. To understand the challenges associated with the treatment of infection due to MDR bacteria, mainly in terms of choice of antimicrobials, de-escalation approach, and discontinuation of therapy. Finally, these recommendations where future efforts should be directed in AMS programs, adequate treatment and clinical trials regarding MDR infections in hematological critically ill patients can be proposed.

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Footnote

Conflicts of Interest: J Rello was a consultant for MercK. The other authors have no conflicts of interest to declare.

Ethical Statement: C.H.I.P.S will be an online questionnaire requiring no specific data of patients, no interventions and no specific ethical clearance is required.

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