

DIRECTIVES/GUIDELINES

2016 LEBANESE SOCIETY OF INFECTIOUS DISEASES & CLINICAL MICROBIOLOGY GUIDELINES ON THE MANAGEMENT OF FEBRILE NEUTROPENIA IN ADULT CANCER PATIENTS IN THE ERA OF GROWING ANTIMICROBIAL RESISTANCE

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ABSTRACT • Febrile neutropenia is common in cancer patients managed with chemotherapy. Many published international guidelines have included detailed recommendations on the management of various aspects of febrile neutropenia seen in this population. Various factors play a role in the management of febrile neutropenia in cancer patients including, local microbiology epidemiology, availability of diagnostic tests and available antimicrobial agents on the local market. On behalf of the Lebanese Society of Infectious Diseases and Clinical Microbiology, the panel members hope that the guidelines on the management of infections in patients with febrile neutropenia in an era of rising antimicrobial resistance will help health care providers standardize the care of these patients.

Keywords : fever, neutropenia, cancer, chemotherapy, immunocompromised, sepsis, prophylaxis, empiric therapy, guidelines

RÉSUMÉ • La neutropénie fébrile est une complication fréquente après un traitement anticancéreux. Des directives internationales ont été publiées concernant les recommandations détaillées traitant cette complication. Cependant, lorsqu'un médecin est confronté à un patient, beaucoup de facteurs affectent la décision de prise en charge, y compris l'épidémiologie bactérienne locale, le profil de résistance aux antimicrobiens ainsi que la disponibilité des tests diagnostiques et des agents antimicrobiens sur le marché local. Les membres de la Société Libanaise des Maladies Infectieuses et Microbiologie Clinique ont mis en place des recommandations pour la prise en charge de la neutropénie fébrile chez les sujets immunodéprimés à l'ère de l'augmentation des taux de résistance aux antimicrobiens. Ces directives visent à aider les médecins libanais dans le traitement des patients à haut risque.

Mots-clés : fièvre, neutropénie, cancer, chimiothérapie, immunodéprimé, septicémie, prophylaxie, thérapie empirique, directives

BACKGROUND AND PURPOSE

Antimicrobial resistance is a global public health concern. Its burden is substantial and likely to grow [1]. In Lebanon, recent hospital and community based data showed an increase in antimicrobial resistance among a number of microorganisms [2-5]. The main drivers of increasing antimicrobial resistance include uncontrolled use of antimicrobial agents and healthcare transmission of resistant microorganisms [1]. Judicious use of antimicrobial agents through the development of stewardship and infection control programs has been shown to mitigate this problem [6]. Resistance to current antimicro-

bials, coupled with a paucity of novel agents in the pipeline to treat multidrug resistant (MDR) pathogens have reinforced the need for evidence-based treatment guidelines focusing on the judicious use of antimicrobial agents.

Multidrug resistant microorganisms have emerged as a significant threat to patients undergoing chemotherapy for hematologic malignancies [7]. Despite its omnipresence, there is a significant variation in the spectrum of resistant pathogens across continents, countries and healthcare institutions [8]. Scientific societies from the United States and other regions of the world have developed and reported their own guidelines on the management of neutro-

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penic fever addressing regional microbial ecology of infections [9-16]. Treatment guidelines should be tailored to local microbial resistance patterns, taking into consideration the microcosm of the population in which these guidelines would be applied.

The aim of these guidelines is to develop national consensus-based clinical recommendations for the management of neutropenic fever in adult cancer patients. These proposed guidelines were based on a review of the international literature tailored to the local epidemiology of Lebanon.

These recommendations take into account the local variation in practice patterns, best available evidence, and where appropriate, cost-effectiveness. We hope that these guidelines would assist health care providers in developing treatment pathways for the multidisciplinary management of patients with neutropenic fever, leading to improved institutional efficiency while optimizing patient health outcomes.

METHODS

Organization of the Lebanese guidelines-development committee

Contributing members of the Lebanese Society of Infectious Diseases and Clinical Microbiology (LSIDCM) met several times in 2013 to discuss international guidelines and the local epidemiology of infections in cancer patients. The contributing members have chosen the best treatment options that are supported by international guidelines and would fit the microbial ecology in Lebanon. Panel members also took into consideration the disease spectrum and the local medication cost. A subgroup of the panel was tasked with drafting the guidelines. The final version of the recommendations was approved by all panel members. The final draft of the guidelines was reviewed and approved by the LSIDCM executive committee.

Literature search

The latest clinical practice guidelines on the management of febrile neutropenia (FN) were reviewed.

These included: The 2010 Infectious Diseases Society of America (IDSA) guidelines [9], the 2013 National Comprehensive Cancer Network (NCCN) guidelines [11], the 2011 Fourth European Conference on Infections in Leukemia (ECIL-4) guidelines on empirical antibacterial therapy of FN [10], the 2013 ECIL-5 guidelines on primary antifungal prophylaxis [12], the 2010 European Society for Medical Oncology (ESMO) guidelines [13], the 2010/2011 Australian-Consensus guidelines [14], the 2011 Korean guidelines [15], and the 2009 American Society for Blood and Marrow Transplantation (ASBMT) guidelines for preventing infectious complications among hematopoietic stem cell transplant (HSCT) recipients [16]. The panel also reviewed the Lebanese literature on neutropenic fever in cancer patients [2,17-20].

Formulation of key questions

The following major themes were selected for discussion:

1. Definition of fever and neutropenia
2. Epidemiology of local resistance
3. Diagnostic and clinical evaluation
4. Risk assessment and site of care
5. Antimicrobial prophylaxis
6. Strategic approach based on local epidemiology
7. Initial strategy of management and after 72-96 hours
8. Antifungal therapy after 72-96 hours of initial management
9. Environmental precautions.

Strength of recommendations and quality of evidence

For strength of recommendations and quality of evidence, the methods used in the NCCN guidelines were adopted and modified to fit LSIDCM recommendations [11]. (Refer to Table I)

TABLE I
THE LEBANESE SOCIETY OF INFECTIOUS DISEASES AND CLINICAL MICROBIOLOGY (LSIDCM)
GRADING OF STRENGTH OF RECOMMENDATION AND QUALITY OF EVIDENCE *

Category	Definition
1	Based upon high-level evidence with multiple well-designed, controlled, randomized blinded studies and meta-analysis. There is uniform LSIDCM consensus that the intervention is adequate.
2A	Based upon lower level of well-controlled, non-blinded or randomized studies, with retrospective reviews. There is uniform LSIDCM consensus that the intervention is adequate.
2B	Based upon lower level of well-controlled, non-blinded or randomized studies, with retrospective reviews. There is majority LSIDCM consensus that the intervention is adequate.
3A	Based upon any evidence that is less than well-controlled, or randomized, or large sample studies, mostly retrospective. There is uniform LSIDCM consensus that the intervention is adequate.
3B	Based upon any evidence that is less than well-controlled, or randomized, or large sample studies, mostly retrospective. There is no uniform LSIDCM consensus that the intervention is adequate.
3C	Based upon any evidence that is less than well-controlled, or randomized, or large sample studies, mostly retrospective. There is no LSIDCM consensus that the intervention is adequate.
4A	There is any level of evidence from literature against the intervention. There is uniform LSIDCM consensus against the intervention.

* Adapted from reference [11].

DEFINITIONS

Febrile neutropenia

Fever in neutropenic patients is defined as single oral temperature $> 38.5^{\circ}\text{C}$ or two consecutive readings of $> 38.0^{\circ}\text{C}$ for 2 hours [13].

Neutropenia is defined as an absolute neutrophil count (ANC) $< 1,000$ cells/microL and severe neutropenia is defined as an ANC < 500 cells/microL or that is expected to decrease below 500 cells/microL during the next 48 hours. Profound neutropenia was defined as an ANC < 100 cells/microL [9,14]. Fever during chemotherapy-induced neutropenia may be the only indication of a severe underlying infection, because other signs and symptoms of inflammation are typically attenuated. An infectious source is identified in approximately 20 to 30% of episodes of neutropenia and fever [21].

Neutropenic fever in cancer patients is considered an emergency. Urgent empiric broad-spectrum antimicrobial therapy is the cornerstone for the management of patients with febrile neutropenia. A delay in appropriate antimicrobial administration may result in serious and adverse outcomes in this patient population [22].

Clinical instability

A clinically unstable cancer patient with neutropenic fever is defined as a patient undergoing systemic anticancer therapy with neutropenic sepsis [23].

Neutropenic sepsis is defined as a core body temperature of $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$ with a neutrophil count of less than $0.5 \times 10^9/\text{L}$ [23] with evidence of organ hypoperfusion or dysfunction [24].

Septic shock is a clinical-pathophysiologic state in which the host response to infection is manifested by acute onset hypotension (defined as a systolic BP < 90 mmHg or mean arterial pressure < 65 mmHg) that does not recover with an adequate fluid challenge (> 20 ml/kg over 1 hour) [24]. This process is often accompanied by multi-organ dysfunction and lactic acidemia (> 2 mmol/L) [24].

Multi-drug resistant bacteria

A bacterial isolate is considered non-susceptible to a specific antimicrobial, using approved *in vitro* susceptibility tests, according to clinical breakpoints by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) or Clinical and Laboratory Standards Institute (CLSI) [10]. Definitions of multi-drug resistance vary among authors and although no uniform definition was used, it usually presumed resistance to at least two antibiotics used in empirical therapy (3rd or 4th generation cephalosporins, carbapenems or piperacillin/tazobactam) or resistance to at least three of the following antibiotic classes: antipseudomonal penicillins, cephalosporins, carbapenems, aminoglycosides and fluoroquinolones [10].

In our guidelines, multi-drug resistance is defined as resistance to at least three of the following antibiotics: piperacillin/tazobactam, cefepime, aminoglycosides and fluoroquinolones. Extensive drug resistant organisms

(XDRO) are multi-drug resistant organisms (MDRO) that are also resistant to carbapenems.

Empirical therapy in patients with neutropenic fever

It is the choice of antimicrobial regimen in patients with fever and neutropenia without a known source of the fever. It could be at the beginning of the febrile illness (new empiric), or in a persistent fever that started 72 to 96 hours before and did not subside with the initial empiric regimen [9].

Pre-emptive therapy in patients with neutropenic fever

It is to treat suspected infections based on radiologic studies, laboratory markers, or both (rather than fever alone) to stratify the likelihood of such infections. Certain pre-specified criteria trigger preemptive initiation or modification of antimicrobial therapy [9].

Targeted therapy in patients with neutropenic fever

It targets the organism implicated in infection based on definitive cultures, antimicrobial *in vitro* susceptibility tests and relevant laboratory markers [9].

Escalation

Escalation of therapy occurs in patients initially treated with empirical monotherapy regimen (e.g. cefepime or piperacillin-tazobactam) that covers most *Enterobacteriaceae* and *P. aeruginosa*, except those that produce extended-spectrum beta-lactamases or carbapenemases, or which are otherwise MDR [10]. (ECIL-4: BII) (LSIDCM: 2A)

If the patient shows signs of clinical deterioration, or when a resistant pathogen is isolated, therapy is escalated to a different antibiotic or a combination of antibiotics with a broader spectrum. Treatment options, after an initial therapy with piperacillin/tazobactam or cefepime, include an antipseudomonal carbapenem (imipenem or meropenem) (IDSA: A-I), and/or a glycopeptide or linezolid in case of glycopeptide intolerance (IDSA: B-III) (ECIL: C-III) [9, 10].

Escalation strategy in febrile neutropenia is indicated in uncomplicated presentation, with persistent bacteremia after 72-96 hours, even in the context of no previous colonization or infection with resistant bacteria, and in healthcare institutions where infections due to resistant pathogens are rarely seen at the onset of febrile neutropenia [10].

De-escalation

De-escalation applies in patients treated with an initial broad empirical antimicrobial regimen, aiming to cover highly resistant pathogens, e.g. ESBL-producing *Enterobacteriaceae* and MDR *P. aeruginosa*. Therapy is subsequently de-escalated to a narrower-spectrum therapy once the microbiologic results are available [10].

Situations where de-escalation strategies apply include complicated presentations such as sepsis/septic shock, known colonization or previous infection with

resistant microorganisms, and in centers where antimicrobial resistance is regularly seen at the onset of febrile neutropenia [10]. (ECIL-4: B-II) (LSIDCM: 2A)

Treatment options include [10]:

1. Carbapenem monotherapy (imipenem or meropenem); (ECIL-4: B-II) (LSIDCM: 2A) (In terms of efficacy as first-line treatment of febrile neutropenia, carbapenems are graded A-I (LSIDCM: 1).
2. Combination of anti-pseudomonal beta-lactam (carbapenem in seriously ill patients) + aminoglycoside or fluoroquinolone; (ECIL-4: B-III) (LSIDCM: 2A); (Fluoroquinolones are recommended as a possible component of a combination therapy in patients who are not receiving fluoroquinolones prophylaxis).
3. Colistin + beta-lactam ± rifampicin for suspected carbapenem resistant Gram-negative bacteria (GNB) such as: *P. aeruginosa*, *Acinetobacter spp.*, *S. maltophilia*, and carbapenem-resistant *Enterobacteriaceae*; (ECIL-4: C-III) (LSIDCM: 2B).
4. Early coverage of resistant Gram-positive bacteria (GPB) with a glycopeptide if risk factors for GPB are present or with linezolid, in case of glycopeptide intolerance (IDSA: B-III) (LSIDCM: 2A).

MICROBIOLOGICAL CONSIDERATIONS

In Lebanon, the epidemiology of bacteremia in neutropenic febrile patients and susceptibility patterns of causative organisms have been described in a few studies reporting on the experience in single healthcare institutions [17-20]. Only one study reported the results of *in vitro* susceptibility data on blood isolates in patients admitted with blood stream infection and neutropenic fever [2].

In the period from 1995 to 1998 the ratio of Gram-negative to Gram-positive organisms that were isolated from blood cultures of patients with fever and neutropenia, was 1.5:1, 1.8:1 in 1999, and 2.4:1 from 2001 to 2004 [18-20]. Data extending over the past two decades have consistently found a higher prevalence of Gram-negative blood stream infections, yet the gap widened between Gram-positive and Gram-negative pathogens over time [17-20]. Among the GNB, *Escherichia coli* has been consistently the most commonly isolated organism, followed by *Pseudomonas aeruginosa*. In the GPB group, coagulase-negative staphylococci continue to represent the majority of isolates [17-20].

In a recent study of bloodstream infections in febrile neutropenic patients from a single hospital in Lebanon between 2009 and 2012 [2], Gram-positive pathogens were more common reaching 43% of isolated pathogens compared to the previously reported lower incidence of Gram-positive (33%) described by Kanafani *et al.* [20], during the years 2001 to 2003. In both studies, coagulase-negative staphylococci represented the majority of encountered GPB. Among Gram-negative species, *Escherichia coli* and *Klebsiella* species were the most commonly isolated pathogens as reported by Moghnieh *et al.* [2]. Around

29% of the bacteremic episodes were caused by third-generation cephalosporin (3GC) resistant GNB and 9% were caused by GNB resistant to both 3GCs and carbapenems [2]. Also, fluoroquinolone resistant and to a lesser extent carbapenem resistant GNB were isolated from blood cultures of patients who were hospitalized for only 2 days or less (38% and 10% of the cases respectively) [2].

INITIAL EVALUATION AND DIAGNOSTIC INVESTIGATIONS

A detailed history should be taken to include the type of chemotherapy, date of previous hospitalizations, previous use of prophylactic antimicrobials, prior surgical procedures and presence of indwelling catheters [9,13].

It is important to check the patient's medical record for any evidence of colonization or infection with antibiotic-resistant organisms during the current or prior hospitalizations, which could guide the type of empiric antimicrobial therapy [9,13]. (LSIDCM: 2B)

An initial assessment of vital signs with vigorous resuscitation when necessary, should be followed by careful examination of oral mucosa, skin, and perirectal inspection looking for signs of potential foci of infection [9,13].

Laboratory tests should include a blood cell count with leukocyte differential and measurement of serum creatinine levels. In patients requiring hospitalization, measurement of electrolytes, hepatic transaminase enzymes, and total bilirubin is recommended [9,13]. (IDSA: A-III) (LSIDCM: 2A)

In case of suspected sepsis, coagulation screening is advisable [9,13]. (LSIDCM: 2B)

Testing systemic inflammatory markers such as C-reactive protein may play a limited role, but occasionally can gauge the response to therapy [9].

Blood culture volumes should be limited to less than 1% of total blood volume [9,13]. Accordingly, at least 2 sets of blood culture specimens should be obtained. A "set" consists of 1 venipuncture or catheter access draw of approximately 20 mL of blood to be inoculated into 1 aerobic and 1 anaerobic blood culture bottles [9,13]. In patients with indwelling intravenous catheters, one set should be obtained from the catheter and one from peripheral access [9,13]. (IDSA: A-III) (LSIDCM: 2A)

When clinically indicated, urinalysis and culture, sputum microscopy and culture, stool microscopy and culture, and/or skin lesion samples (aspirate/biopsy/swab), should be obtained before initiation of empirical broad-spectrum antimicrobial therapy [9,13]. (IDSA: A-III) (LSIDCM: 2A)

A chest radiograph is indicated for hospitalized patients with neutropenic fever, as well as for those with respiratory signs or symptoms [9,13]. (LSIDCM: 2B)

Even after the initial evaluation, the specific etiology of fever will remain undetermined in many patients [9,13]. All patients should be examined on a daily basis

to identify foci that may not have been apparent during the initial evaluation.

At 72-96 hours of initiating antimicrobial therapy, reevaluation of the patient treatment regimen is recommended [9,13]. (IDSA: A-II) (LSIDCM: 1)

INITIAL RISK ASSESSMENT AND SITE OF CARE

Patients with neutropenia can be categorized either at low-risk or high-risk for developing medical complications [9]. Assessment of risk status should be undertaken at the initial presentation according to tables II and III [9]. (IDSA: A-II) (LSIDCM: 1)

The risk assessment has direct implications on the site of care (inpatient vs. outpatient) and choice of empirical antimicrobial therapy [9]. (IDSA: A-II) (LSIDCM: 1)

High-risk patients should be managed in hospital setting and initiated on empirical parenteral antimicrobial therapy [9]. (IDSA: A-II) (LSIDCM: 1)

Low-risk patients are typically managed in an outpatient setting and with oral antimicrobial therapy [9]. (IDSA: A-II) (LSIDCM: 1)

Resistance rates, to 3GCs among hospital-acquired and community-acquired GNB in Lebanon, have reached 30% [2,3,4] and around 70% of the 3GC resistant organisms are also resistant to 4th generation cephalosporins [2,4]. Thus, assessing the risk of antibiotic resistance in the setting of neutropenic patients with fever is recommended, as this will guide decisions regarding hospitalization as well as the choice of empirical therapy. (LSIDCM: 1)

It is advisable that each institution performs surveillance of 3GC resistant GNB in neutropenic and especially bacteremic patients. (LSIDCM: 1)

In Lebanon, only one single center study reported the rate of 3GC resistance in GNB causing bacteremia in febrile neutropenia patients upon hospital admissions. (33%) [2].

Risk stratification

Antimicrobial prophylaxis is warranted in selected categories of immunocompromised cancer patients who are at risk for specific bacterial, fungal or viral opportunistic infections. Risk stratification to such infections is based on several factors, including the type of underlying malignancy, remission status, duration of neutropenia, type of chemotherapy, and intensity of immunosuppressive therapy [11]. (Table IV)

TABLE II
THE MULTINATIONAL ASSOCIATION FOR SUPPORTIVE CARE
IN CANCER RISK-INDEX SCORE*

Characteristic	Weight
Burden of febrile neutropenia with no or mild symptoms ^a	5
No hypotension (systolic blood pressure > 90 mmHg)	5
No chronic obstructive pulmonary disease ^b	4
Solid tumor or hematologic malignancy with no previous fungal infection ^c	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms ^a	3
Outpatient status	3
Age < 60 years	2

N.B. The maximum value of the score is 26.

^aBurden of febrile neutropenia refers to the general clinical status of the patient as influenced by the febrile neutropenic episode. It should be evaluated on the following scale: no or mild symptoms (score of 5); moderate symptoms (score of 3); and severe symptoms or moribund (score of 0). Scores of 3 and 5 are not cumulative.

^bChronic obstructive pulmonary disease means active chronic bronchitis, emphysema, decrease in forced expiratory volumes, need for oxygen therapy and/or steroids and/or bronchodilators requiring treatment at the presentation of the febrile neutropenic episode.

^cPrevious fungal infection means demonstrated fungal infection or empirically treated suspected fungal infection.

* Adapted from reference [29]

TABLE III
INITIAL RISK ASSESSMENT AND EVALUATION OF FEBRILE NEUTROPENIA PATIENTS*

Low risk (MASCC risk score ≥ 21) OR	High risk (MASCC risk score < 21) OR
<ul style="list-style-type: none"> No associated acute comorbid illness Anticipated short duration of severe neutropenia (< 7 days) Good performance status: Eastern Cooperative Oncology Group (ECOG) performance status (0-1) No hepatic insufficiency No renal insufficiency 	<ul style="list-style-type: none"> Inpatient status at time of development of fever Significant medical comorbidity or clinical instability Anticipated prolonged severe neutropenia (ANC < 100 cells and > 7 days) Hepatic insufficiency (5 times upper limit of normal for aminotransferases) Renal insufficiency (a creatinine clearance < 30 mL/min) Uncontrolled/progressive cancer (any leukemic patient not in complete remission, or non-leukemic patients with evidence of disease progression after > 2 courses of chemotherapy) Pneumonia or other complex infections at clinical presentation Alemtuzumab therapy Mucositis grade 3-4

ANC: absolute neutrophil count

MASCC: Multinational Association for Supportive Care in Cancer

* Adapted from reference [11]

TABLEAU IV

ANTIFUNGAL AND ANTIVIRAL PROPHYLAXIS ACCORDING TO THE TYPE OF CANCER AND OVERALL INFECTION RISK			
Overall infection risk in cancer patients ^a	Hematologic Disease	Antifungal Prophylaxis ^b	Antiviral Prophylaxis ^{b,c}
Low	- Standard chemotherapy regimens for most solid tumors - Anticipated neutropenia < 7 days	None (A-II) ¹ (LSIDCM: 2A)	None unless prior HSV episode (A-II) ¹ (LSIDCM: 2A)
	Autologous HSCT recipients with mucositis	- Fluconazole (I) ¹ (LSIDCM: 1) - Micafungin (I) ¹ (LSIDCM: 1) *Consider prophylaxis against <i>Pneumocystis jirovecii</i> using TMP/SMX for 3-6 months after transplant (B-II) ¹ (LSIDCM: 2B)	- Acyclovir or Valacyclovir for HSV and VZV during neutropenia and at least 30 d after HSCT (A-II) ¹ (LSIDCM: 2A)
Intermediate	Autologous HSCT recipients without mucositis	None (B-II) ¹ (LSIDCM: 2B)	- Consider VZV prophylaxis given for at least 1 year after HSCT (A-II) ¹ (LSIDCM: 2A) (Refer to tables VI and VII)
	Chronic Lymphocytic Leukemia	None except fluconazole in prolonged neutropenia (> 6 months), elderly, advanced & unresponsive disease (A-II) ¹ (LSIDCM: 2A) Continue until resolution of neutropenia	
	Lymphoma	None except against oral and/or esophageal candida infections: fluconazole (B-III) ² (LSIDCM: 2A) Continue until resolution of neutropenia	
	Multiple Myeloma	None except against oral and/or esophageal candida infections: fluconazole (B-III) ² (LSIDCM: 2A) Continue until resolution of neutropenia	
	Anticipated neutropenia 7-10 days	Fluconazole (A-I) ¹ (LSIDCM: 2A) Continue until resolution of neutropenia	
Leukemia patients, induction/salvage chemotherapy including AML undergoing intensive chemotherapy		- Fluconazole (B-I) ² (LSIDCM: 1) - Posaconazole (A-I) ² (LSIDCM: 1) - Voriconazole (B-II) ² (LSIDCM: 2A) - Echinocandins (C-II) ² (LSIDCM: 2B) - L-AMB/ABLC (C-II) ² (LSIDCM: 2B) - Aerosolized L-AMB (B-I) ² (LSIDCM: 1) combined with oral fluconazole Continue until resolution of neutropenia	Acyclovir or Valacyclovir for HSV during neutropenia (A-II) ¹ (LSIDCM: 2A) (Refer to table VI)
		*Consider prophylaxis against <i>Pneumocystis jirovecii</i> using TMP/SMX throughout anti-leukemic therapy (I) ¹ (LSIDCM: 1) • High risk of mold infection - Voriconazole (B-I) ² (LSIDCM: 1) - Posaconazole (B-II) ² (LSIDCM: 2A) - Micafungin (C-I) ² (LSIDCM: 2B) - L-AMB (C-II) ² (LSIDCM: 2B) - Aerosolized L-AMB (B-II) ² (LSIDCM: 2A) combined with micafungin (LSIDCM: 3B) - Fluconazole (A-III) ² (against its use) (LSIDCM: 4A)	

<p>High</p>	<p>Allogeneic HSCT recipients, initial neutropenic pre-engraftment phase</p>	<p>Continue during neutropenia and for at least 75 d after transplant *Consider prophylaxis against <i>Pneumocystis jirovecii</i> using TMP/SMX for at least 6 months and while receiving immunosuppressive therapy (I)¹ (LSIDCM: 1) • Low risk of mould infection - Fluconazole (A-I)² (in centers with majority predominance of <i>Candida albicans</i>) (L-SIDCM: 1) - Voriconazole (B-I)² (L-SIDCM: 1) - Posaconazole (B-II)² (L-SIDCM:2A) - Micafungin (B-I)² (L-SIDCM: 1) - L-AMB (C-II)² - Aerosolized L-AMB (C-III)² combined with oral fluconazole or micafungin Continue during neutropenia and for at least 75 d after transplant Consider prophylaxis against <i>Pneumocystis jirovecii</i> using TMP/SMX for at least 6 months and while receiving immunosuppressive therapy (I)¹ (LSIDCM: 1)</p>	<p>Refer to Table VI for antiviral prophylaxis against HSV Table VII for antiviral prophylaxis against VZV & Table VIII for prevention of CMV infection</p>
<p>Allogeneic HSCT recipients, post-engraftment GVHD phase</p>	<p>High - Voriconazole (B-I)² (L-SIDCM: 1) - Posaconazole (A-I)² (L-SIDCM: 1) - Micafungin (C-II)² (L-SIDCM:2B) - L-AMB (C-II)² (L-SIDCM:2B) - Fluconazole (A-III)² (against its use) (L-SIDCM:4A) Continue until resolution of significant GVHD Consider prophylaxis against <i>Pneumocystis jirovecii</i> using TMP/SMX for at least 6 months and while receiving immunosuppressive therapy (I)¹ (LSIDCM: 1)</p>	<p>None² Primary antifungal prophylaxis as in AML patients² Primary antifungal prophylaxis as in allogeneic HSCT recipients² Anti-mould (C-III)³ (L-SIDCM:3B) No specific agent (A-II)² (L-SIDCM:2A) Choice should be based on the causative fungal pathogen of the previous IFI and the previous response to antifungal agents.</p>	
<p>MDS excluding those undergoing AML-like chemotherapy MDS transformed to AML/ Patients receiving AML-like induction therapy MDS after allogeneic HSCT Prolonged period of neutropenia immediately prior to HSCT Secondary prophylaxis after invasive fungal infection (IFI)</p>	<p>ABL: acute myeloid leukemia CMV: cytomegalovirus AMLC: amphotericin B lipid complex AML: acute myeloid leukemia AMV: herpes simplex virus AMB: liposomal amphotericin B TMP/SMX: trimethoprim/sulfamethoxazole VZV: varicella zoster virus N.B. Categories of risk are based on several factors, including underlying malignancy, whether disease is in remission, duration of neutropenia, prior exposure to chemotherapy, and intensity of immunosuppressive therapy. Refer to table V for antifungals dosing and to tables VI, VII and VIII for antiviral dosing. In non-transplant high-risk patients, prophylaxis should be administered to patients who are seropositive for HSV or VZV (or with a history of chicken pox). In HSCT recipients, prophylaxis is only indicated if either the donor or recipient is seropositive for the virus in question.</p>		
<p>* Adapted from references [9, 11, 12]</p>			

Antibacterial prophylaxis

Antibacterial prophylaxis is not routinely recommended for low-risk patients who are anticipated to remain neutropenic for < 7 days [9]. (IDSA: A-III) (LSIDCM: 2A)

The IDSA [9], NCCN [11], and ESMO [13] guidelines recommend antibacterial prophylaxis with a fluoroquinolone for intermediate and high-risk patients. The use of fluoroquinolones in this setting has been shown to reduce the rate of neutropenic fever episodes, microbiologically documented infections, invasive Gram-negative bacilli infection, and mortality [24,25].

However, a systematic strategy for monitoring the development of fluoroquinolone resistance among Gram-negative bacilli is recommended [9]. (IDSA: A-II) (LSIDCM: 1).

Addition of a Gram-positive active agent to fluoroquinolone prophylaxis is generally not recommended [9]. (IDSA: A-I) (LSIDCM: 1)

The Australian Consensus Guidelines suggest that the evidence to recommend antibiotic prophylaxis with fluoroquinolones in most high-risk patients is not strong enough, except for patients undergoing stem cell transplantation and patients with bone marrow failure [14]. This is stemming from the high resistance rates to this class of antimicrobials [14].

Several studies from Lebanon have addressed the issue of increasing fluoroquinolone resistance in *Enterobacteriaceae* implicated in community-acquired infections [3,4,5]. Resistance rates range between 36% and 42% in *Escherichia coli* [3,4,5] and 19% and 35% in *Klebsiella spp.* [3,4].

Despite these limitations, the LSIDCM recommends fluoroquinolone prophylaxis, preferably using levofloxacin (500 mg once daily), in high-risk patients when mucositis is expected [16]. (ASBMT: B-I) (LSIDCM: 1)

A national surveillance study that aims to look into the rates of Gram-negative fluoroquinolone resistance in bacteremic cancer patients with fever and neutropenia within the first 4 days of presentation is underway.

While awaiting the results of this national data, individual healthcare centers should monitor their own local fluoroquinolone resistance patterns and decide on whether or not to use quinolone prophylaxis (LSIDCM: 2B).

We concur with NCCN guidelines [11] and ASBMT guidelines [16] in recommending the addition of oral penicillin (500-1000 mg once daily) in the prophylaxis of allogeneic HSCT recipients with GVHD.

Antifungal prophylaxis

- No antifungal prophylaxis is recommended in low-risk patients [11]. (NCCN: 2A) (LSIDCM: 2A)
- Antifungal chemoprophylaxis, with fluconazole against *Candida* infections, is initiated in intermediate-risk patients and continued until resolution of neutropenia [11] (NCCN: 2A) (LSIDCM: 2A). Prophylaxis against *Pneumocystis jirovecii* using TMP/SMX for 3 to 6 months after autologous HSCT is recommended [11]. (NCCN: 2A) (LSIDCM: 2A)
- A wide range of mold- and yeast-active antifungals is recommended in high-risk patients including voriconazole, posaconazole, micafungin and lipid formulation of Amphotericin B [9,11,12]. In high-risk patients, prophylaxis against *Pneumocystis jirovecii* using TMP/SMX for at least 6 months and while receiving immunosuppressive therapy should be considered [11]. (NCCN: 2A) (LSIDCM: 2A). Table IV provides information on antifungal recommendation per each indication. Table V lists the antifungal dosing regimens.

TABLE V
DOSES OF ANTIFUNGALS FOR THE PROPHYLAXIS AND MANAGEMENT OF FEBRILE NEUTROPENIA

Antifungal Agent	Dose
Fluconazole	400 mg IV/PO daily
Voriconazole	IV 6 mg/kg every 12 h x 2 doses, then 4 mg/kg every 12 h; oral 200 mg PO BID Prophylaxis: 200 mg (5 ml) PO TID
Posaconazole	Salvage therapy: 200 mg (5 ml) PO QID followed by 400 mg (10 ml) PO BID once infection has stabilized
Liposomal amphotericin B (L-AMB)	3-5 mg/kg/d IV
Amphotericin B lipid complex (ABLC)	3-5 mg/kg/d IV
Micafungin	Prophylaxis: 50 mg/day IV 100-150 mg daily
Caspofungin	70 mg IV x 1 dose, then 50 mg IV daily
Anidulafungin	200 mg IV x 1 dose, then 100 mg/d IV daily
Trimethoprim/sulfamethoxazole (TMP/SMX) (Prophylaxis against <i>P. jirovecii</i>)	Single or double strength daily or Double strength 3 times per week

BID: twice a day IV: intravenous IM: intramuscular PO: per os QID: 4 times a day TID: three times a day

N.B. Consider dose adjustment of the above listed antifungals when necessary in cases of renal insufficiency, hepatic insufficiency and obesity.

* Adapted from reference [11]

Viral infections and antiviral prophylaxis

Antiviral treatment for HSV or varicella-zoster virus (VZV) infection is only indicated if there is clinical or laboratory evidence of active viral disease (IDSA: C-III) (LSIDCM: 2B) [9]. (Tables IV, VI and VII)

- In low-risk patients, antiviral prophylaxis is warranted during neutropenia in case of a previous infection with herpes simplex virus (HSV) [11]. (NCCN: 2A) (LSIDCM: 2A)
- In intermediate-risk patients, antiviral prophylaxis is initiated using acyclovir or valacyclovir against HSV during neutropenia and for at least 30 days after autologous HSCT and against varicella zoster virus (VZV) during neutropenia and for at least one year after autologous HSCT (NCCN: 2A) (LSIDCM: 2A) [11].
- In high-risk HSV or VZV seropositive patients, acyclovir or valacyclovir are recommended as prophylactic

agents against HSV (IDSA: A-I) (LSIDCM: 1) and VZV [9].

- Prophylaxis should be given until recovery from neutropenia or resolution of mucositis [9]. (LSIDCM: 2A)
- Duration of prophylaxis can be extended for persons with frequent recurrent HSV infections or those with GVHD or can be continued as VZV prophylaxis for up to one year [9]. (LSIDCM: 2A)

Respiratory virus polymerase chain reaction (PCR) testing for influenza, respiratory syncytial virus, or multiplex nested PCR when available, and chest radiography are indicated for patients with upper respiratory symptoms and/or cough [9]. (IDSA: B-III) (LSIDCM: 2B)

Yearly influenza vaccination with inactivated vaccine is recommended for all patients being treated for cancer [9]. (IDSA: A-II) (LSIDCM: 1)

TABLE VI
HSV CHEMOPROPHYLAXIS IN HSCT RECIPIENTS*

Indication	First Choice	Alternatives
Prevention of early reactivation among seropositive HSCT recipients (regardless of donor HSV serostatus) ¹	Acyclovir: 400-800 mg orally twice daily; or 250 mg/m ² /dose IV every 12 hours (A-I) (LSIDCM: 1)	Valacyclovir: 500 mg orally daily (C-III) (LSIDCM: 3B), or 500 mg orally twice daily in highly immune suppressed patients (eg, T cell depletion, anti-T cell antibodies, high-dose steroids) (B-III) (LSIDCM: 3A)
Prevention of late reactivation among seropositive HSCT recipients	Acyclovir: 800 mg orally twice daily during the first year after HCT (B-III) ² (LSIDCM: 3A)	Valacyclovir: 500 mg orally twice daily throughout the first year after HCT (B-III) (LSIDCM: 3A)

HSCT: hematopoietic stem cell transplantation HSV: herpes simplex virus

N.B. For patients requiring prophylaxis for cytomegalovirus and herpes simplex virus after engraftment, ganciclovir alone provides effective prophylaxis for both pathogens. Consider dose adjustment of the above listed antivirals when necessary in cases of renal insufficiency, hepatic insufficiency and obesity.

¹ Start prophylaxis at the beginning of conditioning therapy and continue until engraftment or until mucositis resolves.

² For long-term prophylaxis, the higher dose of acyclovir is recommended for maximal viral suppression and minimization of resistance.

Grading: (Centers for Disease Control and Prevention (CDC). 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *Morb Mortal Wkly Rep* 1999; 48: 1-66.)

* Adapted from reference [16]

TABLE VII
VARICELLA-ZOSTER VIRUS CHEMOPROPHYLAXIS IN HSCT RECIPIENTS*

Indication	First Choice	Alternatives
Postexposure prophylaxis ¹ HSCT recipients who are exposed to varicella (A-II) or zoster (A-II) : (LSIDCM: 1) < 24 months after HSCT; or > 24 months after HSCT and on immune suppressive therapy or have chronic GVHD	Varicella-zoster immunoglobulin, if available: 625 units total dose intramuscularly (A-II) (LSIDCM: 1)	Valacyclovir: 1 g 3 times per day, day 3-22 after exposure (C-II) (LSIDCM: 3A) (continue until 22 days post-exposure)
Prophylaxis of disease reactivation following: Allogeneic HSCT (B-I) (LSIDCM: 1) Autologous HSCT (C-II) (LSIDCM: 3A)	Acyclovir ² : 800 mg orally twice daily for 1 year (B-I) (LSIDCM: 1)	Valacyclovir: 500 mg orally twice daily (B-II) (LSIDCM: 2A)

GVHD: graft-versus-host disease HSCT: hematopoietic stem cell transplantation

N.B. Consider dose adjustment of the above listed antivirals when necessary in cases of renal insufficiency, hepatic insufficiency and obesity.

¹ Ideally, administer prophylaxis within 96 hours (preferably, within 48 hours) after close contact with a person who has chickenpox or shingles.

² Lower doses of acyclovir, as low as 200 mg twice daily (B-II) (LSIDCM: 2A) (at this dose there is no prevention of HSV reactivation disease).

Grading: (Centers for Disease Control and Prevention (CDC). 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *Morb Mortal Wkly Rep* 1999; 48:1-66.)

* Adapted from reference [16]

Optimal timing of vaccination is not established, but serologic responses may be best between chemotherapy cycles (> 7 days after the last treatment) or > 2 weeks before chemotherapy starts [9]. (IDSA: B-III) (LSIDCM: 2B)

Influenza virus infection should be treated with neuraminidase inhibitors (IDSA: A-II) (LSIDCM: 1).

In the setting of an influenza exposure or outbreak, neutropenic patients presenting with influenza-like illness should receive treatment empirically (IDSA: C-III) (LSIDCM: 2B [9]).

Routine treatment of RSV infection in neutropenic patients with upper respiratory disease should not be

given (IDSA: B-III) (LSIDCM: 2B) [9].

Cytomegalovirus (CMV) disease prevention strategy is accomplished either through a prophylactic or pre-emptive approach [16]. (Tables IV and VIII)

- Antiviral chemoprophylaxis against CMV or pre-emptive treatment is indicated in allogeneic HSCT recipients at risk for post-transplant CMV disease (i.e., all CMV-seropositive allogeneic HSCT recipients, and all CMV-seronegative recipients with a CMV-seropositive donor) [16]. It is initiated from the time of engraftment and continued for at least 100 days after allogeneic HSCT [16]. (ASBMT: AI) (LSIDCM: 1)

TABLE VIII
PROPHYLAXIS AND PRE-EMPTIVE THERAPY OF CYTOMEGALOVIRUS
IN HEMATOPOIETIC STEM CELL TRANSPLANTATION RECIPIENTS*

Indication	First Choice	Alternative
<p>Preemptive Therapy (< 100 days post-HSCT)¹ (A-I) (LSIDCM: 1)</p> <ul style="list-style-type: none"> - Administer to all allogeneic HSCT recipients with evidence of CMV infection in blood by antigenemia or viral PCR. - CMV seropositive autologous HSCT recipients at high risk when CMV antigenemia is ≥ 5 cell/slide (or any level for recipients of CD34⁺ selected grafts) 	<p>Ganciclovir: 5 mg/kg/dose IV Allogeneic HSCT² Induction: Twice daily for 7-14 days Maintenance: Daily if CMV is still detectable and declining and continue until the indicator test is negative (A-I) (LSIDCM: 1) Autologous HSCT³ Induction: Twice daily for 7 days Maintenance: Continue daily until the indicator test is negative but a minimum of 2 weeks (B-II) (LSIDCM: 2A)</p>	<p>Foscarnet⁴ IV (A-I) (LSIDCM: 1) Induction: 60 mg/kg twice daily Maintenance: 90 mg/kg daily Valganciclovir⁴ (oral) (persons > 40 kg with good oral intake) (B-II) (LSIDCM: 2A) Induction: 900 mg twice daily Maintenance: 900 mg/kg daily</p>
<p>Prophylactic Therapy (engraftment to day 100 post-HSCT) (A-I) (LSIDCM: 1)</p> <ul style="list-style-type: none"> - Allogeneic HSCT recipients 	<p>Ganciclovir: 5 mg/kg/dose IV Induction: Twice daily for 5-7 days Maintenance: Daily until day 100 after HSCT (A-I) (LSIDCM: 1) (Once ganciclovir is initiated, acyclovir should be discontinued.)</p>	<p>Foscarnet: 60 mg/kg IV twice daily for 7 days, followed by 90-120 mg/kg IV once daily until day 100 after HCT (C-III) (LSIDCM: 3B) Acyclovir (in combination with screening for CMV reactivation): 500 mg/m² IV 3 times per day, or 800 mg orally 4 times daily (C-I) (LSIDCM: 3A) Valacyclovir: in combination with screening for CMV reactivation: 2 g 3-4 times per day (C-I) (LSIDCM: 3A)</p>
<p>Preemptive Therapy (>100 days post-HSCT) (B-III) (LSIDCM: 3A) for:</p> <ul style="list-style-type: none"> - Allogeneic HSCT recipients - All patients receiving steroids for GVHD - All patients who received CMV therapy < 100 days after HSCT when: <ul style="list-style-type: none"> 1) antigenemia is ≥ 5 cells/slide; or 2) ≥ 2 consecutively positive viremia or PCR tests 	<p>Ganciclovir: 5 mg/kg/dose IV Induction: Twice daily for 7-14 days Maintenance: Daily for 7-14 days or until the indicator test is negative (B-III) (LSIDCM: 3A) Or Valganciclovir: Induction: 900 mg orally twice daily for 7-14 days Maintenance: 900 mg orally daily for 1-2 weeks until indicator test is negative (B-III) (LSIDCM: 3A)</p>	<p>Foscarnet: 60 mg/kg IV twice daily for 14 days; continue treatment at 90 mg/kg/day daily for 7-14 days or until the indicator test is negative (A-I) (LSIDCM: 1)</p>

GVHD: graft-versus-host disease HSCT: hematopoietic stem cell transplantation IV: intravenous PCR: polymerase chain reaction CMV: cytomegalovirus
N.B. Consider dose adjustment of the above listed antivirals when necessary in cases of renal insufficiency, hepatic insufficiency and obesity. Prehydration is required for foscarnet administration.

¹ Continue screening for CMV reactivation and re-treat if screening tests become positive after discontinuation of therapy (BI) (LSIDCM: 1).

² Minimum total induction and maintenance treatment is 2 weeks when 14 days of twice daily is used and 3 weeks when a 7-day induction course is used (AI) (LSIDCM: 1).

³ CMV detection methods should be negative when therapy is stopped.

⁴ Criteria for duration of induction and maintenance doses are the same as those listed for ganciclovir.

Grading: (Centers for Disease Control and Prevention (CDC). 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *Morb Mortal Wkly Rep* 1999; 48:1-66.)

* Adapted from reference [16]

- Certain CMV-seropositive autologous recipients are at increased risk for symptomatic CMV replication or disease [16]. These include patients undergoing conditioning regimens including total body irradiation (TBI); patients receiving grafts manipulated to remove T-cells; and patients who have recently (e.g., within 6 months prior to HSCT) received fludarabine or other purine analogs [16].

- Such patients may benefit from the use of a preemptive strategy that includes monitoring for CMV reactivation for 60 days after HSCT [16]. (ASBMT: CII) (LSIDCM: 3A)
- Patients transplanted with CD34-selected grafts should be treated at any level of antigenemia or viremia [16]. (ASBMT: BII) (LSIDCM: 2A)
- Other autologous recipients at high-risk who experience moderately high levels of CMV antigenemia or CMV DNA should receive 2 weeks of preemptive treatment with ganciclovir or foscarnet [16]. (ASBMT: CIII) (LSIDCM: 3B)

We recommend a preemptive approach of CMV management in allogeneic HSCT recipients where CMV antigenemia or viral detection by PCR is carried on a weekly basis during the first 100 days post-transplant (LSIDCM: 2B).

An empiric prophylactic approach can be applied when weekly CMV antigenemia or molecular detection of CMV nucleic acid cannot be performed (LSIDCM: 2B).

Intravenous ganciclovir prophylaxis is an effective strategy for the prevention of CMV disease in subgroups of allogeneic HSCT patients at high-risk for CMV disease (LSIDCM: 2B).

Also acyclovir or valacyclovir at high doses can be used for CMV prophylaxis in allogeneic HSCT recipients (LSIDCM: 2B); however, this approach must be combined with serial CMV monitoring and preemptive therapeutic intervention (LSIDCM: 2B).

COLONY STIMULATING FACTORS PROPHYLAXIS AGAINST NEUTROPENIA

Several controlled clinical trials and meta-analyses have demonstrated a significant reduction in the risk of FN in patients randomized to receive primary prophylaxis with granulocyte colony-stimulating factors (G-CSF) following the initiation of chemotherapy [25]. Current clinical guidelines recommend routine primary prophylaxis with G-CSF when the risk for FN is $\geq 20\%$ [25-28].

We concur with the IDSA guidelines in recommending G-CSF to patients with expected profound and prolonged neutropenia [9]. (IDSA: A-II) (LSIDCM: 1)

INITIAL EMPIRIC THERAPY BASED ON SURVEILLANCE OF ANTIMICROBIAL RESISTANCE IN LEBANON

Resistance to first-line empiric antibiotic therapy for febrile neutropenia recommended by international guidelines, namely cefepime and piperacillin/tazobactam, has

reached 30% according to Lebanese community data [4,5] and Lebanese hospital data [2]. In order to address this high level of resistance, the LSIDCM decided to follow a de-escalation approach in the choice of initial empiric therapy in the treatment of FN patients upon initial presentation [10]. (ECIL 4: B-II) (LSIDCM: 2A)

The initial therapy should also consider whether the patient is at risk for infection/colonization with MDR, XDR and resistant GPB. (cf. ANNEX/Algorithm 1)

- It is preferable to reserve first line empiric carbapenems (imipenem, meropenem) to complicated presentations like sepsis/septic shock (ECIL-4: B-II) (LSIDCM: 2A); to patients known to have been colonized and/or infected with MDR bacteria (ECIL-4: B-II) (LSIDCM: 2A); or to patients having received broad spectrum antibiotics including anti-pseudomonal cephalosporins, or piperacillin/tazobactam or fluoroquinolones within the past 30 days [10]. (ECIL-4: B-II) (LSIDCM: 2A)
- In situations where the patient is febrile but hemodynamically stable upon initial presentation; with no history of MDR bacteria-associated infection/colonization; with no history of third/fourth generation cephalosporins, or piperacillin/tazobactam or fluoroquinolones intake within the past 30 days; cefepime or piperacillin/tazobactam with or without amikacin should be initiated [10]. (ECIL-4: B-III) (LSIDCM: 2B)
- In patients where there is history of colonization/infection with methicillin resistant *Staphylococcus aureus*, or suspected catheter-related infection, or a skin and soft tissue infection at any site, or recent history of admission to a unit endemic with MRSA; a glycopeptide should be added to the initial regimen. Linezolid is recommended only in cases of confirmed resistant Gram-positive infections or as an alternative in cases of glycopeptide intolerance [9]. (IDSA: B-III) (LSIDCM: 2A)

Patients at risk for colonization/infection with XDRO fulfill the following criteria:

- Patient is referred from a country of origin where XDRO like carbapenem-resistant organisms (such as *Enterobacteriaceae* or *Pseudomonas aeruginosa* or *Acinetobacter sp.* or *Stenotrophomonas*), have been shown to be prevalent in patients with neutropenic fever, and has been previously hospitalized in the same country.
- History of prior colonization/infection with XDRO.
- Recent admission to an ICU within the past two months.

In such cases, a combination of carbapenem (imipenem or meropenem) + colistin \pm rifampin is warranted [10]. (ECIL-4: C-III) (LSIDCM: 2B) (Algorithm 3.0)

Modification of the initial regimen after 72-96 h should be based on the patient's response to therapy and the radiologic and laboratory evaluations [9]. (IDSA A-II) (LSIDCM: 1).

For antibiotics dosing, refer to Table IX.

MANAGEMENT OF FN AT 72-96 HOURS

The management of patients with FN after 72 to 96 hours depends on the following factors:

1. Hemodynamic stability.
2. The identification of the foci of infection.
3. Whether treatment for XDR Gram-negative or MDR Gram-positive bacteria was started empirically at the initial assessment, if the patient was judged to be at risk for colonization or a proven carrier of such organisms.
4. The risk for fungal infection, and concurrent use of antifungal prophylaxis.
5. The risk for opportunistic viral infection.

In each of the following clinical situations at 72-96 hours post hospital admission, the suggested corresponding algorithm(s) and table(s) as listed below:

1. Management of febrile neutropenia at 72-96 hours post presentation: Patient with no risk of XDRO upon presentation yet clinically deteriorating (Algorithm 2.0 and Table IX).
2. Management of febrile neutropenia at 72-96 hours post presentation: Patient with no risk of XDRO upon presentation and clinically stable (Algorithm 2.1 and Table IX).
3. Management of febrile neutropenia at 72-96 hours post presentation: Patient with no risk of XDRO upon presentation and initially septic (Algorithm 2.2 and Table IX).
4. Management of febrile neutropenia at 72-96 hours post presentation: Patient at risk of XDRO upon

presentation yet with no initial focus of infection (Algorithm 3.1 and Table IX).

5. Management of febrile neutropenia at 72-96 hours post presentation: Patient at risk of XDRO upon presentation, clinically stable, febrile with an initially confirmed infection (Algorithm 3.2 and Table IX).

Duration of antibacterial therapy

Empirical parenteral antibiotics can be discontinued after ≥ 72 h in patients who have been hemodynamically stable since presentation and have been afebrile for ≥ 48 h, irrespective of their neutrophil count or expected duration of neutropenia [10]. (ECIL-4: B-II) (LSIDCM: 2A)

Prophylactic antimicrobials, if indicated according to risk, can be renewed upon discontinuation of the empirical therapy in case of persistent neutropenic [10]. (ECIL-4: C-III) (LSIDCM: 2B)

When empiric antibiotic therapy is discontinued in the setting of persistent neutropenia, it is recommended that patients be observed in a hospital setting for 24-48 hours to ascertain sustained defervescence. If fever recurs, urgent reinstatement of antibiotics after repeating the clinical and laboratory assessment is warranted. [10]. (ECIL-4: C-III) (LSIDCM: 2B)

ANTIFUNGAL THERAPY AT 72-96 HOURS

In patients who remain febrile at 72-96 h after the initiation of empiric antibiotic therapy, fungal infections should be considered [9,11,12]. (LSIDCM: 2B)

Risk factors for fungal infections and prior use of antifungal chemoprophylaxis are important determinants in defining the approach and choice of subsequent antifungal agents [9,11,12]. For antifungal dosing, refer to Table IV. (LSIDCM: 2B) For management, refer to Algorithms 4.0 to 4.3.

MANAGEMENT OF DOCUMENTED INFECTIONS

The management of patients with documented infections is beyond the scope of these guidelines, we advise clinicians to refer to local, when available, or international guidelines for each specific infection.

ENVIRONMENTAL PRECAUTIONS FOR NEUTROPENIC PATIENTS

Prevention of spread of infection to patients with neutropenia from the environment, food, healthcare workers and visitors is primordial [9].

LSIDCM recommendations on this topic are enlisted in Table X.

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TABLE IX

DOSES OF ANTIBIOTICS FOR EMPIRICAL TREATMENT OF FEBRILE NEUTROPENIA

Antibiotic	Dose
Amikacin	15-20 mg/kg/day IV
Cefepime	2 g IV q8h
Colistin	Loading dose: 9 MIU IV Maintenance dose: 4.5 MIU IV every 12 h. Range: 3-9 MIU/day
Imipenem	1 g IV q8h or q6h
Linezolid	600 mg PO/IV every 12 h
Meropenem	1-2 g IV q8h
Piperacillin/Tazobactam	4.5 g IV q8h or q6h
Rifampin	10 mg/kg (600 mg/dose) PO once daily
Teicoplanin	Loading dose: 400-800 mg (or 6-12 mg/kg) IV/IM every 12 h for 3-5 doses Maintenance dose: 400-800 mg (or 6-12 mg/kg) IV daily.
Vancomycin	15-20 mg/kg IV q12h

IV: intravenous IM: intramuscular MIU: million international units PO: per os
N.B. Consider dose adjustment of the above listed antibiotics when necessary in cases of renal insufficiency, hepatic insufficiency and obesity.

- Dosing of amikacin, cefepime, linezolid, meropenem, piperacillin/tazobactam and vancomycin is adapted from references [11] and [30].
- Dosing of colistin is adapted from reference [31].
- Dosing of rifampin is adapted from reference [32].
- Dosing of teicoplanin is adapted from reference [33].

TABLE X

LSIDCM RECOMMENDATIONS ON ENVIRONMENTAL PRECAUTIONS TO BE TAKEN WHEN MANAGING FEBRILE NEUTROPENIA PATIENTS*

Precaution Measures	LSIDCM Recommendation
Hand Hygiene	It is the most effective means for preventing the transmission of infection in the hospital (WHO 5 moments for hand hygiene) (IDSA: A-II) (LSIDCM: 1)
Standard Barrier Precautions	<ul style="list-style-type: none"> - Standard barrier precautions should be followed for all patients, and infection-specific isolation should be used for patients with certain signs or symptoms (IDSA: A-III) (LSIDCM: 2A). - No specific personal protective equipment (e.g., gowns, gloves, and masks) is required during the routine care of neutropenic patients. - HCWs or visitors who are currently symptomatic with infections transmissible by air, droplet, and direct contact should not engage in patient care or visit patients unless appropriate barrier protection is established [9]. (LSIDCM: 2B) - For HCWs, hospital work exclusion policies should be designed to encourage HCWs to report their illnesses or exposures (IDSA: A-II) (LSIDCM: 1).
Patient Isolation	<ul style="list-style-type: none"> - HSCT recipients should be placed in private (i.e., single-patient) rooms (IDSA: B-III) (LSIDCM: 2B). - Allogeneic HSCT recipients should be placed in rooms with > 12 air exchanges/h and HEPA filtration (IDSA: A-III) (LSIDCM: 2B). The air pressure in the patient rooms should be positive compared with adjoining areas, such as hallways, toilets, and anterooms. - Patients with neutropenia, other than HSCT recipients, do not need to be placed into a single-patient room.
Neutropenic Diet	This usually consists of well-cooked foods. Well-cleaned, uncooked raw fruits and vegetables are also acceptable when the cleaning is controlled with sterile water with antiseptics. (LSIDCM: 2B)
Oral Hygiene	Patients and their caregivers should be taught how to maintain good oral and dental hygiene during neutropenia. For those with ongoing mucositis, this includes oral rinses 4-6 times/day with sterile water, normal saline, or sodium bicarbonate solutions. Patients should brush their teeth \geq 2 times/day with a soft regular toothbrush. (LSIDCM: 2B)
Presence of Plants and Flowers	This should not be allowed in the rooms of hospitalized neutropenic patients. (IDSA: B-III) (LSIDCM: 2B).
Vaccination of HCWs & Visitors	This includes annual influenza. Measles, mumps, rubella, and varicella vaccination for non immune HCW.

* Adapted from reference [9] HEPA: high efficiency particulate air HCW: healthcare worker HSCT: hematopoietic stem cell transplant WHO: World Health Organization

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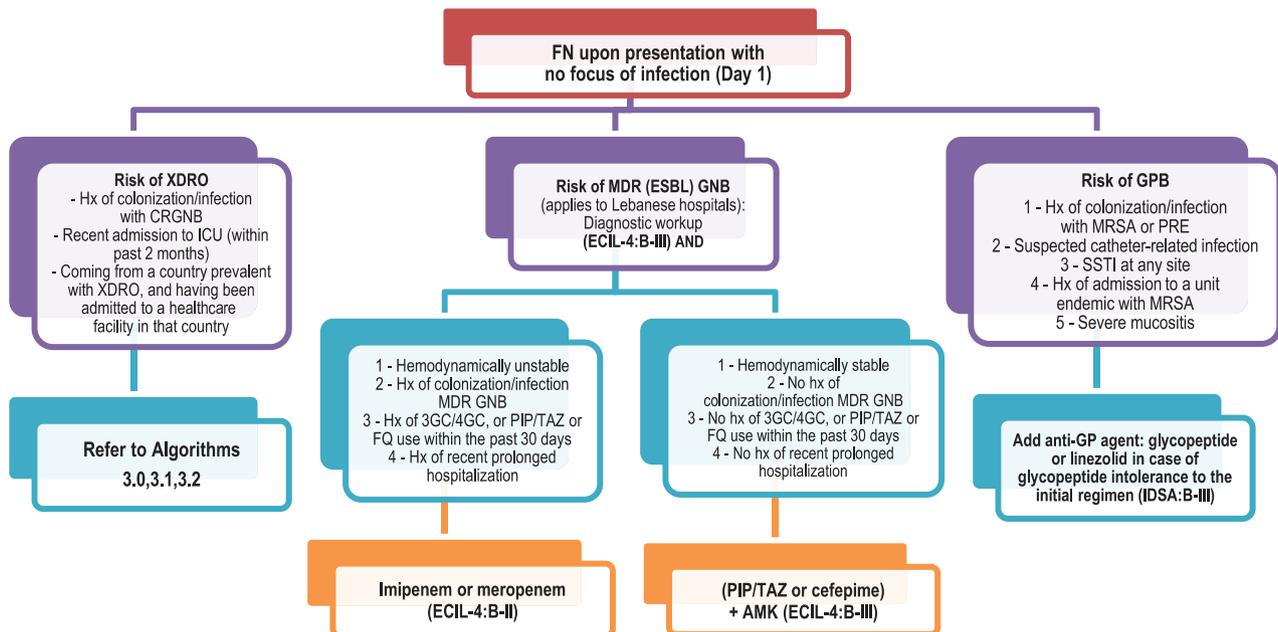
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ANNEX • ALGORITHMS

Algorithm 1

Management of a patient with fever and neutropenia with no focus of infection at initial presentation (Day 1) (All LSIDCM recommendations are category 2B unless otherwise indicated.)

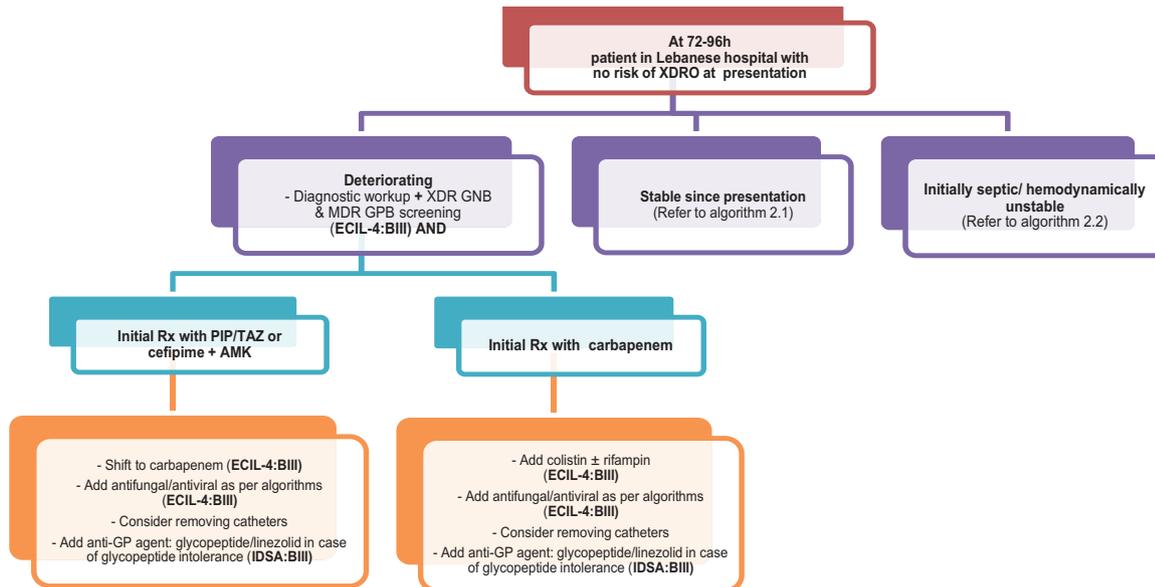


AMK: amikacin ESBL: extended spectrum beta-lactamase FN: febrile neutropenia FQ: fluoroquinolone GNB: Gram-negative bacteria GP: Gram-positive GPB: Gram-positive bacteria ICU: intensive care unit MDR: multi-drug resistant MRSA: methicillin resistant *Staphylococcus aureus* PIP/TAZ: piperacillin/tazobactam PRE: penicillin resistant *Enterococci* SSTI: skin and soft tissue infection, XDRO: extensively drug resistant organism 3GC: third generation cephalosporin 4GC: fourth generation cephalosporin.

N.B. 1. MDR in Gram-negative organisms is defined as resistance to at least three of the following antibiotics: piperacillin/tazobactam, cefepime, aminoglycosides and fluoroquinolones. 2. XDROs are MDR Gram-negative organisms resistant to carbapenems. 3. ECIL-4: B-II is equivalent to LSIDCM: 2A. 4. IDSA: B-III is equivalent to LSIDCM: 2B.

Algorithm 2.0

Management of febrile neutropenia at 72-96 hours post presentation: Patient with no risk of XDRO upon presentation yet clinically deteriorating (All LSIDCM recommendations are category 2B unless otherwise indicated.)

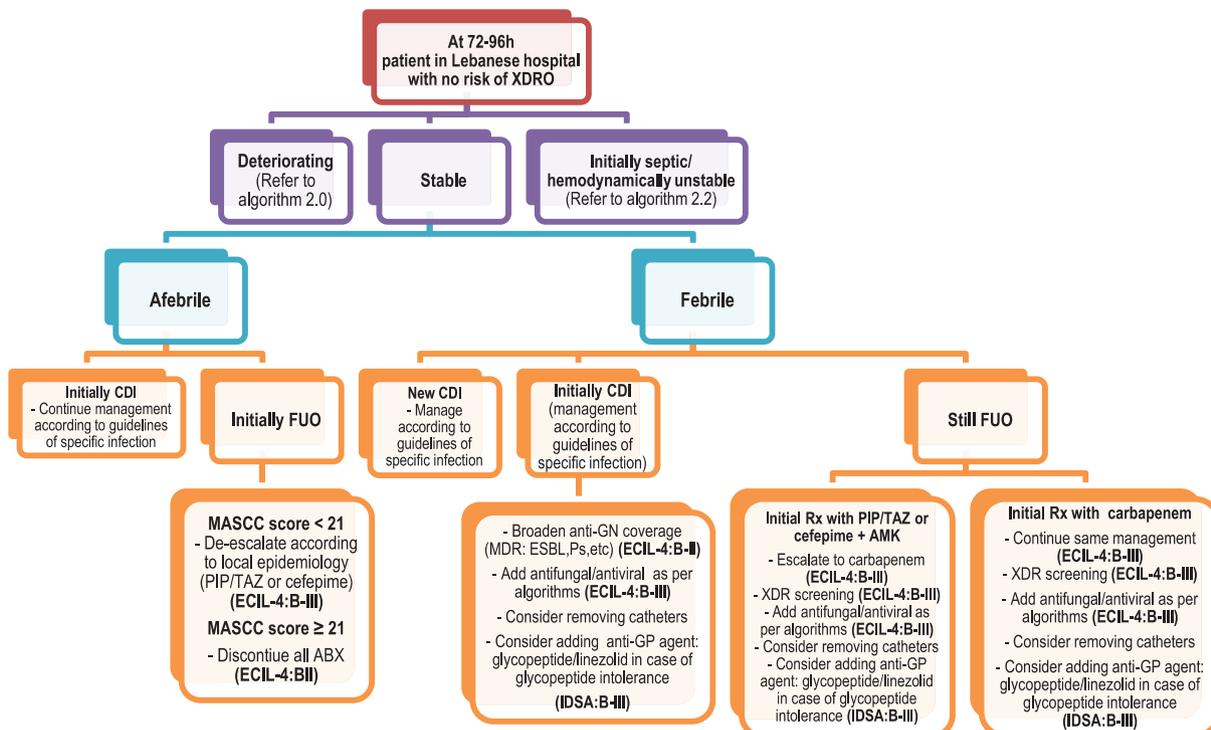


AMK: amikacin GNB: Gram-negative bacteria GP: Gram-positive GPB: Gram-positive bacteria MDR: multi-drug resistant PIP/TAZ: piperacillin/tazobactam XDR: extensively drug resistant XDRO: extensively drug resistant organism

N.B. 1. MDR in Gram-negative organisms is defined as resistance to at least three of the following antibiotics: piperacillin/tazobactam, cefepime, aminoglycosides and fluoroquinolones. **2.** XDROs are MDR Gram-negative organisms resistant to carbapenems. **3.** Carbapenem: imipenem or meropenem. **4.** ECIL-4: B-III is equivalent to LSIDCM: 2A. **5.** IDSA: B-III is equivalent to LSIDCM: 2B.

Algorithm 2.1

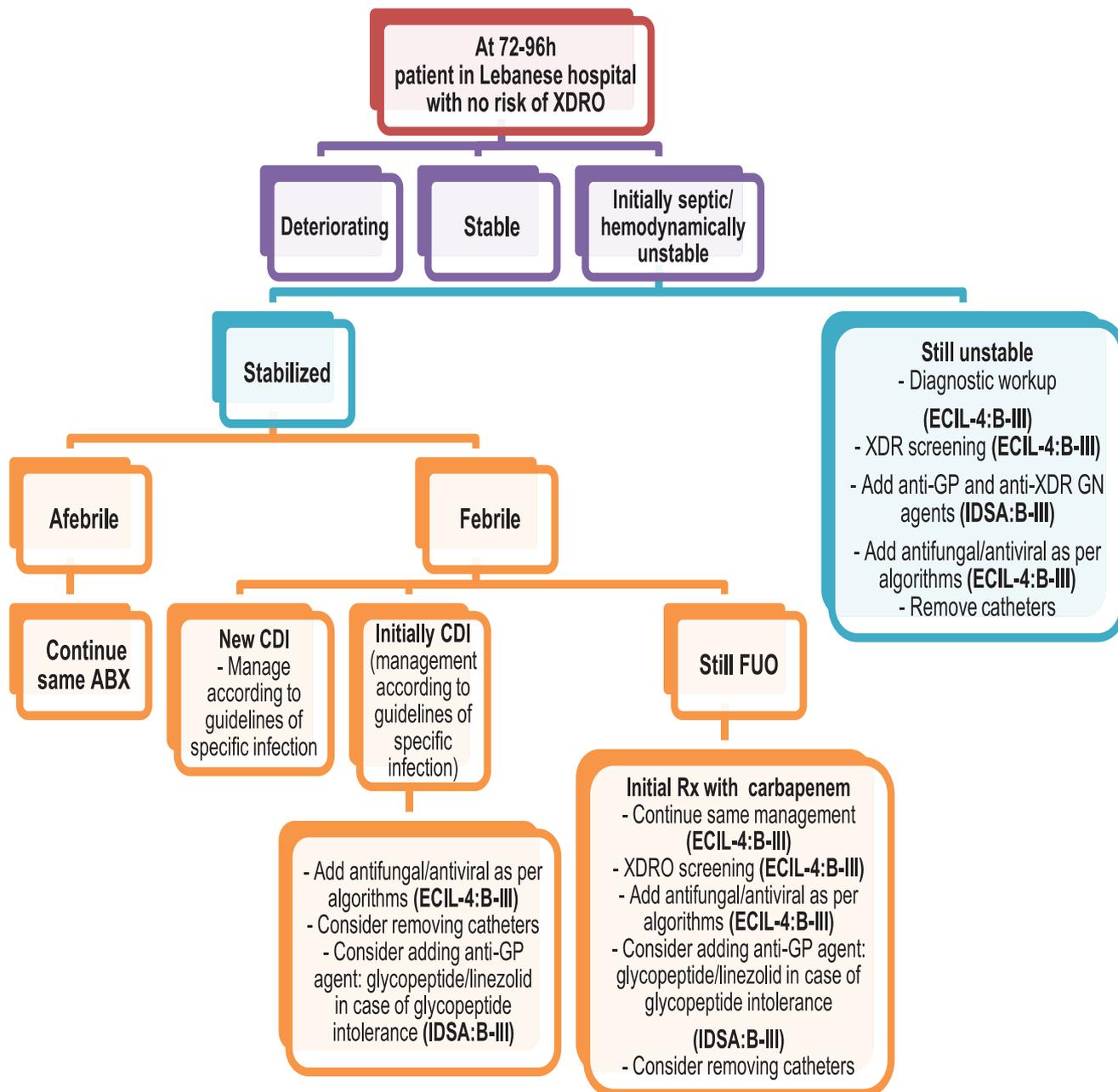
Management of febrile neutropenia at 72-96 hours post presentation: Patient with no risk of XDRO upon presentation and clinically stable (All LSIDCM recommendations are category 2B unless otherwise indicated.)



ABX: antibiotics AMK: amikacin CDI: clinically documented infection ESBL: extended spectrum beta-lactamase. FUO: fever of unknown origin GN: Gram-negative GP: Gram-positive MASCC: Multinational Association for Supportive Care in Cancer MDR: multi-drug resistant PIP/TAZ: piperacillin/tazobactam Ps: *Pseudomonas species* XDR: extensively drug resistant XDRO: extensively drug resistant organism

N.B. 1. MDR in Gram-negative organisms is defined as resistance to at least three of the following antibiotics: piperacillin/tazobactam, cefepime, aminoglycosides and fluoroquinolones. **2.** XDROs are MDR Gram-negative organisms resistant to carbapenems. **3.** Carbapenem: imipenem or meropenem. **4.** ECIL-4: B-III is equivalent to LSIDCM: 2A **5.** IDSA: B-III is equivalent to LSIDCM: 2B

Algorithm 2.2 Management of febrile neutropenia at 72-96 hours post presentation: Patient with no risk of XDRO upon presentation and initially septic (All LSIDCM recommendations are category 2B unless otherwise indicated.)



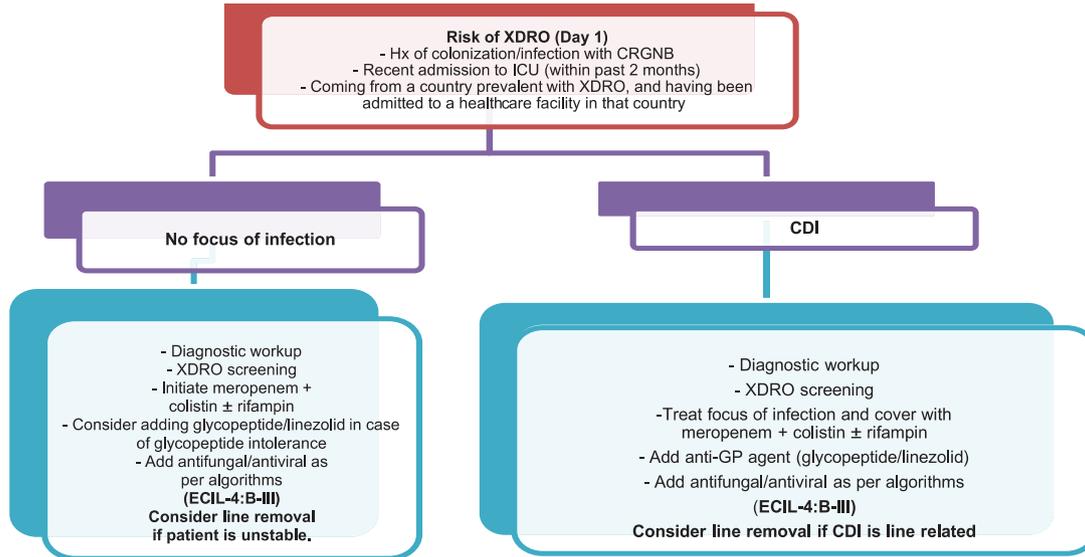
ABX: antibiotics AMK: amikacin CDI: clinically documented infection ESBL: extended spectrum beta-lactamase. FUO: fever of unknown origin GN: Gram-negative GP: Gram-positive MDR: multi-drug resistant PIP/TAZ: piperacillin/tazobactam Ps: *Pseudomonas species* XDR: extensively drug resistant XDRO: extensively drug resistant organism

N.B. 1. MDR in Gram-negative organisms is defined as resistance to at least three of the following antibiotics: piperacillin/tazobactam, cefepime, aminoglycosides and fluoroquinolones. 2. XDROs are MDR Gram-negative organisms resistant to carbapenems.

3. Carbapenem: imipenem or meropenem. 4. Anti-XDR GN: High-dose prolonged infusion meropenem (2g q8 h), colistin ± tigecycline or rifampin. 5. ECIL-4: B-III is equivalent to LSIDCM: 2A 6. IDSA: B-III is equivalent to LSIDCM: 2B.

Algorithm 3.0

Management of a patient with fever and neutropenia at risk of XDRO upon presentation (Day 1)
(All LSIDCM recommendations are category 2B unless otherwise indicated.)

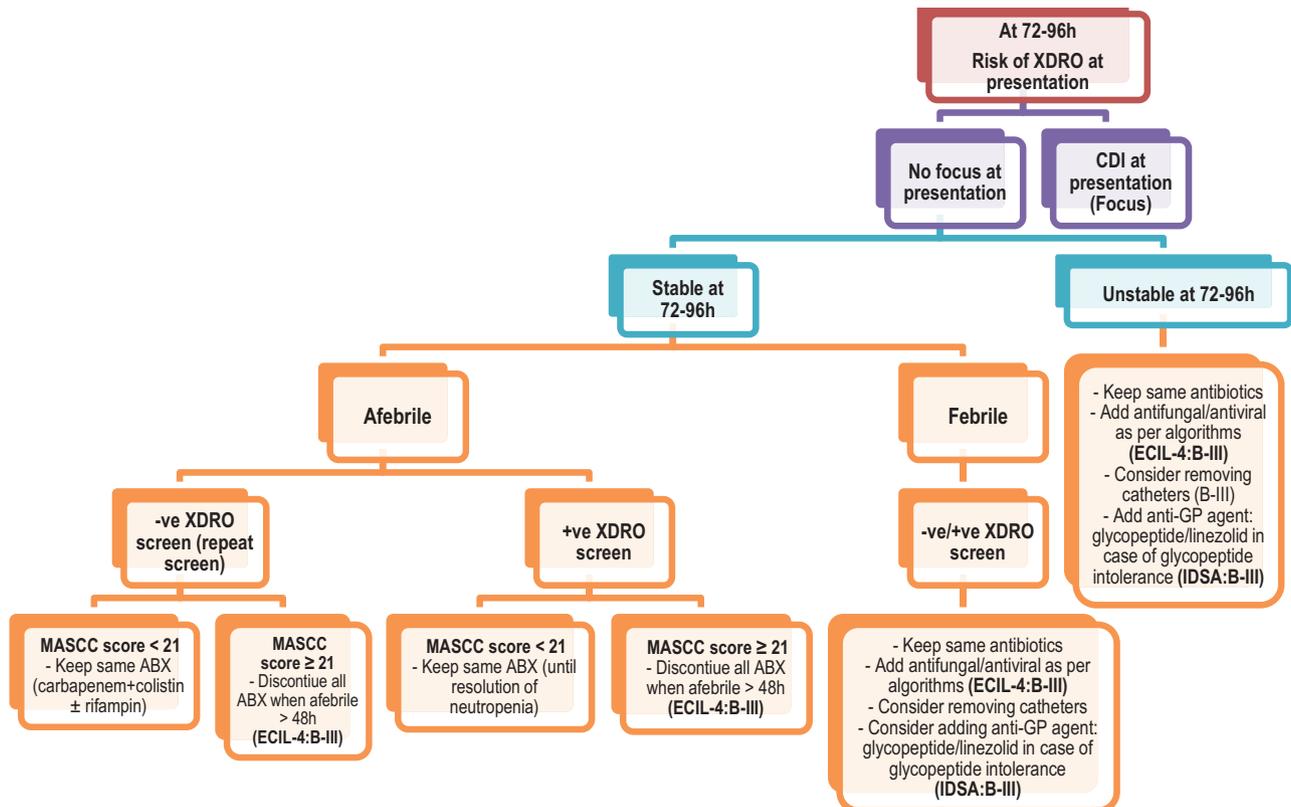


CDI: clinically documented infection CRGNB: carbapenem resistant Gram-negative bacteria FN: febrile neutropenia ICU: intensive care unit XDR: extensively drug resistant XDRO: extensively drug resistant organism

N.B. 1. MDR in Gram-negative organisms is defined as resistance to at least three of the following antibiotics: piperacillin/tazobactam, cefepime, aminoglycosides and fluoroquinolones. **2.** XDROs are MDR Gram-negative organisms resistant to carbapenems. **3.** Dosing of meropenem: 2g IV q8h with each dose to be administered at least over 3 hours. **4.** ECIL-4: B-III is equivalent to LSIDCM: 2A.

Algorithm 3.1

Management of febrile neutropenia at 72-96 hours post presentation: Patient at risk of XDRO upon presentation yet with no initial focus of infection (All LSIDCM recommendations are category 2B unless otherwise indicated)

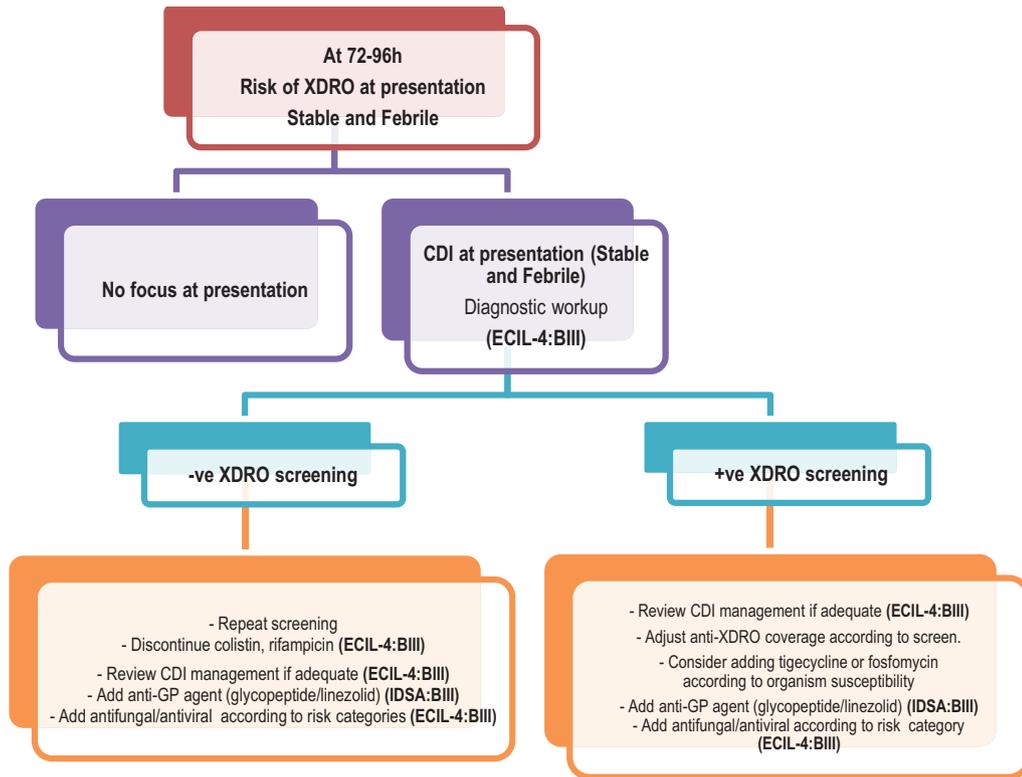


ABX: antibiotics AMK: amikacin CDI: clinically documented infection origin GP: Gram-positive MASCC: Multinational Association for Supportive Care in Cancer XDRO: extensively drug resistant organism -ve: negative +ve: positive

N.B. 1. MDR in Gram-negative organisms is defined as resistance to at least three of the following antibiotics: piperacillin/tazobactam, cefepime, aminoglycosides and fluoroquinolones. **2.** XDROs are MDR Gram-negative organisms resistant to carbapenems. **3.** Carbapenem: imipenem or meropenem. **4.** ECIL-4: B-III is equivalent to LSIDCM: 2A **5.** IDSA: B-III is equivalent to LSIDCM: 2B.

Algorithm 3.2

Management of febrile neutropenia at 72-96 hours post presentation: Patient at risk of XDRO upon presentation, clinically stable, febrile with an initially confirmed infection. (All LSIDCM recommendations are category 2B unless otherwise indicated.)

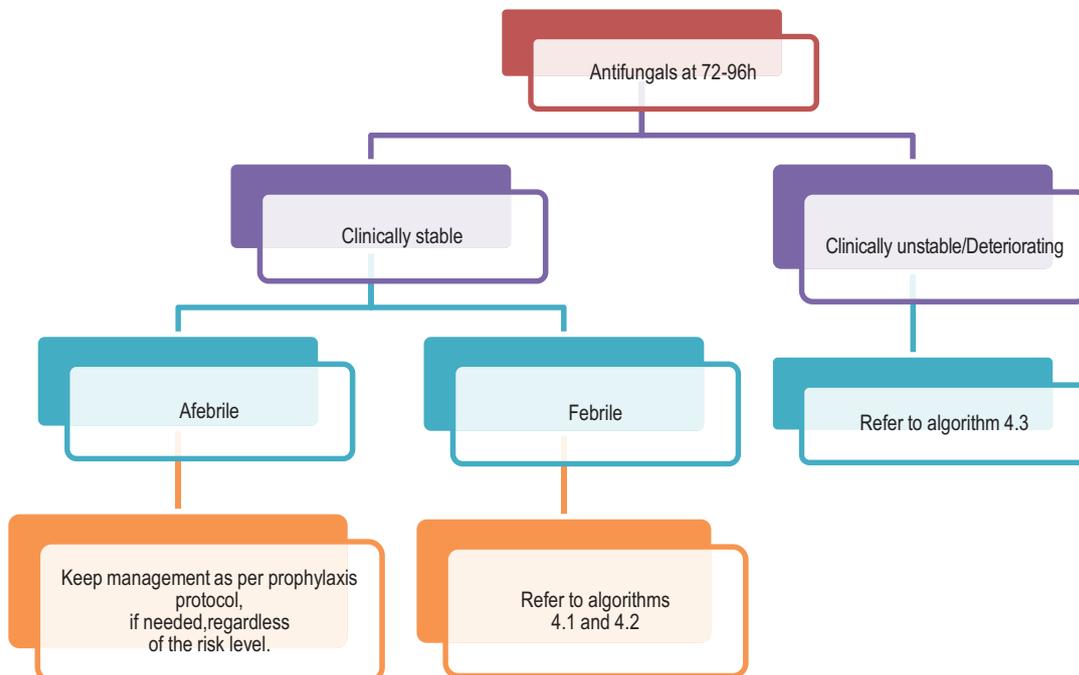


CDI: clinically documented infection GP: Gram-positive XDRO: extensively drug resistant organism -ve: negative +ve: positive.

- N.B. 1.** MDR in Gram-negative organisms is defined as resistance to at least three of the following antibiotics: piperacillin/tazobactam, cefepime, aminoglycosides and fluoroquinolones. **2.** XDROs are MDR Gram-negative organisms resistant to carbapenems. **3.** Anti-XDRO: High-dose prolonged infusion meropenem (2g q8 h), colistin ± tigecycline or rifampin. **4.** ECIL-4: B-III is equivalent to LSIDCM: 2A. **5.** IDSA: B-III is equivalent to LSIDCM: 2B.

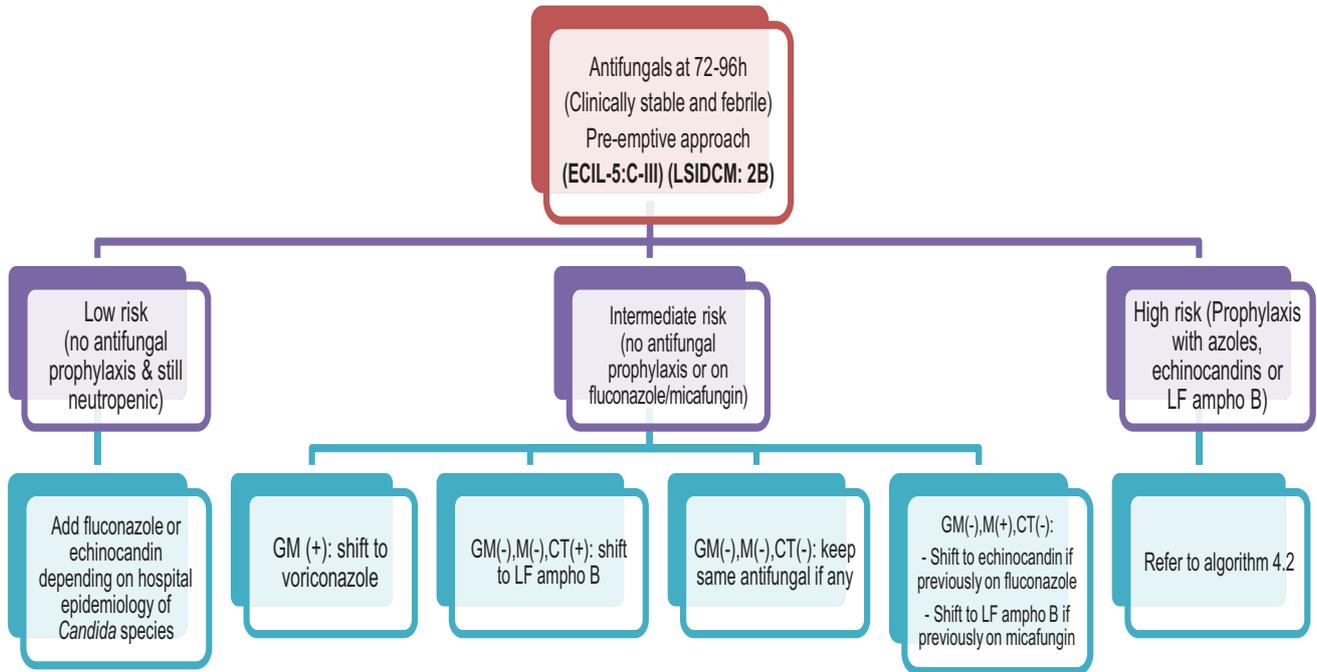
Algorithm 4.0

Management of febrile neutropenia at 72-96 hours post presentation: Antifungal therapy. (All LSIDCM recommendations are category 2B unless otherwise indicated.)



Algorithm 4.1

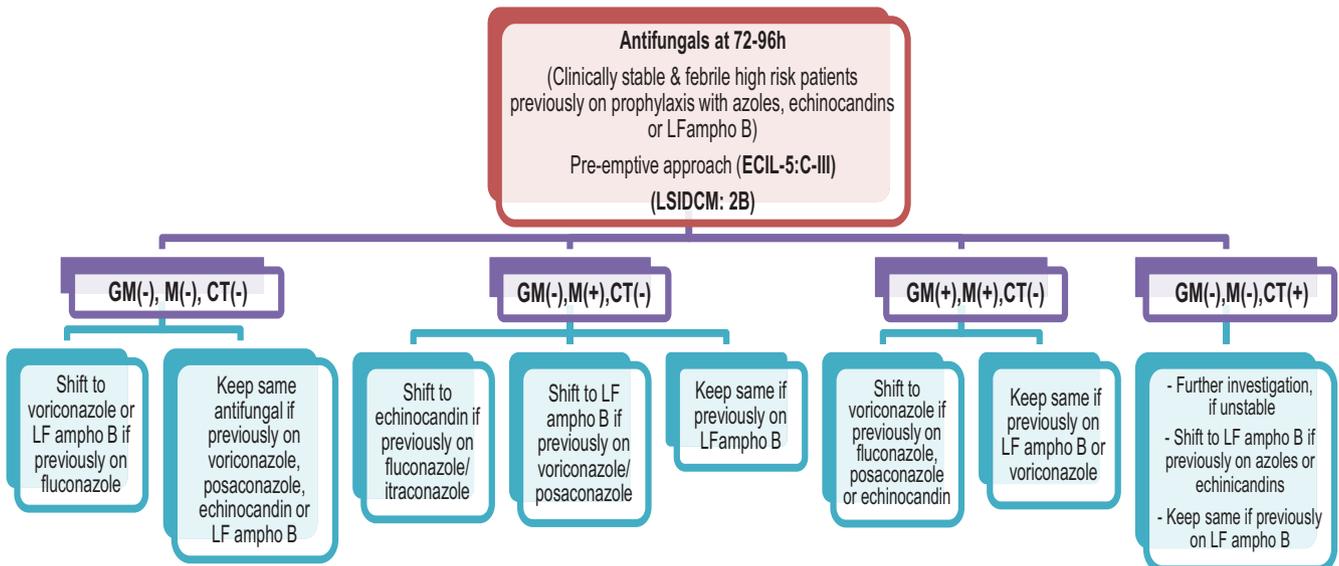
Management of febrile neutropenia at 72-96 hours post presentation: Pre-emptive antifungal therapy in clinically stable yet febrile patients (All LSIDCM recommendations are category 2B unless otherwise indicated.)



LF: ampho B: lipid formulation amphotericin B GM: galactomannan CT: computerized tomography M: mucositis (+): positive (-): negative. **N.B.** Serum galactomannan assay and high-resolution chest/sinus CT are recommended on a weekly basis (LSIDCM: 2B).

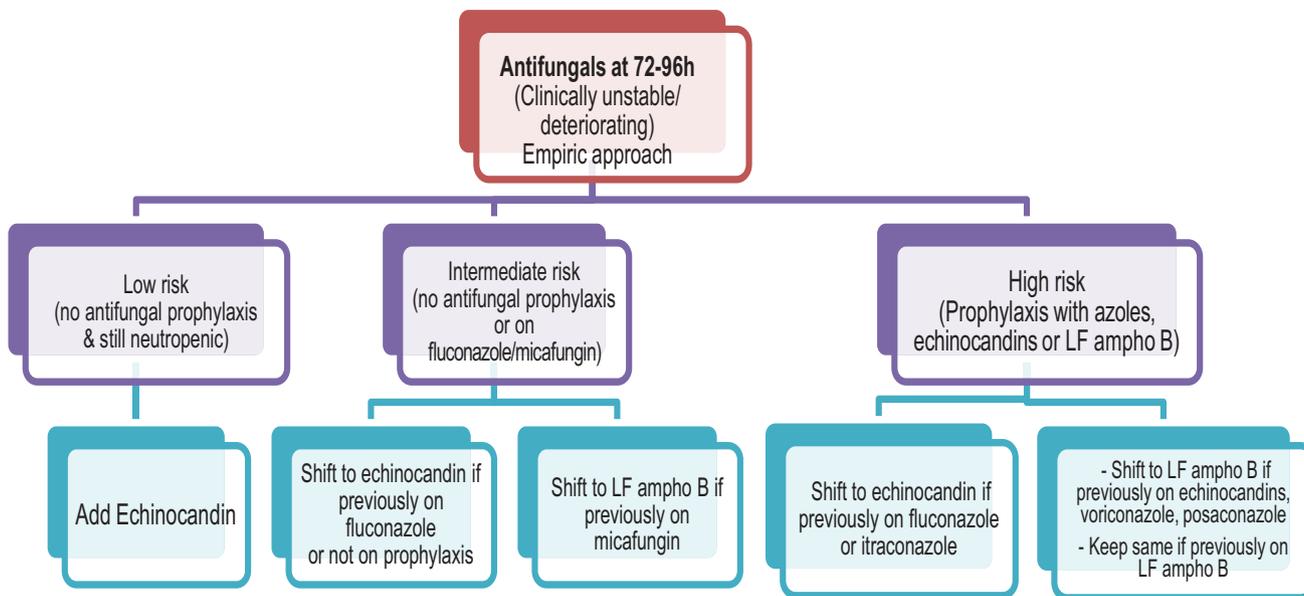
Algorithm 4.2

Management of febrile neutropenia at 72-96 hours post presentation: Pre-emptive antifungal therapy in clinically stable yet febrile high-risk patients previously on prophylaxis with azoles, echinocandins or lipid formulation amphotericin B (All LSIDCM recommendations are category 2B unless otherwise indicated.)



LF ampho B: lipid formulation amphotericin B GM: galactomannan CT: computerized tomography M: mucositis (+): positive (-): negative. **N.B.** Serum galactomannan assay and high-resolution chest/sinus CT are recommended on a weekly basis (LSIDCM: 2B).

Algorithm 4.3 Management of febrile neutropenia at 72-96 hours post presentation: Empiric antifungal therapy in clinically unstable/deteriorating patients (All LSIDCM recommendations are category 2B unless otherwise indicated.)



LF ampho B: lipid formulation amphotericin B

N.B. Serum galactomannan assay and high-resolution chest/sinus CT are recommended on a weekly basis (LSIDCM: 2B).