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REVIEW ARTICLE

RASCANDIS 1.0 Form: Therapeutic Approach of Systemic Anti-Candidiasis for Non-Transplant Patients

Formulir RASCANDIS 1.0: Pendekatan Terapi Anti-Kandida Sistemik untuk Pasien Non-Transplantasi

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ABSTRACT

It has been a concern that using antifungals may induce some fungi to develop antifungal resistance in the future. Therefore, systemic anti-candidiasis agents should become a focus in controlling antifungal drugs since it is quite commonly used. There are currently three approaches to using systemic anti-candidiasis agents based on their indication, i.e. definitive, empiric and pre-emptive indication. These can be applied by observing supportive findings such as the presence of *Candida sp* infection or colonization, the severity of the infection and the patient's risk factors. The severity of invasive candidiasis is usually severe, and various risk factors need to be considered, such as Total Parenteral Nutrition (TPN), catheterization including deep vein catheter, central venous catheter (CVC), etc.

Antifungal stewardship program, including management of systemic anti-candidiasis, is essential nowadays. Therefore, it is necessary to have a program that can serve as a guideline for clinicians to implement a treatment approach for systemic anti-candidiasis. *RASPRO Alur Anti Candida Sistemik (RASCANDIS)* 1.0 form or the Indonesian Regulation on the Prospective Antimicrobial System on Systemic Anti-Candidiasis Flowchart 1.0 form is an actual implementation to provide guidelines for clinicians to administer systemic anti-candidiasis agents for non-transplant patients. The form is not a diagnostic tool, but it is more likely to serve as a review and summary of knowledge obtained from various scientific journals, which is expected that it can be proposed as an effort to administer therapeutic management of systemic anti-candidiasis appropriately.

Keywords: systemic anti-candidiasis; non-transplant; RASCANDIS 1.0; appropriately

ABSTRAK

Penggunaan obat anti jamur dikhawatirkan dapat memicu resistensi jamur terhadap obat anti jamur di masa-masa yang akan datang. Penggunaan obat anti candida sistemik perlu menjadi fokus dalam pengendalian obat anti jamur, karena obat anti candida sistemik merupakan obat anti jamur yang cukup banyak digunakan. Saat ini terdapat tiga pendekatan indikasi penggunaan obat anti candida sistemik, yaitu: indikasi definitif, indikasi empirik, dan indikasi pre-emtif. Indikasi pemberian obat anti candida sistemik dapat dilakukan dengan melihat temuan pendukung adanya infeksi atau kolonisasi *Candida sp*, severitas, dan faktor risiko pasien. Severitas pada pasien-pasien dengan candidiasis invasif umumnya berat dan berbagai faktor risiko pasien yang dipertimbangkan antara lain penggunaan *Total Parenteral Nutrition* (TPN), penggunaan kateter-kateter pembuluh darah dalam, termasuk kateter vena dalam, *Central Venous Catheter* (CVC) dan yang lainnya.

Program penatagunaan anti jamur, termasuk pengaturan penggunaan obat anti candida sistemik, mulai diperlukan saat ini. Dibutuhkan program yang bisa mengarahkan klinisi dalam melakukan pendekatan pemberian anti candida sistemik tersebut. Formulir RASPRO Alur Anti Candida Sistemik (RASCANDIS) 1.0 merupakan upaya untuk dapat memberikan arahan kepada klinisi dalam pemberian obat anti candida sistemik pada pasien-pasien non transplantasi. Formulir ini bukanlah alat diagnostik, melainkan merupakan sebuah kajian dan rangkuman dari berbagai jurnal ilmiah yang diharapkan dapat diusulkan sebagai upaya pemberian terapi obat anti candida sistemik bijak.

Kata Kunci: anti candida sistemik; non transplantasi; RASCANDIS 1.0; bijak

INTRODUCTION

Along with the growing issue of the wide use of systemic antifungal agents in hospitals, measures for taking control of it must be taken as soon as possible. Systemic antifungal drugs can be misused when the use is not based on the prevailing theory principles. Therefore, in addition to controlling the use of antibiotics, controlling the use of anti-fungal is essential as a part of the hospital's commitment to controlling the widespread use of antimicrobial agents. The wide impact of antifungal resistance must be taken into caution. Candidemia and deep organ fungal infection are manifestations of invasive candidiasis that often provide progressive clinical manifestation. *Candida sp,* which has become the most common etiology of invasive candidiasis, include *Candida albicans*, *Candida parapsilosis*, *Candida grablata*, *Candida tropicalis* and *Candida krusei*.[1,2] The mortality rate caused by invasive candidiasis is relatively high that may, range from 40-60%.[2] Candidemia can reach over 15 per cent of *Health Care Associated Infections*, formerly known as nosocomial infection. At the same time, the mortality rate of invasive candidiasis in the Intensive Care Unit (ICU) varies about 25-60%.[3] Some researchers have also described that *Candida sp* can produce a biofilm that frequently becomes a complication in treatment.[4–6] *Candida sp* also causes mortality in elderly patients.[7]

The wide use of systemic anti-candidiasis in hospital wards without clear indication can undoubtedly greatly impact extensive antifungal drug resistance. It has been said that there might be an indication of increased resistance of *C. grablata* and *C. krusei* to Azole antifungals.[1] The use of echinocandins agents has brought good results in managing invasive candida infection.[8] The antifungal stewardship program is essential, and it should become a public concern so that the therapeutic use of antifungals can become more appropriate. The antifungal stewardship program is coordinated between managing treatment for fungal infection and good monitoring to achieve optimal treatment objectives. At the same time, keep carefully evaluating the possible emergence

of resistance and side effects.[9] The largest use of systemic antifungals is Azoles antifungals reaching 28.5 / 1000 Patient Days (PDs), followed by Echinocandin, which reaches 5.0/1000 PDs.[10] Both Azoles and Echinocandins serve as systemic anti-candidiasis drugs. A systematic review suggests that implementing an antifungal stewardship program may impact the reduced quantity of systemic antifungal usage; however, it does not mention further evaluation of clinical improvement.[11] Implementing an antifungal stewardship program increases adherence to systemic antifungal use; however, it does not significantly improve mortality and reduce the length of stay (LOS).[12]

A. Implementation of Antifungal Stewardship Program and Therapeutic Indication of Systemic Anti-Candidiasis Drugs

The antifungal stewardship program must be executed by considering therapeutic indications. Focusing on systemic anti-candidiasis, various indications of administering systemic anti-candidiasis agents are definitive, empiric, and pre-emptive therapy. In definitive therapy, systemic anti-candidiasis drugs are given based on the rationale of suitability on etiologic findings, which is obtained from the results of culture; while in empiric and definitive therapy, the treatment must be based on clinical condition along with various risk factors for invasive candidiasis; hence, the use of systemic anti-candidiasis agents becomes appropriate.[3]

B. Definitive Therapy for Invasive Candidiasis (Proven Diagnostic (EORTC))

European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) 2008 emphasizes that confirmed diagnosis of invasive and systemic fungal infection caused by *Candida sp* must be made through an evaluation obtained from sterile specimens.[13,14] Definitive therapy is given based on findings from sterile specimens following criteria of definitive diagnosis.

C. Empiric and Pre-Emptive Therapy Based on Reviews of Invasive Candidiasis Risk Factors

The invasive candidiasis empiric therapy approach is carried out based on considering progressive clinical conditions, sepsis, sepsis shock, and associated risk factors.[2,3,15] Meanwhile, a pre-emptive therapy approach is made based on concern about findings of non-definitive specimens or Candida sp colonization obtained from various areas along with associated risk factors.[2,3] Reviews on risk factors of invasive candidiasis treatment are categorized into two parts: reviews on risk factors for neutropenic patients and reviews on risk factors for non-neutropenic patients.

D. Reviews on Risk Factors of Invasive Candidiasis in Neutropenic Patients

In high-risk neutropenic cases or conditions suggested by the Multinational Association for Supportive Care in Cancer (MASCC), i.e. those with Risk Index Score < 21, persistent fever or unknown origin of fever, they can receive empirical treatment of systemic antifungal agents.[16] It sets neutropenia as one of the risks for invasive candidiasis. Moreover, the pre-emptive therapy for systemic anti-candida in those with stable neutropenic fever can be considered when there are supportive findings such as serologic results and results from another laboratory workup.[16]

E. Reviews on Risk Factors of Invasive Candidiasis in Non-Neutropenic Patients

E.1 Review on General Risk Factors of Invasive Candidiasis in Non-Neutropenic Patients

Studies on risk factors of invasive candidiasis have been extensively carried out, and the results serve as a consideration in administering systemic anti-candidiasis agents. Invasive candidiasis is clinically progressive. In non-neutropenic patients, invasive candidiasis can be found in patients with immunocompromised backgrounds, such as patients with a history of using immunosuppressants, chemotherapy and steroids.[3] However, various other risk factors often accompany immunocompromised patients that need to be evaluated further, and when we summarize those factors from various references, we could say that the overall risk factors are as the following:[3,13,17]

Sepsis
Long ICU stay
Using Total Parenteral Nutrition (TPN)
Candida sp multifocal colonization findings
Using deep vein catheters, including Central Venous Catheter (CVC)
Hemodialysis
History of long-term use of wide-spectrum antibiotics
History of abdominal surgery
Transplantation
Long ICU stay
Babies with low birth weight in ICU

In previous reviews, the use of medical instruments, including venous catheters, hemodialysis patients, patients with a history of surgery and history of antibiotic use is the high-risk factors for invasive candidiasis.[17] Other reviews include the history of abdominal surgery, antibiotic use, comorbidities, medical instruments, and extended ICU stay as risk factors for invasive candidiasis.[3,13]

E.2 The Use of Total Parenteral Nutrition (TPN) and Various Supportive Findings of *Candida Sp* Colonization as Non-Neutropenic Risk Factors for Invasive Candidiasis

The use of TPN and the presence of *Candida sp* colonization, confirmed through various laboratory workups, biomarkers, cultures, etc., are risk factors that must also be considered for invasive candidiasis. Many researchers have confirmed that the use of TMN and the presence of *Candida sp* colonization must be considered.[3,13,17]

E.3 Vascular Catheterization as a Non-Neutropenic Risk Factor for Invasive Candidiasis

Blood Stream Infection (BSI) can be caused by deep vein catheterization such as CVC or a peripheral venous catheter.[18,19] Some researchers subsequently have associated the use of deep vascular catheters (including deep venous catheters and deep arterial catheters) with the higher risk of developing invasive candidiasis. Using a deep vascular catheter and CVC of > 96 hours can increase the risk of developing BSI caused by *Candida sp*. infection.[3] BSI caused by *Candida sp*, often called candidemia, is a manifestation of invasive candidiasis. Another review suggests that early disconnection of CVC in candidemia cases caused by *Candida parapsilosis* is an important factor that should be done to reduce mortality rate caused by candidemia.[20]

Such a conclusion has brought a perspective that the use of deep vascular catheters, including deep venous catheters such as CVC, has significantly resulted in some effects, and it serves as a risk factor for invasive candidiasis. A survey conducted between 2002 and 2013 has demonstrated that the use of peripheral catheters such as Peripheral Venous Catheters (PVC) can also become one of the risk factors for candidemia. However, from an overall perspective, the study provides the impression that using CVC still dominates the risk factor for invasive candidiasis.[21] Therefore, it can be explained that the use of deep vascular catheters, including CVC, is still the main risk factor for invasive candidiasis compared to the use of peripheral catheters. Considering the extremely high progressiveness of invasive candidiasis, it is recommended to perform an observation on the probability of candidiasis occurrence within 48 hours following the installation of a deep venous catheter, including CVC, which is in accordance with the general onset of BSI incident.[3,19]

E.4 History of Antibiotic Use as Non-Neutropenic Risk Factor for Invasive Candidiasis

It has been known that using deep vascular catheters increases the risk of developing invasive candidiasis. Various researchers then put some additional information that the history of using antibiotics increases the risk of invasive candidiasis in such conditions.[3,13,17,22] In Some studies in some Asian regions, a bacterial infection is still found as the major finding for BSI etiology, which is associated with the installation of deep venous catheters, including CVC.[23–25] The main cause of infection due to CVC installation is still dominated by negative-gram bacteria (39.2%) followed by positive-gram bacteria (33.2%) and *Candida sp* (27.6%) with an onset mean of 8 days following insertion.[23] A study conducted from 2010 to 2016 has also found that negative-gram bacteria (59.3%) are dominant as etiologic findings, with 9% of bacteria classified as Multi-Drug Resistant Microorganisms (MDROs) including *Acinetobacter sp*, *Enterobacter sp* and *Sternotrophomonas maltophilia*.[24] Another researcher has also noted the same issue, i.e. BSI findings that are associated with deep vascular catheter installation, *Central Line Associated Blood Stream Infection* (CLABSI), include 52% negative-gram bacteria, 27% positive-gram bacteria and 21% *Candida sp*.[26]

The abovementioned findings show that bacteria is the main cause of BSI associated with installing deep vascular catheters. However, invasive candidiasis still needs to be a concern considering that a history of antibiotic use is a risk factor for developing invasive candidiasis, especially in patients with deep vascular catheterization.

E.5 Abdominal Surgery as Non-Neutropenic Risk Factor for Invasive Candidiasis

Various studies have demonstrated that surgery is one of the risk factors for invasive candidiasis. Gastrointestinal surgery is one of the risk factors that must be considered in developing invasive candidiasis.[3] There is a significant correlation between the history of abdominal surgery and the risk of developing invasive candidiasis.[27] The history of wide-spectrum antibiotic use, long ICU stay and the use of CVC have also been documented as a condition that increases the risk for invasive candidiasis in patients with intra-abdominal surgery.[28,29] Moreover, intra-abdominal perforation and anastomosis leak with the previous use of antibiotics has also been noted to increase the risk of intra-abdominal invasive candidiasis.[30,31] Early diagnosis will increase prompt treatment, and in this case, hence it will reduce the mortality rate of intra-abdominal invasive candidiasis.[31,32]

F. RASCANDIS Flowchart as a Proposal for Using Systemic Anti-Candidiasis Appropriately in Non-Transplant Patients

Based on various reviews on risk factors, the Indonesian Regulation on the Prospective Antimicrobial System or *Regulasi Antimikroba Sistem Prospektif (RASPRO)* Indonesia Study Group in 2019 has attempted to create a collective review associated with the effort to use systemic anti-candidiasis agents appropriately.

RASPRO Indonesia Study Group has put some effort into creating a flowchart known as the *RASPRO Alur Anti Candida Sistemik (RASCANDIS) 1.0*, which is limited for non-transplant patients and is expected that it can serve as a guideline for clinicians to use systemic anti-candidiasis agents based on reviews of present literature.

RASCANDIS 1.0 Flowchart

RASPRO Flowchart on systemic Anti Candidiasis (RASCANDIS 1.0)

No.	Specification	Flow	Explanation	Approach
1	**Clinical progressive :** With positive culture finding from sterile	Yes	STOP Circle : *Blood *Liver biopsy *Spleen biopsy *Etc,...	Definitive Systemic Anti Candida
		No		
2	**Clinical progressive :** (With≥48-hours use of deep vascular catheter AND/OR TPN) without improvement with antibiotic use	Yes	STOP	Empiric Systemic Anti Candida
		No		
3	**Clinical progressive :** Post Extensive intraabdominal surgery without improvement with antibiotic use	Yes	STOP	Empiric Systemic Anti Candida
		No		
4	**Clinical progressive :** High risk neutropenia AND / OR with MASCC Index<21	Yes	STOP	Empiric Systemic Anti Candida
		No		
5	(Found ≥1 candida colonization AND/OR positive of other candida biomarker) with neutropenic condition	Yes	STOP Circle : *Oropharynx *Faeces *Skin *Etc,... *Urine	Pre-emptive Systemic Anti Candida
		No		
6	(Found ≥1 candida colonization AND/OR positive of other candida biomarker) with >48 hours of deep vascular catheterization AND/OR TPN	Yes	STOP Circle : *Oropharynx *Faeces *Skin *Etc,... *Urine	Pre-emptive Systemic Anti Candida
		No		
7	(Found ≥1 candida colonization AND/OR positive of other candida biomarker) following extensive intraabdominal surgery	Yes	STOP Circle : *Oropharynx *Faeces *Skin *Etc,... *Urine	Pre-emptive Systemic Anti Candida
		No	Systemic Anti Candidiasis is not necessary	

Explanation:

1. The RASCANDIS 1.0 form may be altered from time to time in accordance with the advancement of research and references.

2. The use of the RASCANDIS 1.0 form is not obligatory; it only serves as an alternative that can be offered in daily clinical practice in hospitals, and its use must be supervised by the hospital's *Komite Pengendalian Resistensi Antimikroba (KPRA)* or Antimicrobial Resistance Control Committee.
3. The RASCANDIS 1.0 form certainly still can not cover various real conditions. When it has not been accommodated in the form, clinicians must consult experts of hospital KPRA so that the aim of using systemic anti-candida appropriately can be achieved.

When providing systemic anti-candida agents for non-transplant patients, clinicians can fill out the RASCANDIS form and answer the YES/NO questions from top to bottom. Then, when the answer stops on the column, precisely parallel with the word STOP, then STOP, and you can see the given therapeutic approach either is definitive, empiric, pre-emptive or does not necessarily provide systemic anti-candida.

The RASCANDIS 1.0 form is not a diagnostic tool but a collective literature review, which aims to perform a more directed treatment approach for invasive candidiasis. In this form, it is conveye d when clinicians can perform definitive, empiric and pre-emptive therapeutic approaches. The RASCANDIS 1.0 form also can not replace the hospital Antimicrobial Stewardship Team or *Tim Penatagunaan Antimikroba (PGA),* which must monitor the appropriate use of antimicrobial agents and always prioritize the principle of patient safety. The RASCANDIS 1.0 form needs a further review of its use, which is associated with quality and cost control. It is expected that the form may become an academic stimulus in increasing the appropriate use of systemic anti-candidiasis in the future, and it is also expected as a tool to obtain inputs and critics in the implementation of anti-fungal stewardship programs.

CONCLUSION

It is essential to carry out the antifungal stewardship program so that antifungal agents can be more appropriate. Systemic anti-candidiasis is a common antifungal frequently used in daily clinical practice, and it must be used in accordance with proper indication. There are three types of indication approaches in systemic anti-candidiasis agents which are definitive, empiric and pre-emptive. The RASCANDIS 1.0 form is a form that has been established based on a literature review as an effort to increase the appropriate use of systemic anti-candidiasis agents. It is expected to be an academic stimulus that can be criticized as an endeavor of quality and cost control in implementing an antifungal stewardship program.

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