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The personalized treatment of invasive candidiasis still has a long way to go

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We have taken great interest in reading two recent studies published in Critical Care regarding the safety and efficacy of rezafungin in the treatment of candidemia and/or invasive candidiasis (IC) [1, 2]. Both studies conducted a pooled analysis of the randomized controlled trials (RCTs) ReSTORE and STRIVE, which demonstrated that rezafungin is comparable to caspofungin in terms of safety and efficacy. However, rezafungin has a longer half-life, allowing for reduced dosing frequency, which improves patient compliance [3, 4]. Additionally, it shortens the long of hospital stay and intensive care unit (ICU) stay. We look forward to the clinical application of this novel echinocandin antifungal drug in multiple countries and regions. However, the road to achieving personalized treatment for candidemia and/or IC still has a long way to go.

The individualization of treatment duration for candidemia and/or IC remains challenging.

The prolonged use of antibiotics can disrupt the host's microbiota and induce resistance in pathogens, leading to suggestions from guidelines such as the Surviving Sepsis Campaign's sepsis and septic shock guidelines to use shorter courses of treatment whenever possible [5]. However, these suggestions are limited to bacterial causes of pneumonia, intra-abdominal infections, urinary tract infections, and bloodstream infections, excluding candidemia and/or IC. Currently, treatment continues for two weeks after two negative blood cultures, following infectious diseases society of America (IDSA) and European society of clinical microbiology and infectious diseases (ESCMID) guidelines, to prevent recurrence [6, 7]. However, this "one-size-fits-all" approach may not suit all patients and could unnecessarily prolong hospital stays, increase the risk of hospital-acquired infections (HAIs) and antibiotic resistance, and escalate healthcare costs.

Exploration and attempts on individualized treatment duration for candidemia and/or IC.

In recent years, medical professionals have consistently attempted to shorten the duration of treatment for candidemia and/or IC. Early studies involving clinical pharmacists revealed that approximately 45% of antifungal prescriptions exceeded the treatment duration recommended by international guidelines, with some even extending beyond two or three weeks. Even when prescriptions were issued under the guidance of

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clinical pharmacists, this only reduced some irrational empirical or prophylactic antifungal therapies, without affecting the treatment duration for candidemia and/or IC [8]. However, some small-scale piolt studies have suggested that for specific patients with candidemia and/or IC, a shorter course of treatment may be safe, with no impact on disease recurrence rates and patient outcomes. Carl's piolt study found that for patients with non-neutropenic and uncomplicated candidemia, if they had had 1 day of positive cultures, a 7-day short-course antifungal therapy can achieve the same therapeutic effect [9]. Another study also indicates that if a patient consistently tests negative for (1,3)-β-D-Glucan (BDG) throughout their disease course, their likelihood of developing sepsis or multi-organ failure significantly decreases, and such patients may require only a short-course antifungal therapy targeting Candida. Additionally, as T2 magnetic resonance (T2MR) technology is increasingly applied in clinical settings, its sensitivity in distinguishing complicated candidemia has been further validated, potentially offering a basis for determining the duration of treatment in the future.

Insights into the use of a short-course strategy for the treatment of candidemia.

In recent years, the incidence of candidemia originating from the urinary system has been increasing annually, primarily occurring in patients with urinary stones following extracorporeal shock wave lithotripsy (ESWL). This procedure can lead to the disruption of the ureteral or renal mucosal barriers, allowing Candida to enter the bloodstream and cause systemic dissemination. These patients are at risk of developing septic shock due to candidemia and often require treatment in the ICU. Once their hemodynamics stabilize and shock is alleviated, they are typically transferred back to the urinary surgery department for further treatment. In our recent observations, none of the 63 patients in this category completed the "full-course" treatment for candidemia, with an average treatment duration of only 9 days. Furthermore, only 31.7% of these patients received de-escalation therapy. However, none of them experienced recurrence of candidemia or mortality (Table 1). All patients included in our study underwent ureteroscopic procedures to relieve urinary tract obstructions and had no immunosuppressive conditions, thus benefiting from the shorter treatment course. In the future, we aim to further identify patient groups that can benefit from shorter treatment courses and strive for individualized adjustments to antifungal therapy.

Table 1 Patients with urinary calculi who developed candidemia and septic shock after undergoing extracorporeal shock wave lithotripsy

Variable	*n* = 63
Male gender, *n* (%)	45 (71.4)
Age, median (IQR)	48 (32,75)
Types of candida	
Candida albicans, *n* (%)	39 (61.9)
Candida glabrata, *n* (%)	17 (26.9)
Candida parapsilosis, *n* (%)	7 (11.2)
Lymphocyte, median (IQR), 10^9 count/L	1.43 (0.72,1.94)
Time of positive blood culture, median (IQR), hour	21 (13,45)
(1,3)-β-D-Glucan, median (IQR), pg/mL	175 (102,427)
De-escalation therapy, n (%)	17 (31.7)
Course of antifungal therapy, median (IQR), day	9 (6,13)
Long of ICU stay, median (IQR), day	5 (3,8)
Long of hospital stay, median (IQR), day	10 (7,16)
Mortality, *n* (%)	0 (0)
Recurrence rate, *n* (%)	0 (0)

Abbreviations: ICU, intensive care unit; IQR, interquartile range

The personalized treatment of candidemia and/or IC requires multidisciplinary collaboration.

The diagnosis and treatment of IC are extremely complex, presenting numerous difficulties and challenges. Currently, there is a lack of accurate epidemiological data on IC, and clinicians often rely on candidemia data as a substitute. Therefore, future efforts must focus on obtaining more precise analyses of deep tissue Candida infections. Second, alongside traditional culture-based methods and staining techniques for Candida detection, novel diagnostic technologies such as matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS), droplet digital PCR (dd-PCR), metagenomic next-generation sequencing (mNGS), and even T2MR have rapidly advanced and are gradually being integrated into clinical practice. These innovations have significantly improved the detection rates of IC. However, ICU physicians still require guidance from microbiologists to accurately understand the principles of these tests, appropriately interpret results, and formulate effective anti-Candida treatment plans. Furthermore, for newer antifungal agents like rezafungin, key questions remain: 1) While the once-weekly administration significantly improves patient compliance, the pathophysiological status of critically ill patients, particularly liver function, can change rapidly. Whether therapeutic drug monitoring (TDM) is required during treatment and whether it is unnecessary to adjust the drug dosage based on liver function still need further investigation; 2) Patients with candidemia who are in shock still

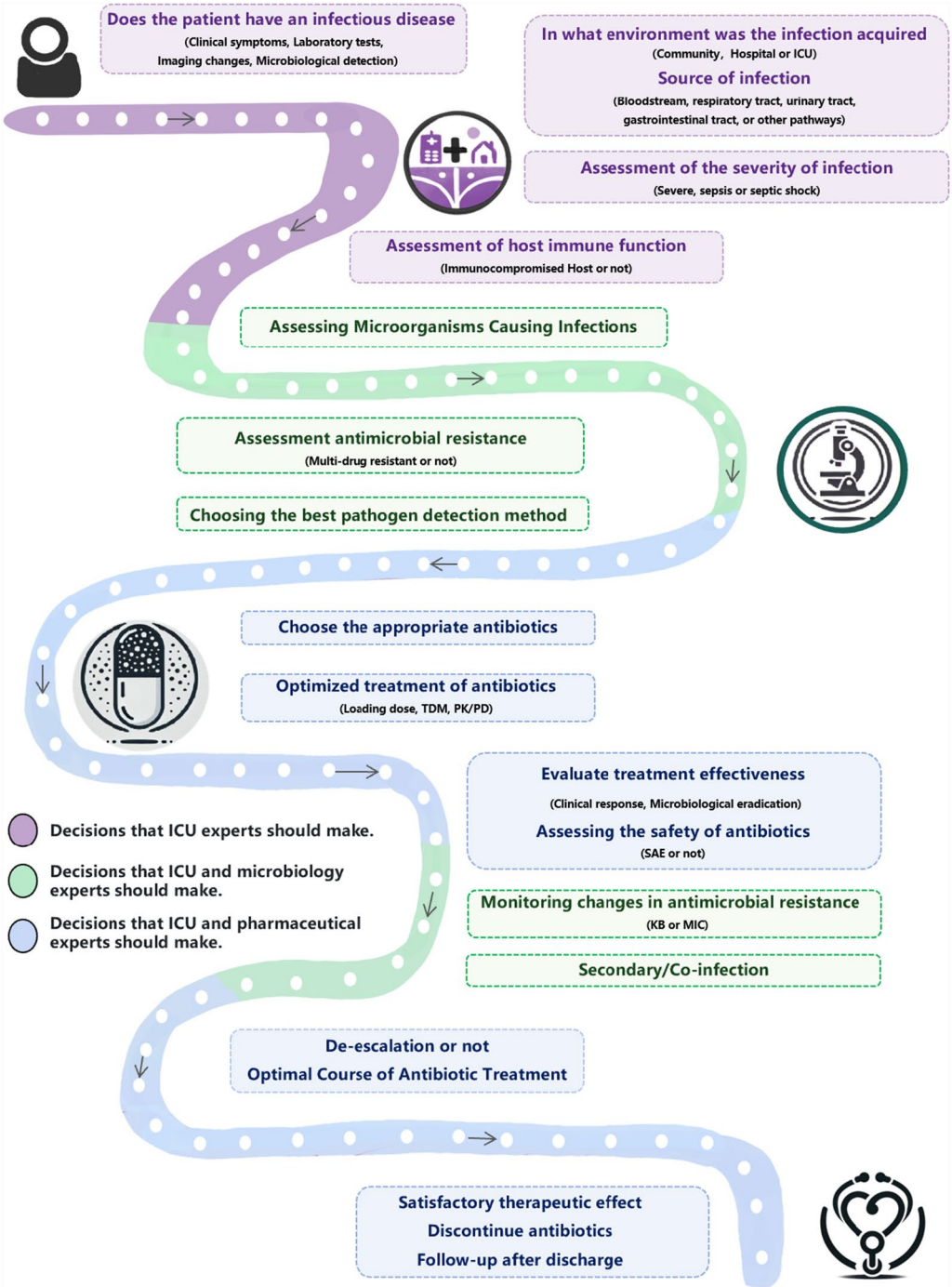

Fig. 1 Multidisciplinary collaboration model for the diagnosis and treatment of severe infectious diseases (Drawn by Chunhui Xu). ICU, intensive care unit; MIC, minimal inhibitory concentration; PK/PD, pharmacokinetic/ pharmacodynamic; TDM, therapeutic drug monitoring; KB, Kirby-Bauer; SAE, severe adverse effect

require hospitalization, even in the ICU. How to accurately select the antifungal drugs based on susceptibility breakpoints, whether repeat blood cultures are necessary, and whether the time to negativity in blood cultures has clinical significance if individualized treatment is not feasible remain questions. 3) Is it necessary to routinely test for rezafungin susceptibility? When the treatment outcome is unsatisfactory, should FKS mutations be screened? These questions require guidance from professors specializing in pharmacy. 4) Is it necessary to further

consider the cost implications from a health economics perspective? Currently, rezafungin has not yet been launched in China. Currently available fluconazole is priced at 200 mg for USD 6.5, and caspofungin is priced at 50 mg for USD 11, both of which are within an acceptable range. If rezafungin is appropriately priced and can shorten hospital stay, it would be the optimal choice to alleviate the economic pressure in the current context. Therefore, the management of IC, from early identification to post-discharge follow-up, reflects a holistic, full-cycle management approach and necessitates interdisciplinary collaboration (Fig. 1).

Abbreviations

BDG	(1,3)-β-D-Glucan
DD-PCR	Droplet digital PCR
ESWL	Extracorporeal shock wave lithotripsy
HAIs	Hospital-acquired infections
ICU	Intensive care unit
IC	Invasive candidiasis
IDSA	Infectious diseases society of America
ESCMID	European society of clinical microbiology and infectious diseases
MALDI-TOF MS	Matrix-assisted laser desorption ionization time-of-flight mass spectrometry
mNGS	Metagenomic next-generation sequencing
RCTs	Randomized controlled trials
T2MR	T2 magnetic resonance
TDM	Therapeutic drug monitoring

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Declarations

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Not applicable.

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Competing interests
The authors declare no competing interests.

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