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Antifungal agents for invasive candidiasis in non-neutropenic critically ill adults: What do the guidelines recommend?

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ABSTRACT

Objectives: Recommendations in clinical practice guidelines (CPG) may differ and cause confusion. Our objective was to appraise CPGs for antifungal treatment of invasive candidiasis (IC) in non-neutropenic critically ill adult patients.
Methods: We systematically searched the literature for CPGs published between 2008 and 2018. We assessed the quality of each guideline using six domains of the AGREE II instrument. We extracted and compared recommendations for different treatment strategies and assessed content quality.
Results: Of 19 guidelines, the mean overall AGREE II score was 58%. The domain 'clarity of presentation' received the highest scores (88%) and 'applicability' the lowest (18%). CPGs provided detailed recommendations on antifungal prophylaxis (n = 10), with fluconazole recommended as initial prophylaxis in all seven CPGs citing a specific drug. Echinocandin was recommended as the initial drug in all 16 CPGs supporting empirical/pre-emptive treatment; and in 18 of 19 for targeted invasive candidiasis treatment. However, it remains unclear when to initiate prophylaxis, empirical or pre-emptive therapy or when to step down.
Conclusions: The methodological quality of CPGs for antifungal treatment of IC in non-neutropenic critically ill patients is suboptimal. Some treatment recommendations were inconsistent across indications and require local guidance to help clinicians make better informed decisions.

Introduction

Invasive candidiasis (IC) is one of the most common health care-associated infections contracted by patients in intensive care units (ICUs), and is widely recognized as a major cause of mortality, morbidity and considerable health expenditure (Calandra et al., 2016, Dodds Ashley et al., 2012, Kollef et al., 2012, Lortholary et al., 2014, Vincent et al., 2009, Wisplinghoff et al., 2004). The increased use of newer antifungal agents with improved tolerability is due to wider availability and use by non-expert practitioners in both the prevention and treatment of IC, leading to drug resistance and wasted resources (Arendrup and Patterson, 2017).

Clinical practice guidelines (CPGs) aim to bridge the gap between research and practice (Bero et al., 1998). Clinicians rely on guideline recommendations to inform practice and assume they are consistent and based on evidence. Recommendations in CPGs are often used to assess the appropriateness of adherence to antifungal prescribing (Nivoix et al., 2012, Valerio et al., 2014) but the information in CPGs is sometimes conflicting and confusing. The reasons for the difference in recommendations among CPGs could include insufficient evidence, different interpretation of the evidence, or non-systematic methods for guideline development (Burgers et al., 2002, Eisinger et al., 1999, Fahey and Peters, 1996). CPGs for antifungal treatment differ in their aims and objectives,

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methods, rigor of development, and overall recommendations (Agrawal et al., 2012, Deshpande et al., 2013, Leroux and Ullmann, 2013). These inconsistences in guidelines can limit clinicians' appropriate treatment decisions.

CPG recommendations for antifungal treatment may differ within particular patient groups, for example pediatric (Morgan et al., 2017) and adult hematology/oncology (Agrawal et al., 2012) patients. Studies reporting on the transparency of the guideline process for antifungal treatment of IC in non-neutropenic critically ill adult patients and how this relates to recommendations are lacking. We aimed to analyze and compare the recommendations in CPGs for antifungal treatment of IC in non-neutropenic critically ill adult patients. In order to review the guideline development process, we aimed to evaluate the quality of CPGs using a systematic critical appraisal approach (Appraisal of Guidelines for Research and Evaluation [AGREE II] instrument).

Materials and methods

Searches

A librarian guided a systematic search of four databases (PubMed, Cochrane, Embase, CINAHL, and China National Knowledge Infrastructure [CNKI]) to identify articles published between 1 January 2008 and 30 December 2018, using the terms of fungal disease (fung* OR mycoses OR antifung* OR Candida* OR yeast*) and classified as "clinical guidelines" using 'Practice Guidelines as Topic' as MeSH terms and 'guideline*' as text word. We also searched four guideline repositories: Guidelines International Network (GIN) (http://www.g-i-n.net/), the National Institute for Health and Care Excellence (NICE) (http://www.nice.org.uk/), National Health and Medical Research Council (NHMRC) (http://www.nhmrc.gov.au/), and the National Guideline Clearinghouse (NGC) (http://www.guideline.gov/). References of retrieved articles were searched manually for further references to guidelines. No language restriction was applied.

Inclusion criteria

The following inclusion criteria were applied:

1) Published guideline by a reputable health organization, society or college of health professionals, or in a national or international guideline repository;
2) Use of any antifungal agents in the setting of either prophylaxis, empiric, pre-emptive, or targeted therapy for invasive Candida infections (Guery et al., 2009);
3) Adult patients (defined by each guideline);
4) Explicit treatment recommendations for non-neutropenic patients.

CPGs were excluded if:

1) the study population only involved children;
2) they were solely in the hemato-oncology or solid organ-transplantation setting;
3) they only focused on other fungal infections, e.g., aspergillosis, mucormycosis or trichosporonosis.

Study selection and data extraction

Two authors (YW and TM) independently screened the titles, abstracts, and full texts of eligible articles. The final inclusion of articles was agreed by consensus with a third author (MVD).

The following data were extracted: country of origin, year of publication, guideline developer, type of infection, and type of antifungal treatment described. If the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was adopted in the guideline, this was noted (Guyatt et al., 2008).

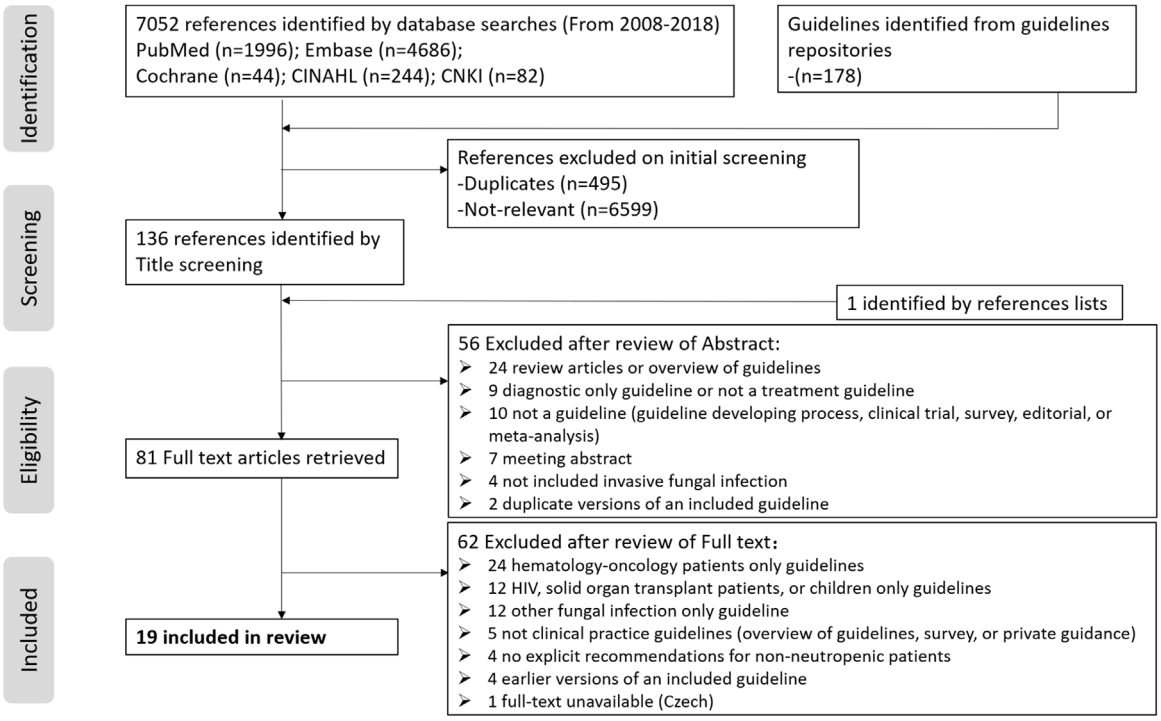

Figure 1. PRISMA flow diagram of clinical practice guidelines selection.

Table 1
Characteristics of the included CPGs.

Guideline title	Year	Geographic region	Name of organization	Type of treatment covered	Type of infection
IDSA guidelines Pappas et al. (2016)	2016	USA	Infectious Diseases Society of America	Prophylaxis Empirical or pre-emptive therapy Targeted therapy	Systematic candidiasis
MEDICAL: Consensus proposal Scudeller et al. (2016)	2016	Italy	Italian Society for Anti-Infective Therapy (SITA) Italian Federation of Associations of Hospital Doctors on Internal Medicine (FADOI)	Empirical or pre-emptive therapy Targeted therapy	Systematic candidiasis
2016 IFI Taiwan guidelines Kung et al. (2018)	2016	Taiwan	Infectious Diseases Society of Taiwan	Empirical or pre-emptive therapy Targeted therapy	Systematic candidiasis
French IAI guidelines Montravers et al. (2015)	2015	France	French Society of Anesthesia and Reanimation	Empirical or pre-emptive therapy Targeted therapy	Intra-abdominal candidiasis
Middle East guidelines Alothman et al. (2014)	2014	Middle East	King Saud Bin Abdulaziz University for Health Sciences	Empirical or pre-emptive therapy Targeted therapy	Systematic candidiasis
Australian guidelines Chen et al. (2014)	2014	Australia	Royal Australasian College of Physicians	Empirical or pre-emptive therapy Targeted therapy	Systematic candidiasis
Iranian IC guidelines Elhoufi et al. (2014)	2014	Iran	IFI clinical forum comprising an Iranian panel of intensive care experts	Prophylaxis Empirical or pre-emptive therapy Targeted therapy	Systematic candidiasis
JMF guidelines Kohno et al. (2016)	2014	Japan	Japanese Mycoses Forum	Prophylaxis Empirical or pre-emptive therapy Targeted therapy	Systematic candidiasis
EPICO 2.0 project Zaragoza et al. (2014)	2014	Spain	Spanish Association of Mycology (AEM) Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) Spanish Society of Anesthesiology, Reanimation and Pain Therapeutics (SEDAR) Spanish Society of Critical, Intensive and Coronary Medicine Units (SEMICYUC) Spanish Society of Chemotherapy (SEQ)	Empirical or pre-emptive therapy Targeted therapy	Intra-abdominal candidiasis
Chinese burn IFI guidelines Luo et al. (2014)	2013	China	Chinese Society of Burn Surgeons	Prophylaxis Empirical or pre-emptive therapy Targeted therapy	Burn invasive fungal infection
Italian IAI guidelines Bassetti et al. (2013)	2013	Italy	Italian Society of Intensive Care International Society of Chemotherapy	Prophylaxis Empirical or pre-emptive therapy Targeted therapy	Intra-abdominal candidiasis
ITALIC Scudeller et al. (2014)	2013	Italy	The Italian Society of Antimicrobial Therapy	Prophylaxis Empirical or pre-emptive therapy Targeted therapy	Systematic candidiasis
JSMM Guidelines JSMM (2013)	2013	Japan	The Japanese Society for Medical Mycology	Empirical or pre-emptive therapy Targeted therapy	Systematic candidiasis
ESCMID guidelines Cornely et al. (2012)	2012	Europe	European Society for Clinical Microbiology and Infectious Diseases	Prophylaxis Empirical or pre-emptive therapy Targeted therapy	Systematic candidiasis
Brazilian guidelines Colombo et al. (2013)	2012	Brazil	Sociedade Brasileira de Infectologia Sociedade Paulista de Infectologia Sociedade Brasileira de Medicina Tropical	Prophylaxis Empirical or pre-emptive therapy Targeted therapy	Systematic candidiasis
ATS guidelines Limper et al. (2011)	2011	USA	The American Thoracic Society	Targeted therapy	Systematic candidiasis
German guidelines Ruhnke et al. (2011)	2011	Germany	German Speaking Mycological Society and the Paul-Ehrlich-Society for Chemotherapy	Empirical or pre-emptive therapy Targeted therapy	Systematic candidiasis
Spanish guideline for IC Aguado et al. (2011)	2011	Spain	Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)	Prophylaxis Targeted therapy	Systematic candidiasis
Canadian guidelines Bow et al. (2010)	2010	Canada	The Association of Medical Microbiology and Infectious Disease Canada	Prophylaxis Empirical or pre-emptive therapy Targeted therapy	Systematic candidiasis

Assessment: methodological quality of CPG development

We used the AGREE II tool (http://www.agreetrust.org/) to assess the quality of the CPGs' development process. It consists of 23 items grouped within six domains (scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence) (Brouwers et al., 2010a). In AGREE II, each item is scored using a seven-point Likert scale where 1 represents a poor score and 7 represents excellent demonstration of key quality criteria. Two authors (YW and MVD) independently extracted data related to the AGREE tool and discrepancies were resolved through discussion (YW, MVD, TM). The final item scores were combined to provide a scaled domain score (in percent). Inter-rater agreement was determined using intraclass correlation coefficients (ICC) with a two-way random effects model (Bartko, 1966). We calculated ICCs with 95% confidence intervals for each domain and overall rating scores. We classified level of reliability as poor (ICC < 0.40), moderate (ICC 0.40–0.59), substantial (ICC 0.60–0.79) or excellent level of agreement (ICC 0.80–1.00). The Mann–Whitney *U* test ($P < 0.05$) was used to compare the AGREE II scores of all guidelines by separating the median publication time point of included guidelines (i.e. differences in domain scores between the newer and pre-2014 CPGs). Statistical analyses were performed using SPSS version 19.0 (IBM SPSS Statistics, Xi'an, China).

Assessment: CPG recommendations

Each guideline was summarized by one author (YW) to identify key points and recommendations. These summaries were checked by a second author (MVD) for completeness and accuracy. The primary characteristics and details of recommendations were examined. CPG recommendations were tabulated and compared by one author (YW) and then checked by other authors to ensure they were correct for three clinical strategies: (1) antifungal prophylaxis; (2) empirical or pre-emptive treatment; and (3) targeted treatment.

Five key areas were selected to compare the content of the recommendations and to highlight similarities and differences for each of these strategies: the reason for initiating treatment; the first choice of antifungal agents; the alternative choice of antifungal agents; information on dosage, frequency; and information on duration.

Results

Characteristics of selected guidelines

We identified 7230 relevant titles and selected 19 CPGs for inclusion (Figure 1) (Aguado et al., 2011, Alothman et al., 2014, Bassetti et al., 2013, Bow et al., 2010, Chen et al., 2014, Colombo et al., 2013, Cornely et al., 2012, Elhoufi et al., 2014, JSMM, 2013, Kohno et al., 2016, Kung et al., 2018, Limper et al., 2011, Luo et al., 2014, Montravers et al., 2015, Pappas et al., 2016, Ruhnke et al., 2011, Scudeller et al., 2016, Scudeller et al., 2014, Zaragoza et al., 2014). Table 1 presents the main characteristics of included CPGs. Most came from Europe (n = 8) and Asia (n = 5) and most were developed by medical societies (n = 16). Eighteen of the 19 CPGs provided recommendations for systematic (n = 15) and intra-abdominal candidiasis (IAC) (n = 3). Of these 18 CPGs, all provided specific details on targeted therapy, 16 on empirical or pre-emptive therapy and nine on prophylaxis. The single CPG on invasive fungal infection (IFI) in burn patients gave guidance on all three management strategies (targeted, empiric, and prophylaxis). Most (n = 14) CPGs used the GRADE system for grading evidence (Aguado et al., 2011, Alothman et al., 2014, Bassetti et al., 2013, Bow et al., 2010, Colombo et al., 2013, Cornely et al., 2012, JSMM, 2013, Kohno et al., 2016, Kung et al., 2018, Limper et al., 2011, Montravers et al., 2015, Pappas et al., 2016, Ruhnke et al., 2011, Scudeller et al., 2014).

Assessment: methodological quality of CPG development

The standardized scores of each CPG by AGREE II domain and the overall assessment are summarized in Table 2. The mean

Table 2
CPGs AGREE II domain scores and quality assessment (%, ranked by overall assessment scoring).

Guideline title	1. Scope and purpose	2. Stakeholder involvement	3. Rigor of development	4. Clarity of presentation	5. Applicability	6. Editorial independence	Overall assessment
ESCMID guidelines-2012	92	83	74	100	46	88	100
IDSA guidelines-2016	75	33	86	97	44	50	92
Canadian guidelines-2010	83	69	48	100	2	92	92
Italian IAI guidelines-2013[a]	100	50	60	81	10	38	83
ATS guidelines-2011	89	8	51	100	2	42	83
German guidelines-2011	81	19	45	100	6	0	75
French IAI guidelines-2015[a]	100	47	52	69	15	0	67
Middle East guidelines-2014	75	44	46	81	23	50	58
Iranian IC guidelines-2014	89	31	50	92	38	8	58
Brazilian guidelines-2012	58	3	29	89	17	38	58
2016 IFI Taiwan guidelines-2016	75	33	68	75	33	46	50
Australian guidelines-2014	97	8	49	89	8	38	50
JMF guidelines-2014	89	33	29	100	19	25	50
JSMM Guidelines-2013	89	28	44	94	3	0	50
ITALIC-2013	89	33	39	86	23	67	42
MEDICAL: Consensus proposal-2016	100	31	24	86	38	92	33
Spanish guideline for IC-2011	86	36	35	97	2	50	33
EPICO 2.0 project-2014[a]	100	28	47	53	2	17	25
Chinese burn IFI guidelines-2013	89	22	14	72	2	42	17
Mean (SD)	87 (11)	34 (20)	47 (17)	88 (13)	18 (16)	41 (29)	59 (24)
Median (Range)	89 (58–100)	33 (3–83)	47 (14–86)	89 (53–100)	15 (2–46)	42 (0–92)	58 (17–100)

CPGs, clinical practice guidelines; AGREE, Appraisal of Guidelines for Research and Evaluation.
[a] Guidelines for intra-abdominal candidiasis.

overall assessment score for all CPGs was 58% (SD = 24%). The highest domain score was for 'clarity of presentation' (domain 4; mean 88%, SD 13%), followed by 'scope and purpose' (domain 1; mean 87%, SD 11%), while the other four domain scores were less than 50%. 'Applicability' scored the lowest (domain 5; mean 18%, SD 16%). The next lowest score was for 'stakeholder involvement' (domain 2; mean 34%, SD 20%). Differences in domain scores between the newer and pre-2014 CPGs were not detected (see Table S1).

Of the 19 CPGs, five had an overall assessment score of ≥80% (Table 2). These included four CPGs for systematic candidiasis (Bow et al., 2010, Cornely et al., 2012, Limper et al., 2011, Pappas et al., 2016) and one for intra-abdominal candidiasis (Bassetti et al., 2013). Only the CPG from ESCMID had scores greater than 70% in all domains other than 'applicability' (domain 5) (Cornely et al., 2012). Likewise, the applicability score for ESCMID was highest of all CPGs. All five CPGs were either from North America (USA n = 2, Canada n = 1) or Europe (n = 2). All the CPGs (except the American Thoracic Society (ATS) guidelines (Limper et al., 2011)) provided recommendations for all three treatment strategies (i.e. prophylaxis, empirical or pre-emptive, and targeted treatment).The inter-rater reliability was classified as excellent for all domains and substantial for overall assessment score (see Table S1).

Assessment: CPG recommendations

Prophylaxis

Half (n = 9) of the 18 candidiasis CPGs and one burn IFI CPG provided recommendations about prophylaxis, with eight CPGs including specific details for primary prophylaxis recipients (Table 3). Three CPGs recommended antifungal prophylaxis for patients who recently had abdominal surgery and recurrent gastrointestinal perforations or anastomotic leakages (Bassetti et al., 2013, Bow et al., 2010, Cornely et al., 2012). Three guidelines recommended prophylaxis for high-risk patients in ICU with a high rate (>5% (Pappas et al., 2016) or >10% (Bow et al., 2010, Colombo et al., 2013) of IC. Antifungal prophylaxis was generally not recommended by the other two CPGs in non-neutropenic critically ill patients (Kohno et al., 2016, Scudeller et al., 2014). The guideline for burn patients outlined special conditions required for commencing antifungal prophylaxis (e.g. moderate to severe inhalation injury is present) (Luo et al., 2014).

A specific drug was mentioned in seven of the ten guidelines that described prophylaxis: fluconazole was recommended as the initial drug of choice in all seven CPGs (Aguado et al., 2011, Bassetti et al., 2013, Bow et al., 2010, Cornely et al., 2012, Elhoufi et al., 2014, Luo et al., 2014, Pappas et al., 2016). Echinocandin was mentioned as an acceptable alternative in only two CPGs (Bassetti et al., 2013, Pappas et al., 2016).

Only the Canadian CPG mentioned the duration of prophylaxis; until either complete resolution of intra-abdominal disease on development of proven *Candida* species infection requiring directed antifungal therapy, or development of a severe drug-related adverse event (Bow et al., 2010).

Empirical or pre-emptive treatment

Recommendations for empirical or pre-emptive treatment were mentioned in 16 of the 18 candidiasis CPGs (89%) and the single Chinese burn IFI CPG (Luo et al., 2014) (Table 3). Ten guidelines recommended the initiation of empirical or pre-emptive treatment (six IC CPGs, all three IAC CPGs, and the burn IFI CPG). The ESCMID guidelines stated that the optimal time point for initiating empirical antifungal treatment remains unclear in fever patients (Cornely et al., 2012), whereas the JSMM guidelines recommended that patients with unknown fever with ineffective antimicrobial therapy for four days should be given empirical

Table 3
Summary of recommendations for prophylaxis (n = 10) and empirical or pre-emptive treatment (n = 17).

Guideline title	Initiation mentioned	Initial drugs mentioned			Alternative drugs mentioned					Dosage mentioned	Duration mentioned
		ECH	FLU	L-AMB	FLU	L-AMB	VOR	D-AMB	ECH		
Prophylaxis											
IDSA guidelines-2016	✓		✓						✓	✓	
Iranian IC guidelines-2014			✓								
JMF guidelines-2014	✓									✓	
Chinese burn IFI guidelines-2013	✓		✓						✓		
Italian IAI guidelines-2013[a]	✓		✓								
ITALIC-2013	✓									✓	
ESCMID guidelines-2012	✓		✓								
Brazilian guidelines-2012	✓										
Spanish guideline for IC-2011			✓							✓	✓
Canadian guidelines-2010	✓		✓							✓	
Empirical or pre-emptive treatment											
IDSA guidelines-2016		✓			✓	✓				✓	✓
MEDICAL: Consensus proposal-2016		✓				✓					
2016 IFI Taiwan guidelines-2016	✓	✓	✓					✓			
French IAI guidelines-2015[a]	✓	✓	✓								
Middle East guidelines-2014		✓			✓	✓	✓	✓			✓
Australian guidelines-2014		✓				✓	✓	✓			
Iranian IC guidelines-2014		✓	✓							✓	✓
JMF guidelines-2014	✓	✓	✓							✓	
EPICO 2.0 project-2014[a]	✓	✓									✓
Chinese burn IFI guidelines-2013	✓	✓					✓			✓	
Italian IAI guidelines-2013[a]	✓	✓		✓	✓		✓				✓
ITALIC-2013	✓	✓			✓	✓	✓				
JSMM Guidelines-2013	✓	✓	✓			✓		✓		✓	
ESCMID guidelines-2012	✓										
Brazilian guidelines-2012		✓			✓	✓				✓	
German guidelines-2011		✓		✓						✓	
Canadian guidelines-2010	✓	✓	✓							✓	✓

ECH, Echinocandin; FLU, Fluconazole; L-AMB, Liposomal amphotericin B; D-AMB, Amphotericin B deoxycholate; VOR, Voriconazole; ITR, itraconazole.
[a] Guidelines for intra-abdominal candidiasis.

antifungal treatment (JSMM, 2013). Three CPGS advised testing for (1,3)-β-D-glucan in serum or plasma as a prompt for antifungal treatment (Cornely et al., 2012, Kohno et al., 2016, Scudeller et al., 2014). In terms of *Candida* colonization, the ESCMID and Canadian CPGs concluded that antifungal treatment is not recommended in non-neutropenic patients in the presence of colonization (isolation from respiratory secretions) (Bow et al., 2010, Cornely et al., 2012). However, two CPGs regarded *Candida* colonization at more than one site as a reason for initiation (Kohno et al., 2016, Kung et al., 2018). One CPG for IAC recommended all critically ill patients receive antifungal treatment (Bassetti et al., 2013). Two CPGs for IAC recommended antifungal treatment for patients with either secondary nosocomial peritonitis and with risk factors for *Candida* spp. colonization or patients with tertiary peritonitis (Montravers et al., 2015, Zaragoza et al., 2014). One IFI CPG noted the particular conditions required for initiating antifungal empirical treatment in burn patients (e.g. burn patients who have received two different broad spectrum antibiotics for a minimum of five days) (Luo et al., 2014).

With the exception of the ESCMID guideline (Cornely et al., 2012), echinocandins were recommended as the initial drug in all 16 CPGs that supported empirical or pre-emptive treatment (Alothman et al., 2014, Bassetti et al., 2013, Bow et al., 2010, Chen et al., 2014, Colombo et al., 2013, Elhoufi et al., 2014, JSMM, 2013, Kohno et al., 2016, Kung et al., 2018, Luo et al., 2014, Montravers et al., 2015, Pappas et al., 2016, Ruhnke et al., 2011, Scudeller et al., 2016, Scudeller et al., 2014, Zaragoza et al., 2014). Fluconazole and liposomal amphotericin B (L-AMB) were listed as other initial agents in six (Bow et al., 2010, Elhoufi et al., 2014, JSMM, 2013, Kohno et al., 2016, Kung et al., 2018, Montravers et al., 2015) and two (Bassetti et al., 2013, Ruhnke et al., 2011) CPGs, respectively. Fluconazole was recommended as an appropriate alternative drug in five CPGs (Alothman et al., 2014, Bassetti et al., 2013, Colombo et al., 2013, Pappas et al., 2016, Scudeller et al., 2014), L-AMB in seven (Alothman et al., 2014, Chen et al., 2014, Colombo et al., 2013, JSMM, 2013, Pappas et al., 2016, Scudeller et al., 2016, Scudeller et al., 2014), voriconazole in five (Alothman et al., 2014, Bassetti et al., 2013, Chen et al., 2014, Luo et al., 2014, Scudeller et al., 2014), and amphotericin B deoxycholate in four (Alothman et al., 2014, Chen et al., 2014, JSMM, 2013, Kung et al., 2018).

Five CPGs recommended a duration of two weeks for empirical therapy for suspected IC in patients who improve (Alothman et al., 2014, Bow et al., 2010, Elhoufi et al., 2014, Pappas et al., 2016, Zaragoza et al., 2014). Only two CPGs gave specific details about when to stop empirical antifungal treatment, i.e., in the absence of clinical response to empirical antifungal therapy at 4–5 days and if there is no subsequent evidence of IC after starting empirical therapy or a negative non-culture-based diagnostic assay with a high negative predictive value (Bassetti et al., 2013, Pappas et al., 2016).

Targeted treatment for IC

All 18 candidiasis CPGs and the single burn IFI guideline included specific recommendations for targeted treatment of IC (Table 4). All 18 candidiasis CPGs recommended echinocandins as the initial drug for *Candida* spp. (Aguado et al., 2011, Alothman et al., 2014, Bassetti et al., 2013, Bow et al., 2010, Chen et al., 2014, Colombo et al., 2013, Cornely et al., 2012, Elhoufi et al., 2014, JSMM, 2013, Kohno et al., 2016, Kung et al., 2018, Limper et al., 2011, Montravers et al., 2015, Pappas et al., 2016, Ruhnke et al., 2011, Scudeller et al., 2016, Scudeller et al., 2014, Zaragoza et al., 2014) but the burn IFI guideline did not recommend any specific drugs for unidentified *Candida* spp. Fluconazole, L-AMB, amphotericin B deoxycholate (D-AMB), and voriconazole were mentioned in six (JSMM, 2013, Kohno et al., 2016, Kung et al., 2018, Limper et al., 2011, Montravers et al., 2015, Ruhnke et al., 2011), three (Bassetti et al., 2013, Kohno et al., 2016, Limper et al., 2011), two (Kung et al., 2018, Limper et al., 2011), and one (Limper et al., 2011) CPGs, respectively (Table 4). The choice of alternative treatments for *Candida* spp. was variable. Notably, itraconazole was only recommended by two Japanese CPGs (JSMM, 2013, Kohno et al., 2016). Nine CPGs recommended specific agents for ≥2 *Candida* subspecies (Aguado et al., 2011, Elhoufi et al., 2014, JSMM, 2013, Kohno et al., 2016, Kung et al., 2018, Limper et al., 2011, Luo et al., 2014, Montravers et al., 2015, Pappas et al., 2016). None of CPGs mentioning species-specific therapy recommended fluconazole and echinocandin as initial therapy for *C. glabrata* and *C. parapsilosis,* respectively (see Table S2).

Most (14 of 15) systematic candidiasis CPGs recommended a treatment duration of 14 days after documented clearance of *Candida* species from the bloodstream and resolution of symptoms

Table 4
Summary of recommendations for targeted treatment for invasive candidiasis (n = 19).

Guideline Title	Initial drugs for *Candida* spp. mentioned					Alternative drugs for *Candida* spp. mentioned					Dosage mentioned	Duration mentioned	Drugs for ≥2 *Candida* Subspecies mentioned
	ECH	FLU	L-AMB	D-AMB	VOR	FLU	L-AMB	VOR	D-AMB	ITR			
IDSA guidelines-2016	✓					✓	✓	✓			✓	✓	✓
MEDICAL: Consensus proposal-2016	✓						✓						
2016 IFI Taiwan guidelines-2016	✓	✓		✓			✓	✓				✓	✓
French IAI guidelines-2015[a]	✓	✓											✓
Middle East guidelines-2014	✓					✓	✓	✓	✓			✓	
Australian guidelines-2014	✓					✓	✓	✓	✓			✓	
Iranian IC guidelines-2014	✓					✓					✓	✓	✓
JMF guidelines-2014	✓	✓	✓					✓		✓	✓	✓	✓
EPICO 2.0 project-2014[a]	✓											✓	
Chinese burn IFI guidelines-2013											✓		✓
Italian IAI guidelines-2013[a]	✓		✓			✓		✓				✓	
ITALIC-2013	✓					✓	✓	✓				✓	
JSMM Guidelines-2013	✓	✓					✓	✓	✓	✓	✓	✓	✓
ESCMID guidelines-2012	✓					✓	✓	✓			✓	✓	
Brazilian guidelines-2012	✓					✓	✓				✓	✓	
ATS guidelines-2011	✓	✓	✓	✓	✓						✓	✓	✓
German guidelines-2011	✓	✓					✓	✓			✓	✓	
Spanish guideline for IC-2011	✓						✓				✓	✓	✓
Canadian guidelines-2010	✓						✓		✓		✓	✓	

ECH, Echinocandin; FLU, Fluconazole; L-AMB, Liposomal amphotericin B; D-AMB, Amphotericin B deoxycholate; VOR, Voriconazole; ITR, itraconazole.
[a] Guidelines for intra-abdominal candidiasis.

attributable to candidemia (Aguado et al., 2011, Alothman et al., 2014, Bow et al., 2010, Chen et al., 2014, Colombo et al., 2013, Cornely et al., 2012, Elhoufi et al., 2014, JSMM, 2013, Kohno et al., 2016, Kung et al., 2018, Limper et al., 2011, Pappas et al., 2016, Ruhnke et al., 2011, Scudeller et al., 2014). Seven CPGs advised that the end of candidemia should be determined by at least one blood culture every day or every two days until negativity (Alothman et al., 2014, Chen et al., 2014, Cornely et al., 2012, Kohno et al., 2016, Kung et al., 2018, Pappas et al., 2016, Scudeller et al., 2016). Antifungal treatment for IAC should be continued for at least 10–14 days (Bassetti et al., 2013) or 7–10 days (Zaragoza et al., 2014) after the beginning of treatment.

All CPGs for systematic candidiasis (n = 15) recommended the removal of all central lines, if possible (Aguado et al., 2011, Alothman et al., 2014, Bow et al., 2010, Chen et al., 2014, Colombo et al., 2013, Cornely et al., 2012, Elhoufi et al., 2014, JSMM, 2013, Kohno et al., 2016, Kung et al., 2018, Limper et al., 2011, Pappas et al., 2016, Ruhnke et al., 2011, Scudeller et al., 2016, Scudeller et al., 2014). The timing of this removal strategy was varied among CPGs (i.e. as soon as possible (Cornely et al., 2012, Elhoufi et al., 2014, Kung et al., 2018, Pappas et al., 2016, Ruhnke et al., 2011), within 48 h (Chen et al., 2014) or 24 h (Kohno et al., 2016) of a positive blood culture, or waiting 72 h after the initiation of antifungal therapy (Colombo et al., 2013)). When catheter removal is not possible, L-AMB or an echinocandin is preferable (mentioned in three of these CPGs) (Chen et al., 2014, Cornely et al., 2012, Kohno et al., 2016). The timing of step-down treatment was also inconsistent among CPGs (i.e. after 10 days treatment (Cornely et al., 2012, Ruhnke et al., 2011), after 5-7 days treatment (Bassetti et al., 2013, Kung et al., 2018, Pappas et al., 2016), or undetermined (Alothman et al., 2014, Bassetti et al., 2013, Bow et al., 2010, Elhoufi et al., 2014, JSMM, 2013, Kohno et al., 2016, Limper et al., 2011, Scudeller et al., 2016, Scudeller et al., 2014). Most (13 of 15) systematic candidiasis CPGs advised that all non-neutropenic patients with candidemia should have a dilated ophthalmological examination (Alothman et al., 2014, Chen et al., 2014, Colombo et al., 2013, Cornely et al., 2012, Elhoufi et al., 2014, JSMM, 2013, Kohno et al., 2016, Kung et al., 2018, Limper et al., 2011, Pappas et al., 2016, Ruhnke et al., 2011, Scudeller et al., 2016, Scudeller et al., 2014).

Discussion

To our knowledge this is the first systematic appraisal of the methodological quality and content analysis of recommendations in published CPGs on the use of antifungal agents of IC in non-neutropenic critically ill patients. In general, the overall quality score as assessed by the AGREE II tool varied (17% to 100%) and was generally poor. Only five of 19 CPGs scored ≥80%. Only the CPG from ESCMID had scores greater than 70% in all domains except 'applicability' (domain 5) (Cornely et al., 2012). The recommendations were consistent in some areas. For example, fluconazole was commonly recommended as first choice for prophylaxis and echinocandins for empirical or pre-emptive, and targeted therapy. However, most guidelines were unclear about some aspects of treatment, such as when to initiate empirical or pre-emptive therapy or when to step down.

Most CPGs were transparent about their scope and purpose and scored well on clarity of presentation (which included having easily identifiable recommendations). However, they scored very low on editorial independence, descriptions and use of stakeholder engagement, and reporting of applicability. These findings are consistent with other studies that used the AGREE II instrument to evaluate the CPGs for antifungal treatment for pediatric (Morgan et al., 2017) and adult hematology/oncology patients (Agrawal et al., 2012). CPG appraisal studies across a broad range of health conditions (Erickson et al., 2017, Fuentes Padilla et al., 2016, Gavriilidis et al., 2017, Lin et al., 2018, Madera Anaya et al., 2018) showed that poor applicability and lack of editorial independence is a consistent problem. Applicability is closely linked to dissemination and implementation of a CPG. The ESCMID guidelines had the highest score of this domain (46%). Inadequate applicability is a barrier to applying CPG recommendations in practice. To be effective, a CPG needs to be disseminated and implemented with newer and emerging methods such as smartphone apps (Free et al., 2013) or a digital platform for rapid review (Siemieniuk et al., 2016). In terms of 'editorial independence', although financing bodies and conflicts of interest are often declared, the methods employed to avoid conflicts of interest are rarely described within CPG content, leading to low scores.

The issue of using prophylactic antifungals remains controversial. Should this treatment strategy be used to prevent IC in the ICU setting? No consensus was obvious in the CPGs. In fact, only one in three CPGs mentioned prophylaxis in non-neutropenic critically ill patients. Fluconazole prophylaxis was associated with a reduction in IC in ICU patients in three meta-analyses (Cruciani et al., 2005, Playford et al., 2006, Shorr et al., 2005); but only one demonstrated a reduction in mortality from IC (Cruciani et al., 2005). Only two clinical trials examined echinocandins as a prophylactic treatment in ICU patients; neither mortality nor the incidence of IC was improved when micafungin or caspofungin were administered in this population (Knitsch et al., 2015, Ostrosky-Zeichner et al., 2014). There are no clear recommendations on the duration of prophylaxis in non-neutropenic critically ill patients unlike guidelines for hematology or oncology patients (Morgan et al., 2017).

In terms of empirical or pre-emptive treatment, the recommended timing of initiation was slightly different among CPGs: most supported empirical or pre-emptive treatment in critically ill patients with risk factors for IC or IAC. Several studies have developed prediction models to identify patients at highest risk. They are characterized by high specificity, but low sensitivity, thus missing many patients with IC (Cortegiani et al., 2016b, Leon et al., 2006, Ostrosky-Zeichner et al., 2011). Few clinical studies have evaluated the efficacy of empirical or pre-emptive strategies; with only one randomized clinical trial applying preemptive treatment and five trials using empirical treatment, in our recent systematic review (Wang et al., 2017). Although echinocandin was recommended as the initial drug in all 16 CPGs supporting empirical or pre-emptive treatment, two systematic reviews (Cortegiani et al., 2016a, Wang et al., 2017) demonstrated that echinocandins and empirical or pre-emptive treatment did not significantly impact on preventing proven IFIs. There are no data guiding the appropriate duration of empirical or pre-emptive antifungal therapy, but it is reasonable to think that it should not differ from the treatment of documented IC.

For the management of proven IC or IAC, most CPGs recommended treatment with both echinocandins and fluconazole, although these CPGs suggest that echinocandins are increasingly considered as first-line therapy over fluconazole (Cornely et al., 2012, Pappas et al., 2016). The CPGs noted important roles for L-AMB and voriconazole as alternative treatment options. Referring to species-specific therapy, *C. glabrata* and *C. parapsilosis* are the two most problematic infections in determining treatment choice. None of the CPGs mentioning species-specific therapy recommended fluconazole or echinocandin as initial therapy for *C. glabrata* and *C. parapsilosis,* respectively. There is no evidence that the clinical outcome of therapy with fluconazole is inferior to echinocandins in patients with *C. glabrata*, even though *C. glabrata* is less susceptible to fluconazole in vitro (Eschenauer et al., 2013, Reboli et al., 2007). Meanwhile, there was no difference in the risk of clinical failure among 200 patients with candidemia due to

C. parapsilosis who received initial treatment with an echinocandin compared with those who received other regimens (Fernandez-Ruiz et al., 2014), in spite of the laboratory observations of decreased in vitro activity of echinocandin (Pfaller et al., 2011). Additionally, we noted that the timing of step-down therapy was different among CPGs (e.g. 10 days in ESCMID (Cornely et al., 2012) versus 5-7 days in IDSA (Pappas et al., 2016)). CPGs fail to provide adequate information on this issue due to a lack of high-level evidence (Vazquez et al., 2014).

The main strength of our systematic review lies in the integration of methodological quality appraisal with content analysis of recommendations; no other study has provided an inter-dimensional approach to CPG quality assessment. The matrix method used will also enable CPG developers and users to clearly identify gaps in treatment recommendations that can be rectified in subsequent updates.

Our search was not restricted to only English: our multilingual team assessed guidelines in Chinese, Japanese, and Spanish. This enabled a global CGP assessment and reduced the risk of recommendation bias towards CPGs in English. However, we still may have missed relevant non-English language CPGs in journals not indexed by major bibliographic databases.

A study limitation is that the AGREE II scores may reflect the quality of reporting rather than methodological quality. Suboptimal reporting of the development process could potentially undermine the credibility of the CPGs. Nevertheless, the AGREE II is a benchmark for assessing CPG quality that has been extensively validated (Lin et al., 2018). Even though AGREE II only evaluates methodological processes and not necessarily recommendations, we are then able to pay more attention to the recommendations provided by CPGs that scored higher on AGREE II criteria. The AGREE II scores of CPGs were appraised by two reviewers, with three reviewers involved in the quality assurance review; however, ideally four reviewers should be used (Brouwers et al., 2010b).

Conclusions

In summary, the methodological quality of CPGs for the use of antifungal agents in non-neutropenic critically ill patients is suboptimal. These findings highlight the need for better reporting of guideline development processes in the future. Further improvement in the 'applicability' domains of the AGREE II criteria would strengthen the quality of the CPGs. Although these CPGs have access to the same published evidence base, recommendations remain unclear or inconsistent in certain areas. The similarities across CPGs add validity and credibility to the recommendations. The differences point to areas that need further research to strengthen the evidence base; however, they will need careful consideration and adaptation to the local health services context in order to address the key clinical issues that clinicians face.

Ethics approval

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Concept and design: YW, YLD. Acquisition, analysis or interpretation of data: YW, TM, MVD. Drafting of the manuscript: YW, TM, SH, MVD. Critical revision of the manuscript for important intellectual content: all authors. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

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