AMERICAN THORACIC SOCIETY DOCUMENTS

Treatment of Invasive Pulmonary Aspergillosis and Preventive and Empirical Therapy for Invasive Candidiasis in Adult Pulmonary and Critical Care Patients

An Official American Thoracic Society Clinical Practice Guideline

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A data supplement for this article is available via the Supplements tab at the top of the online article.

ABSTRACT:

Background: The incidence of invasive fungal infections is increasing in immune-competent and immune-compromised patients. An examination of the recent literature related to the treatment of fungal infections was performed to address two clinical questions. First, in patients with proven or probable invasive pulmonary aspergillosis, should combination therapy with a mold-active triazole plus echinocandin be administered vs. mold-active triazole monotherapy? Second, in critically ill patients at risk for invasive candidiasis who are non-neutropenic and are not transplant recipients, should systemic antifungal agents be administered either as prophylaxis or as empiric therapy?

Methods: A multidisciplinary panel reviewed the available data concerning the two questions. The evidence was evaluated, and recommendations were generated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.

Results: A conditional recommendation was made for patients with proven or probable invasive pulmonary aspergillosis to receive either initial combination therapy with a mold-active triazole plus an echinocandin or initial mold-active triazole monotherapy based on low-quality evidence. Further, a conditional weak recommendation was made against routine administration of prophylactic or empiric antifungal agents targeting *Candida* species for critically ill patients without neutropenia or a history of transplant based on low-quality evidence.

Conclusions: The recommendations presented in these Guidelines are the result of an analysis of currently available evidence. Additional research and new clinical data will prompt an update in the future.

Keywords: pulmonary aspergillosis; invasive candidiasis; therapeutics; echinocandins; triazoles

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Overview: The purpose of this guideline is to analyze evidence relevant to treatment decisions in selected scenarios encountered by pulmonary and critical care providers. These guidelines examine recent and relevant data to address the potential mortality benefit from the use of different antifungal strategies in two distinct clinical scenarios. The first examined whether, in patients with proven or probable invasive pulmonary aspergillosis (IPA), combination therapy with a mold-active triazole plus echinocandin should be favored over mold-active triazole monotherapy. The second examined whether, in critically ill patients at risk for invasive candidiasis (IC) who are non-neutropenic and are not transplant recipients, systemic antifungal agents should be administered as either prophylaxis or as empiric therapy.

Introduction: The incidence of invasive fungal infections (IFIs) is rising in immune-competent and immune compromised individuals.(1) This is likely multifactorial and a result of expanding therapies for malignancies and rheumatological disorders, increasing indications for solid organ and hematological transplantation, human immunodeficiency virus (HIV), prolonged intensive care unit (ICU) stays, and climate change.(2, 3) Despite available new extended spectrum antifungal agents, the mortality for invasive fungal infections remains high. (4, 5) Many treatment recommendations from the last ATS clinical practice guidelines for the treatment of fungal infections in 2011 remain relevant.(6) For instance, the treatment of endemic mycoses has changed relatively little and limited new literature has become available. In contrast, there are two clinical scenarios, for which recent clinical trials have resulted in a greater understanding of the

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role(s) of extended spectrum antifungals and are the focus of these guidelines. The first focuses on whether combination therapy with a mold-active azole plus echinocandin compared to mold-active azole monotherapy alone improves survival in IPA. The second examines whether prophylactic or empiric systemic antifungal therapy improves survival in critically ill patients at risk for IC.

Methods:

Panel Composition. We convened a panel with broad expertise in the clinical and treatment aspects of fungal infections commonly encountered by pulmonary and critical care providers. Representative backgrounds from pulmonary medicine, critical care and infectious diseases were included, as well as expertise in pharmacology. The guideline included one patient who participated on the guideline panel and provided perspective on patient values and preferences. The committee membership included Oleg Epelbaum, Tina Marinelli, Kelly Pennington, Scott E. Evans, Eva M. Carmona, Shahid Husain, Kenneth S. Knox, Benjamin Jarrett, Elie Azoulay, William Hope, Ashley Meyer-Zilla (patient representative) and Andrew H. Limper and Chadi A. Hage. M. Hassan Murad and Qusay Haydour provided methodological expertise. The committee was co-chaired by Andrew H. Limper and Chadi A. Hage.

Confidentiality Agreement and Conflict-of-Interest Management. All committee members declared and signed conflict of interest declarations at the onset of the project and these were updated annually. All conflicts were declared

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and managed by the chairs and co-chairs who had no conflicts. None of the conflicts affected the final recommendations. When even potential perceived conflicts were present, the individual did not vote or discuss that related recommendation. The Committee Co-Chairs (C.H. and A.L.) solicited updated conflicts of interest declarations routinely at the start of each conference call. The opinions and interests of the ATS did not influence recommendations on either topic.

Meetings and Process. After initial discussions in 2020, the members of the ATS fungal working group convened by conference call to review fungal treatment topics commonly encountered in pulmonary and critical care practice with the express purpose of identifying those fungal treatment topics with new data since the 2011 ATS guidelines. After survey of the available literature, two selected questions were proposed, discussed with the ATS documents chair, and finalized for submission to the project review committee in July 2021. These selected topics were revised and approved for the project beginning in January 2022. All work was performed virtually with monthly or bimonthly conference calls. Literature search and analysis was performed under the direction of ATS designated methodologists (M.H.M. and Q.H.). They presented the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach for guideline development.(7) The committee performed the literature review, data evaluation, GRADE recommendation development, and guideline formation, and drafted the document.

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Formulating Clinical Questions. The panel reviewed emerging literature relevant to commonly encountered fungal treatment topics since the last ATS fungal treatment guidelines.(6) The committee selected two most relevant clinical treatment questions. The topics were selected by committee consensus and included the use of combination antifungal therapy in IPA and the use of prophylaxis and empiric treatment for IC in critically ill patients. Two specific PICO questions were formulated. These PICO questions guided the systematic reviews of the literature, grading, and recommendations. In an ongoing fashion, the committee is currently formulating and reviewing additional questions which will serve as the basis for future guidelines.

Literature Search and study selection. A comprehensive search was conducted from January 1, 2000, to January 11, 2022, and included Medline In-Process & Other Non-Indexed Citations, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus. Search results were limited to English and were designed and executed by a librarian. Controlled vocabulary supplemented with keywords was used to search for studies of fungal diagnosis. The actual strategies for PICO 1 and PICO 2 are available in the online supplementary material and yielded 2260 citations for PICO 1 and 1600 citations for PICO 2. The panel also assisted in identifying additional resources and monitored the literature for studies outside of the search dates and strategies. The methodologists and the committee members selected studies for inclusion by

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consensus.

Evidence Synthesis and Rating of Certainty in the Evidence. When deemed appropriate, random-effects meta-analysis was used to generate pooled relative risk (RR). The quality of evidence (certainty in the estimates) was graded as high, moderate, low, and very low following the GRADE approach for treatment studies.(7) All final recommendations were reached by consensus and were unanimous unless otherwise specified. The panel considered all patient important outcomes but focused on overall mortality as the driver for treatment decisions in these two clinical settings. When deemed necessary, the panel added an Implementation Remark to make a particular recommendation more practical and implementable by clinicians. Implementation Remarks are not derived from the systematic review; rather, they are derived from the clinical experience of the panel and their knowledge of the literature. Therefore, Implementation Remarks should not be conflated with the graded recommendation.

Manuscript Preparation. The writing committee (O.E., K.P., S.E., T.M. E.C., S.H., C.H. and A.L.) provided the initial draft of guideline document sections for review and editing by the entire panel. The entire panel provided input to correct interpretive or factual errors. The final document was integrated, edited, and approved by the committee. The complete guideline was submitted to the American Thoracic Society Documents Committee and then onto the American Thoracic Society Board for review. The guideline underwent anonymous peer review by 4 content experts and one methodologist. Following multiple cycles of review and

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revision, the guideline was reviewed and approved by a multi-disciplinary Board of Directors. The guideline will be reviewed by the ATS three years after publication, and it will be determined if updating is necessary.

Recommendations for Selected Fungal Treatment Questions:

Question 1. In patients with proven or probable IPA, does combination therapy with a mold-active triazole plus echinocandin reduce mortality compared to mold-active triazole monotherapy?

Recommendation. Question 1. In patients with proven or probable IPA, we suggest either initial monotherapy with a mold-active triazole or initial combination therapy with a mold-active triazole plus an echinocandin. (Conditional recommendation, low quality evidence).

Implementation Remark: The available evidence and contextual considerations were insufficient to favor one approach over the other. This recommendation derived exclusively from data on patients with hematological malignancy and/or history of hematopoietic stem cell transplantation. Applicability of this recommendation to patients without hematological malignancy or history of hematopoietic stem cell transplantation is unclear. Combination therapy is likely more appropriate in the setting of critical illness or concern for triazole resistance. Patients diagnosed with IPA by a positive galactomannan assay in serum or bronchoalveolar lavage fluid may be particularly suitable candidates for the dual regimen in any setting.

Background

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Aspergillus is a genus of ubiquitous environmental molds capable of causing invasive human infection in the context of compromised innate or cell-mediated immunity. The classical scenario associated with the former is neutropenia induced by chemotherapy for hematological malignancy (HM) or resulting from a myeloablative conditioning regimen in preparation for hematopoietic stem cell transplantation (HSCT). Cell-mediated immunodeficiency predisposing to IPA is typically related to suppression of T-cell immunity following solid-organ or allogeneic hematopoietic stem cell transplantation, especially when the latter is accompanied by graft-versus-host disease. IPA is the most common invasive fungal infection in both HM,(8) where it accounts for up to 90% of such infections with an attributable mortality of 42%, and HSCT: approximately 70% of isolates with an attributable mortality of 72%.(9) Given the frequency and lethality of IPA in these two populations, prompt and maximally effective antifungal therapy is essential to patient survival. A pivotal randomized controlled trial (RCT)(10) published in 2002 established the superior efficacy and safety of voriconazole, a mold-active triazole, compared to amphotericin B deoxycholate (AmB), the prior standard. As a result, voriconazole has been considered the drug of choice for IPA since that time. Concurrent with the ascent of voriconazole has been the evolution of the echinocandin class of antifungal agents. The currently available evidence does not support replacing voriconazole with an echinocandin as first line monotherapy (11). However, the possible benefit of *adding* an echinocandin to voriconazole as a form of combination therapy has been entertained for many years. Because the triazoles inhibit fungal cell membrane synthesis whereas the echinocandins act at

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the cell wall, the potential for synergy between these compounds in treating *Aspergillus* spp is mechanistically plausible. Results of an *in vitro* experiment (12) and an *in vivo* rabbit model of IPA have lent credence to the notion that adding an echinocandin to a triazole (13) could produce results superior to triazole alone, though positive results have not been replicated in other animal models.(14) Clinically, the addition of an echinocandin to a mold-active triazole for the treatment of IPA could occur in two distinct settings: primary and salvage. Primary combination therapy is defined as the up-front use of both agents in a treatment-naïve individual. Salvage combination therapy refers to conversion from initial monotherapy. Before voriconazole supplanted AmB as the drug of choice for IPA, the trigger for salvage combination therapy would have been failure or toxicity of AmB. In contemporary practice, salvage combination therapy typically means the addition of an echinocandin after inadequate response to treatment with a mold-active triazole alone.

Analysis of Literature

For the purposes of the literature search, mold-active triazole agents included: voriconazole (Vfend), itraconazole (Sporanox, Tolsura), posaconazole (Noxafil), isavuconazole, and isavuconazonium (Cresemba). The echinocandins included: caspofungin (Cancidas), micafungin (Mycamine), and anidulafungin (Eraxis). The literature search produced 2260 references, of which 2140 were excluded based on abstract review. Full-text sources for the remaining 120 references were retrieved and examined in detail. The first screening phase eliminated 103 of these 120

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publications for meeting broad exclusion criteria such as having fewer than 25 subjects or having pediatric participants. Thirteen of the 17 remaining publications were eliminated after a second round of full-text screening based on more nuanced incompatibility with the question (results summarized in Supplementary Table 1S). The two most common reasons for elimination of these 13 publications were lack of a mortality endpoint (7/13, 54%) and use of a monotherapy comparator (e.g., echinocandin or AmB) other than a triazole (4/13, 31%). To the four studies thus identified,(15-18) a fifth study (19) was added based on inspection of the reference list of an existing systematic review(20). The reference list of another systematic review(21) yielded two conference abstracts(22, 23) for which corresponding full-text publications could not be located, so these documents were not included. A flow diagram summarizing the literature search process is depicted in Figure 1. In addition, we also reviewed previous relevant IDSA guidelines and ESICM-ESCMID guidelines.

The characteristics of the five studies that constituted the evidence for this question are presented in Table 1. Four of them are retrospective cohort studies(15-19) of voriconazole with or without caspofungin while the fifth is an RCT of voriconazole with or without anidulafungin.(18) All of the studies included either patients with HM, recipients of HSCT, or a mixed population. The observational studies were limited to cases of proven or probable IPA according to international consensus criteria.(24) The RCT permitted enrollment of possible cases, but to be considered evaluable they needed to have been upgraded to proven or probable in the week

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following randomization. One of the observational studies (15) examined combination therapy exclusively in the salvage setting, and there was a subgroup in another(25) that received salvage therapy; the other studies were restricted to primary therapy only. Overall, in the observational studies, a total of 72 patients received primary combination therapy and 101 patients received primary monotherapy (N=173), while a total of 51 patients received salvage combination therapy and 55 patients received salvage monotherapy (N=106). Three of the four observational studies reported 3-month mortality; the fourth reported 4-month mortality.(16) The RR of death at these time points in combination therapy recipients versus monotherapy recipients stratified by primary versus salvage therapy was the outcome measure analyzed in the pooled analysis for this question. IPA-attributable mortality was used preferentially if it was available as an explicit endpoint. Information on mold-active prophylaxis was provided by two of the observational studies, and was used in greater than 70% of patients in both.(16, 25) The international, multi-center, double-blind, placebo-controlled trial randomized 277 patients with IPA to either voriconazole alone (N=142) or voriconazole plus anidulafungin (N=135) as primary therapy.(18) The mold-active prophylaxis rate was 7.6%. The RCT was not meta-analyzed with the observational studies due to evident methodological heterogeneity. The RCT reported its primary outcome as mortality at 6 weeks and a secondary outcome as mortality at 3 months.

Summary of the Evidence for Primary Therapy

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Meta-analysis of the three observational studies that evaluated primary therapy (16, 17, 19) is shown in Figure 2. The pooled RR of death was 2.13 (95% CI: 1.18-3.83), suggesting possible increase in mortality with the combination of voriconazole and caspofungin compared to voriconazole alone. I^2 revealed no important heterogeneity with a p-value of 0.67. However, these studies were judged to be at high risk of bias in the domain of comparability because the provided estimates were unadjusted (Table 2). Certainty in this pooled estimate was rated as very low due to the observational nature of the studies, lack of adjustment for critical confounders and serious concern related to imprecision (small sample size). Summary of certainty in evidence is presented in Table 3. Contrary to the result obtained when pooling the observational studies, the RCT suggested a nonsignificant but clinically meaningful reduction in mortality with the combination regimen of voriconazole plus anidulafungin compared to voriconazole monotherapy at 3 months: calculated RR 0.75 (95% CI: 0.53-1.04). The absolute reduction in mortality was 98 fewer deaths per 1000 patients (182 fewer to 15 more). Certainty in this estimate was considered low and it was rated down due to very serious concern related to imprecision (small sample size and CI crossing clinically important thresholds as presented in Table 3). Six-week mortality also favored the combination arm but likewise fell short of reaching statistical significance: 19.5% versus 27.8% [absolute risk reduction -8.2 (95% CI: -19.0 to 1.5); p=0.087]. Mortality reduction at 6 weeks did reach statistical significance in the predominant subgroup of patients (80% of participants) with probable IPA based on radiographic abnormalities and positive galactomannan (GM) antigen

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with a calculated RR of 0.57 (95% CI: 0.33-0.98). The absolute reduction in mortality in this subgroup was 117 fewer deaths per 1000 patients (183 fewer to 5 fewer). Certainty in this estimate was considered low due to imprecision (Table 3).

Summary of the Evidence for Salvage Therapy

The pooled estimate for salvage therapy was obtained by combining results of the entire population from one of the observational studies(15) with results of the subgroup of patients from another observational study (25) who received either voriconazole plus caspofungin or voriconazole alone in the salvage setting(15, 17). In these two studies, a total of 51 patients received salvage combination therapy and 55 patients received salvage monotherapy. This analysis is depicted in Figure 3. The pooled RR of death was 1.01 (95% CI: 0.28-3.72) with combination therapy versus voriconazole monotherapy. There was, notably, significant heterogeneity between these studies with I^2 of 78% and p-value of 0.03. These studies were judged to be at high overall risk of bias, and the certainty in this estimate was considered very low due to serious concerns related to imprecision and risk of bias (Table 2 and Table 3).

Rationale and Evidence-to-Decision Considerations

Although the observational studies suggested potential harm of combination therapy, the panel emphasized the results of the lone RCT over those of the observational studies due to the greater methodological rigor of the RCT and thus lower concern about selection bias whereby more severely ill patients may have

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been preferentially administered combination therapy. Therefore, in issuing its conditional recommendation for equipoise, the panel relied heavily on the RCT's imprecise but clinically meaningful estimate of survival benefit with combination therapy. Importantly, the survival benefit of combination therapy in the RCT was more precise in the dominant subgroup of patients who were diagnosed with probable IPA based on a positive GM assay. This result contributed to the recommendation because GM detection is currently the most common pathway for the diagnosis of IPA in clinical practice and is incorporated into the latest international consensus criteria.(26) The panel deemed the outcome of mortality to be universally important for a condition as lethal as IPA and, although certainty of the evidence was low to moderate, the possibility of a survival benefit was believed to offset the potential undesirable effects of combination therapy in the critically ill and in those in whom triazole resistance is a concern. The main undesirable effects that were considered were cost and additive drug toxicity. A cost effectiveness analysis of combination therapy with a triazole plus an echinocandin versus triazole monotherapy for IPA has not been performed, but the incremental cost of an antifungal as widely available as an echinocandin was thought to be acceptable when viewed in the context of the overall cost of care for a critically ill patient with IPA. The RCT reported a higher incidence of hepatobiliary adverse events in the combination therapy arm (12.7% vs. 8.4%), but the difference was not statistically significant and treatment discontinuation rates were similar between the groups. The panel acknowledged the very sparse data pertaining to combination therapy in the salvage setting and therefore did not issue a separate recommendation regarding

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this scenario. The panel deemed that the evidence relied upon to support combination therapy in the primary setting could be extrapolated to the salvage setting in the absence of sufficient direct evidence to guide decision-making.

The panel recognized that its recommendation is based exclusively on voriconazole containing regimens—this reflects the primacy of voriconazole as an anti-*Aspergillus* triazole for the past two decades. The potential advantages of combining a triazole and echinocandin may predominantly relate to the well-described limitations of voriconazole, which include: [1] inherent or acquired resistance to voriconazole that may not necessarily extend to other triazoles (27); [2] highly variable pharmacokinetics and frequent subtherapeutic voriconazole concentrations despite use of standard oral or intravenous loading regimens (28)**;** and [3] unrecognized polymicrobial fungal infections with pathogens that are resistant or inherently less susceptible to voriconazole (e.g., mixed infections of *Aspergillus* spp. and *Mucorales* (29)). Aside from overcoming the specific challenges posed by voriconazole, a generic combination of a triazole and echinocandin may be beneficial by compensating for limitations of monotherapy with a drug in either class. The following are some potential considerations in that regard: [1] differential partitioning of the two drug classes in different tissue compartments, meaning that at least one drug is present at the effect site (30), which may be especially relevant for disseminated disease; [2] overcoming unfavorable drug-drug interactions that may render triazole therapy less effective; [3] possible positive pharmacological interactions (i.e., additive or synergistic

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interactions) in terms of antifungal killing as supported by multiple nonclinical studies (31, 32); and [4] (theoretically at least) prevention of the emergence of resistance—in a way that is increasingly understood with combination therapy for bacterial pathogens.

Implementation Considerations

Clinical Settings

Although the panel refrained from suggesting combination therapy for the diagnosis of IPA as a whole, two clinical settings were proposed as potentially suitable for combination therapy (see Implementation Remark). Neither setting was proposed based on available study data but rather was based on the collective experience of panel members and indirect evidence. One such setting is IPA in the critically ill. For patients admitted to the ICU, the mortality of IPA is particularly high (33), so it would be reasonable to surmise that the potential benefit of combination therapy would be maximized, and the risk of overtreatment minimized, in this high-risk setting. The echinocandins are widely available in the ICU and are routinely used to treat other fungal infections such as IC. Therefore, access of the critically ill to an echinocandin-containing regimen would not be expected to present an obstacle to implementation, except for the most resource limited parts of the globe. Echinocandins also have a favorable use profile in patients with renal or hepatic impairment—both common conditions in the ICU—and do not pose a major challenge with drug-drug interactions.

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impairment—both common conditions in the ICU—and do not pose a major challenge with drug-drug interactions.

The other setting in which the panel favored consideration of combination therapy is when there is concern for triazole resistance. Triazoles are often used for *Aspergillus* prophylaxis in patients at risk for IPA. It is unknown at present whether the prophylactic use of triazoles impacts the efficacy of monotherapy compared to combination therapy for IPA in the context of breakthrough infections. Overall, in Europe, the prevalence of triazole resistance in clinical *A. fumigatus* isolates has bene reported to be 3.2% (34), whereas in the United States that number is substantially lower at 1.4% (35). On a related note, availability and use of antifungal susceptibility testing of *A. fumigatus* isolates in U.S. laboratories is reduced compared to their European counterparts. This has translated into less environmental surveillance, especially on a state-by-state level, in the U.S. and thus more limited awareness of the epidemiology of *Aspergillus* resistance than exists in Europe. On other continents, some countries have registered a prevalence of resistance exceeding 10%, especially when environmental isolates are examined (36). The benefit of initial combination therapy is likelier to outweigh the risk in settings with increased triazole resistance: international expert opinion (37) and European guidelines (38) already advocate for this approach at an environmental resistance threshold of >10%. Subsequent performance of antifungal susceptibility testing on the clinical isolate of a particular patient could enable de-escalation to triazole monotherapy in susceptible cases.

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Patient Characteristics

In the lone RCT, a statistically significant reduction in 6-week mortality with combination therapy was observed in two subpopulations. One was the aforementioned dominant subgroup (80% of subjects) diagnosed with IPA by GM positivity. The result of this *post-hoc* analysis raises the possibility that patients diagnosed in such a contemporary and practical manner could be particularly suitable candidates for the dual regimen (see Implementation Remark). Whether this apparent differential response is explained by pathogen, host, or technical factors is currently unknown. The other was a much smaller prespecified subgroup (99/277, 36% of subjects) consisting of those without neutropenia at diagnosis. The calculated RR for death of 0.42 for this subgroup was associated with a very wide 95% confidence interval: 0.19 – 0.94. Given the methodological limitations of a small subgroup analysis within a single RCT, this result was not incorporated by the guideline panel into the evidence-to-decision process. Nonetheless, the panel acknowledged that special attention to an individual patient's neutrophil count is warranted when deciding whether to administer monotherapy or combination therapy for IPA.

Antifungal Agents

In light of their comparable clinical efficacy with more predictable pharmacokinetics and more favorable toxicity profile, the newer triazoles posaconazole and isavuconazole have been increasingly competing with voriconazole as first-line therapy for IPA in clinical practice even as voriconazole still retains primacy in guidelines (39). By extension, these drugs are also being

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used as part of combination regimens in the clinical arena. In light of their fundamental similarity, the panel considered voriconazole to be a reasonable stand-in for the newer agents and, in the absence of direct data, felt that the current recommendation based on studies of voriconazole could reasonably extend to posaconazole and isavuconazole. Conversely, the most recently approved echinocandin, rezafungin, has not been studied in human trials of IPA and, owing to its extremely long half-life, cannot be considered interchangeable with the conventional echinocandins (micafungin, anidulafungin) that are addressed by this guideline (40).

Areas of Research Need

All of the studies considered for this recommendation compared voriconazole monotherapy with voriconazole-based regimens containing either micafungin or anidulafungin. The newer triazoles posaconazole and isavuconazole have not been investigated as part of a combination regimen for IPA. If conducted in the coming years (none is registered in ClinicalTrials.gov as of this writing), studies of combination therapy using these newer agents might alter subsequent guideline recommendations on this topic. The same may apply to future studies of rezafungin for the treatment of IPA. The number of possible combination regimens is destined to evolve with the advent of novel categories of antifungal agents. Promising animal data for efficacy against *Aspergillus spp* are already available for regimens containing fosmanogepix (41), ibrexafungerp (42), and olorofim (43), but results of human trials have not been reported to date.

Additionally, the studies considered herein were limited to patients with HM and

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HSCT; future studies involving other high-risk populations such as lung transplantation recipients would fill an important data gap. No existing study of triazole plus echinocandin combination therapy has addressed breakthrough infections despite mold-active prophylaxis, infections in the setting of suspected or documented triazole resistance, or infections in the critically ill. Once combination therapy is initiated, its optimal duration remains to be established as do strategies for de-escalation to monotherapy. Also, as mentioned, a cost-effectiveness analysis of combination therapy versus monotherapy for IPA has yet to be performed. Finally, future trials of combination therapy for IPA will need to account for the possibility that patients diagnosed by means of GM positivity respond differently to treatment than those diagnosed by culture as suggested by the RCT that underpinned this recommendation (18).

Question 2. In critically ill patients who are non-neutropenic and are not transplant recipients, should systemic antifungal agents be administered as either prophylaxis or empiric therapy to reduce mortality?

Recommendation. In critically ill patients without neutropenia or a history of transplant, we suggest against routine administration of prophylactic or empiric antifungal agents targeting *Candida* species. (Conditional recommendation based on low-quality evidence).

Background

Candida species are frequent colonizers of mucosal and cutaneous surfaces of

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healthy individuals; however, when there is breakdown of mechanical or immunologic defenses, invasion can occur. (44) This may manifest as deep-seated IC and/or candidemia, and the latter can lead to metastatic complications including, but not limited to, endophthalmitis, bone and joint infections, endovascular infections, and hepatosplenic abscesses.(45, 46) In critically ill patients, the incidence of candidemia varies from 3.5 to 16.5 episodes per 1000 ICU admissions (47-52); however, the incidence of deep-seated IC without concomitant candidemia is less clear due to challenges associated with confirming the diagnosis. Outcomes associated with IC are poor with a crude mortality of 40-55% (47-49, 53). Host risk factors for IC in critically ill patients include diabetes, systemic immunosuppression, organ failure, total parenteral nutrition, malignancy, *Candida* colonization, and genetic polymorphisms. Clinical risk factors encompass breaches in barrier of defense because of surgery, loss of mucosal integrity (e.g., of an abdominal viscus), burns, indwelling vascular access catheters, and hemodialysis (45, 54).

Candida colonization logically precedes infection, and in critically ill patients the presence and density of *Candida* colonization is predictive of development of IC (55, 56). Deep-seated IC, particularly intra-abdominal IC, occurs in critically ill patients and, due to limitations of available diagnostics, is likely under-diagnosed (46). Nonetheless, IC complicates a minority of ICU admissions (57). The use of antifungal therapy in the ICU, whether as prophylaxis or empiric therapy, is of great interest to providers treating critically ill patients. To our knowledge, no

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clear recommendations on the subject have been published.

Available Literature

For this analysis, we categorized the use of systemic anti-*Candida* therapy into three categories: prophylactic, pre-emptive, and empiric by definitions described in the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guideline for the diagnosis and management of *Candida* diseases (58). A prophylaxis strategy entails administration of antifungals to high-risk patients without microbiologic or radiographic evidence of infection; a pre-emptive strategy entails administration of antifungals to high-risk patients based on presence of positive surrogate markers (e.g., BDG, mannan, anti-mannan antibody); an empiric strategy entails administration of antifungals to high-risk patients based on signs of infection but absence of microbiologic confirmation of infection.

We included randomized controlled trials that assessed the mortality effect of systemic antifungal therapy compared to placebo in non-neutropenic, non-transplant critically ill adult patients. The primary outcome was all-cause mortality. We excluded studies on pediatric population, non-absorbable antifungal agents, and studies that used antifungal therapy for "anti-inflammatory" effect. We also excluded studies with fewer than 25 patients, commentaries, editorial letters, and case reports.

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The initial literature search yielded 1600 references of which 1526 were excluded after abstract screening (Flow diagram in Figure 4). The full-text articles of the remaining 74 references were reviewed. Of these, nine studies were not RCTs and 60 studies did not include the relevant population, intervention, control and/or outcome, leaving five RCTs (59-63) that met the inclusion criteria (Supplementary Table 2S).

Three published systematic reviews and meta-analyses (64-66) were examined for potentially eligible studies not identified by the primary literature search. An additional three eligible studies were thus identified (67-69). Data from a fourth study by Alexander et al (70) was included in the meta-analysis performed by Dupont et al (66); however, since this trial was discontinued early due to inadequate enrollment and a detailed description of the methods and results remains unpublished, it was not included in this analysis. In total, eight randomized controlled trials (RCTs) were finally included. The characteristics of these trials are summarized in Table 4 and Supplementary Table 3S.

We examined mortality outcome based on the antifungal strategy used. Five placebo controlled RCTs, examined the impact of antifungal prophylaxis, totaling 441 patients in the intervention groups and 421 in the control. Three RCTs examined fluconazole (59, 67, 68) and two an echinocandin (61, 69). Three RCTs were from a single center (59, 67, 68) and two were multi-center (61, 69). Although all RCTs exclusively enrolled critically ill-patients, some had other

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specific inclusion criteria such as: trauma or surgical patients (59, 67); mechanically ventilated (MV) patients with ventilator-associated pneumonia (69); MV patients receiving selective digestive decontamination (SDD) (68); and patients with positivity of a clinical prediction rule for IC (61). Duration of antifungal prophylaxis varied from a defined duration of 14 days (59) to ICU length of stay (LOS) (59, 61, 67) to development of IC (59, 67, 68). None of the RCTs designated mortality as a primary outcome; however, these data were extractable from the published articles. The study by Albert et al (69) was included in the prophylaxis rather than empiric category as the indication for empiric antifungals was ventilator-associated pneumonia (VAP) in the presence of *Candida* isolated from the respiratory tract. While *Candida* spp are frequent colonizers of the respiratory tract, *Candida* pneumonia is rare and would require visualization of invasive forms of *Candida* on histopathologic examination of lung parenchyma to confirm the diagnosis, which was not achieved in this study (71).

None of the eligible studies identified by our search examined pre-emptive therapy as per the definition used herein. In the trial by Ostrosky-Zeichner et al (61), some patients were subjected to two different antifungal strategies: initial prophylaxis with either caspofungin or placebo with a permitted switch to open-label drug therapy for placebo recipients who developed proven or probable IC during follow up. The authors termed such crossover therapy "pre-emptive." The panel considered this trial to be one of prophylaxis, and thus it was analyzed in that antifungal strategy category. Based on the definitions used herein, the "pre-

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emptive" therapy in this trial would be classified as either empiric (probable IC) or directed (proven IC) antifungal therapy. Recipients of open-label empiric antifungal therapy in this trial were not analyzable for the purposes of the present guideline as there was no comparison group.

Three studies examined empiric antifungal therapy, all multi-center, placebo-controlled trials (60, 62, 63) totaling 372 patients in the intervention group and 376 in the control. Two studies examined micafungin (62, 63) and one fluconazole (60). Infection syndromes serving as inclusion criteria were different in each study: generalized or localized intra-abdominal infection (62); more than four days of fever (60); and ICU-acquired sepsis (63). Twenty eight-day survival without proven IC was the primary outcome in one study only (63); the others examined incidence of IC (62) and resolution of the sepsis syndrome (60).

We also examined mortality outcomes based on the antifungal agent used (fluconazole or an echinocandin). Fluconazole was administered in four studies; however, there was heterogeneity in dosing. Two studies administered a loading dose of 800 mg followed by 400 mg daily (59, 67), one study used 800 mg daily (60) and one used 100 mg daily (60). One of these four studies used fluconazole as empiric therapy (60); the remaining three used fluconazole as prophylaxis (59, 67, 68). Four studies used an echinocandin. One study used anidulafungin 200 mg loading followed by 100 mg daily (69) and one study used caspofungin 70 mg loading followed by 50 mg daily (61), both as prophylaxis. The remaining two

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studies used micafungin 100 mg daily as empiric therapy (62, 63).

Summary of the evidence based on antifungal strategy

Overall

Meta-analysis of the eight RCTs that evaluated either prophylaxis (59, 61, 67-69) or empiric antifungal therapy (60, 62, 63) is shown in Figure 5. This overall analysis consisted of 798 critically ill patients who received systemic antifungals and 779 who received placebo, of whom 183 (22.9%) and 173 (22.2%) died, respectively. The pooled RR of death was 1.03 (95% CI 0.86-1.23), indicating no statistically significant difference in mortality whether systemic antifungals were administered or not. The I^2 value revealed no important heterogeneity with a p-value of 0.90. The absolute change in mortality was 7 more deaths per 1000 (31 fewer to 51 more). Certainty in evidence was rated as low due to concerns related to risk of bias and imprecision as detailed in Table 3 and Table 5.

Antifungal prophylaxis

Meta-analysis of the five RCTs (59, 60, 67-69) that evaluated antifungal prophylaxis is available in Figure 5. The pooled RR of death was 0.99 (95% CI: 0.77-1.27). The absolute mortality was similar in those who received prophylaxis (97/441, 21.9%) compared with those who did not (90/421, 21.3%).

Empiric antifungal therapy

Meta-analysis of the three studies (60, 62, 63) that evaluated empiric antifungal

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therapy is likewise available in Figure 5. The pooled RR of death was 1.07 (95% CI 0.81-1.41). The absolute mortality was similar in those who received empiric antifungal therapy (93/372, 25.0%) compared with those who did not (87/376, 23.1%).

Summary of evidence based on antifungal drug class

Meta-analysis of the four studies[16,24,25,29] that evaluated fluconazole therapy is shown in Figure 6. The pooled RR of death was 1.04 (95% CI 0.82-1.33). Meta-analysis of the four studies (61-63) that evaluated echinocandin therapy is also shown in Figure 6. The pooled RR of death was 1.01 (95% CI 0.86-1.31). The consistency of the results across the two antifungal drug classes suggests that the drug class may not have an effect on mortality, although fluconazole has not been directly compared to an echinocandin in this setting.

Rationale and evidence to decision considerations

The pooled RR from the eight included RCTs suggests little or no mortality benefit of systemic antifungal therapy when used as prophylaxis or as empiric therapy. The rationale for assessing mortality as the outcome of interest rather than IC was two-fold. The first reason is that the purpose of prophylaxis or empiric antifungal therapy in critically ill patients is to prevent or treat IC as a contributor to mortality. The second reason is that within the reviewed and included studies there was heterogeneity of definitions used for IC. In particular,

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Candida colonization was often reported as IC. The latter reflects the uncertainty and evolution of our understanding of IC over recent decades. For example, whereas the 2004 Infectious Disease Society of America Invasive Candidiasis Treatment Guidelines (72) recommended treatment of *Candida* isolated from the respiratory tract, more contemporary guidelines acknowledge this as a state of colonization rather than an etiology of infection (73). While *Candida* colonization is a prerequisite for subsequent invasion, the two states are not synonymous, and progression from the former to the latter depends on various factors, including nutrient availability, the host microbiota, and immune defenses (74). Due to inconsistent or absent reporting in the included studies, the panel was unable to assess the potential harms of antifungal use, including drug side effects, the impact on the mycobiome, and risk of infection with resistant fungi. This uncertainty contributed to the issuance of a negative rather than neutral recommendation.

Implementation considerations

A key consideration when determining whether prophylactic and/or empiric antifungals reduce mortality in ICU is whether IC is driving mortality. Due to reporting biases, the true incidence of IC in ICU is unclear; however, candidemia has been well studied. Mortality in an individual ICU patient with candidemia is reported to be as high as 10-47%; however, when factors such as age, disease severity, the presence of organ failure and immunosuppression are accounted for, the attributable mortality is likely much lower (45, 75, 76). While candidemia is

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more common in critically ill patients than in most other populations, the reported incidence is still relatively low: from 3.6 to 16.5 per 1000 admissions (47-52). In a large study of 60,778 ICU admissions in non-neutropenic patients in the United Kingdom over a two-year period, the incidence of IFI, consisting primarily of IC, was just 0.6% (57). When it did occur, IC was associated with a high rate of mortality (57). Simple risk models for predicting development of IC were developed and incorporated into economic models to advise thresholds for initiating antifungal prophylaxis; however, due to the small number of outcomes the certainty of these models was low. Thus, while it is relatively easy to identify ICU patients at risk of IC, the utility of prophylaxis remains unclear. To further complicate these decisions, ICU practices and the ICU environment are constantly evolving. Factors such as improved vascular access catheter management, more judicious use of total parenteral nutrition with a preference for enteral feeding, a greater focus on more appropriate use of antibiotics and better surgical techniques may contribute to a decreased incidence of IC (54); thus, data produced twenty years ago may not apply to a modern ICU setting.

The examined literature does not support the use of empiric antifungal therapy in critically ill, non-neutropenic, non-transplant patients; however, the subset of these patients who are proven to have IC, early initiation of antifungal therapy is associated with reduced mortality (77, 78). Early diagnosis of IC to allow prompt initiation of targeted antifungal therapy is challenging because blood culture, the standard-of-care diagnostic test, has a sensitivity of less than 50% with results

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delayed for up to 3-4 days (46, 79). Non-culture-based diagnostics, including serum beta-D-glucan (BDG) and the T2Candida assay, were included in the most recent European Organization for Research and Treatment of Cancer (EORTC) and Mycoses Study Group Education and Research Consortium (MSGERC) consensus guidelines as criteria for 'probable' IC (71) and may overcome the limitations of blood cultures. The use of serum BDG is limited by low specificity, which improves with serially positive tests and with results that exceed the positivity threshold (>80 pg/mL) (80). The T2Candida assay has a high negative predictive value for the detection of common *Candida* spp. in whole blood, and while the positive predictive value varies depending on the IC prevalence in the population, the time to diagnosis is shortened when compared to blood cultures with retained sensitivity in the setting of antifungal therapy (80, 81). Interpretation algorithms for these diagnostic assays have been proposed, and further studies are required to understand their place in guiding initiation of antifungal therapy (82).

In the ICU, the prescription of antifungals to prevent or treat IC requires consideration of risks associated with widespread antifungal administration. For the individual patient, antifungals may be associated with adverse effects and drug interactions. The panel was unable to assess adverse effects in this guideline iteration due to inconsistent reporting, but reassuringly echinocandins and fluconazole are generally better tolerated than mold-active azoles and AmB formulations (83). Increasingly, the influence of the gut mycobiome on maintenance of various aspects of human health and disease, particularly the gut

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bacterial microbiome assembly, is being appreciated and is likely perturbed by antifungal use (84). The sequelae of prophylactic and empiric antifungals on the gut mycobiome has not been studied. Beyond the individual, the epidemiology of *Candida* in ICUs is changing. Both the patient and the environment can be reservoirs of resistance (54), but it is not yet clear whether antifungal use is, at least in part, driving this change. In the US, two-thirds of *Candida* isolates are non-albicans, with increasing incidence of *Candida glabrata* (85) with increased minimum inhibitory concentrations to a triazole (86, 87). The global threat of *Candida auris*, which is often resistant to all available antifungals, persists on environmental surfaces and is resiliant to decontamination (88), requires close surveillance. Close surveillance of antifungal use, species causing IC, and fungal epidemiology within ICUs is required for early detection of associations and trends.

Limitations of the current literature.

One of the main limitations of this analysis is the hetereogeneity amongst the included studies. As described, a range of antifungal durations and doses was used, particularly for fluconazole. Some studies utilized additional therapies to reduce infection such as SDD (68). The eligibility criteria for antifungal prophylaxis varied from mechanically ventilated patients receiving SDD (68), to ICU patients with VAP (69), to critically ill surgical patients (59), to critically ill trauma patients (67). Similarly, each of the three studies of empiric antifungal therapy (60, 62, 63) utilized different combinations of risk factors for inclusion.

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Despite the differences in the design of the studies, the outcomes were similar. Further studies of antifungal prophylaxis focused on specific subgroups that are at significantly increased risk of IC, such as those with severe pancreatitis (89), could help to identify populations that may benefit from prophylaxis. We excluded neutropenic and solid organ transplant recipients as, in certain subsets within these groups, the utility of anti-*Candida* prophylaxis has been long-established (90, 91).

The 2016 IDSA guidelines, the 2019 ESICM-ESCMID and the 2021 Australian guidelines recommend empiric therapy for suspected IC in critically ill patients with risk factors for IC (73, 92, 93). The former but not the latter two guidelines recommend prophylactic antifungals for high risk adult ICU patients, although this is a weak recommendation based on low-moderate quality evidence (73).

Areas of Research Need

Given the clinical equipoise that persists regarding the use of prophylactic and empiric antifungals in ICU patients, further study is warranted. With respect to prophylaxis, the specific contribution of IC to ICU mortality requires further delineation. Then the question remains: in ICU patients who are at increased risk of IC, does receipt of a systemic antifungal prevent IC, and if so, which antifungal drug or strategy is most beneficial and what is the number needed to treat to prevent one episode of IC? With regard to preemptive therapy, current implentation of a true preemptive antifungal strategy to prevent IC is limited by

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the availability of a well-studied, sensitive biomarker that can be used to detect pre-clinical disease; however, should such a test become available, this strategy should be revisited. There are several new drugs in the antifungal pipeline (94) that have not been assessed in this context and given the novel mechanism of action of some, warrant consideration. Future studies must take into account risks to the individual, such as adverse effects of the antifungal, the impact on the host mycobiome and the progression to infection with resistant fungi, as well as implications to local fungal ecology.

Recommendations:

Question 1. In patients with proven or probable IPA, we suggest either initial monotherapy with a mold-active triazole or initial combination therapy with a mold-active triazole plus an echinocandin. (Conditional recommendation, low-quality evidence).

Implementation Remark: The available evidence and contextual considerations were insufficient to favor one approach over the other. This recommendation derived exclusively from data on patients with hematological malignancy and/or history of hematopoietic stem cell transplantation. Applicability of this recommendation to patients without hematological malignancy or history of hematopoietic stem cell transplantation is unclear. Combination therapy is likely more appropriate in the setting of critical illness or concern for triazole resistance. Patients diagnosed with IPA by a positive galactomannan assay in serum or bronchoalveolar lavage fluid may be particularly suitable candidates for the dual

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regimen in any setting.

Question 2. In critically ill patients without neutropenia or a history of transplant, we suggest against routine administration of prophylactic or empiric antifungal agents targeting *Candida* species. (Conditional recommendation based on low-quality evidence).

Conclusions: Our multidisciplinary review of the available data provided the following recommendations. A conditional recommendation was made for patients with proven or probable invasive pulmonary aspergillosis to receive either initial combination therapy with a mold-active triazole plus an echinocandin or initial mold-active triazole monotherapy based on low-quality evidence. Furthermore, a conditional weak recommendation was made against routine administration of prophylactic or empiric antifungal agents targeting *Candida* species for critically ill patients without neutropenia or a history of transplant based on low-quality evidence.

This official clinical practice guideline was prepared by an *ad hoc* subcommittee of the ATS Assembly on Pulmonary Infections and Tuberculosis.

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Table 1. Characteristics of studies included in Question 1

Characteristics of studies included in Question 1					
Study ID	Population	Combination regimen	Comparison	Study design	Outcomes
Marr 2004(15)	IPA cases who received salvage therapy after hematopoietic stem cell transplant (HSCT) or cytotoxic chemo for hematologic malignancy	Voriconazole plus caspofungin	Voriconazole	retrospective	3-month IPA attributable mortality after salvage therapy.
Upton 2007(19)	IPA cases who received primary therapy in patient with hematopoietic cell transplantation (HCT)	Voriconazole plus caspofungin	Voriconazole	retrospective	3-month IPA attributable mortality after primary therapy.
Pagano 2010(16)	IPA cases who received primary therapy in patients with acute myeloid leukemia (AML)	Voriconazole plus caspofungin	Voriconazole	retrospective	4-month IPA attributable mortality in patient receiving first line target therapy.
Raad 2015(17)	IPA cases who received primary or salvage therapy in patients with hematological malignancies	Voriconazole plus caspofungin	Voriconazole	retrospective	3-month IPA attributable /all-death mortality after primary therapy, 3-month IPA attributable /all-death mortality after salvage therapy.
Marr 2015(18)	IPA cases who received primary therapy in patients with hematologic malignancies and hematopoietic cell transplantation	Voriconazole plus anidulafungin	Voriconazole	Randomized, double-blind, placebo-controlled multicenter trial	3-month mortality in mITT population, 6-week mortality in mITT population (modified ITT: only probable and confirmed IPA).

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Table 2. Risk of bias assessment for studies included in Question 1

Risk of bias assessment								
Randomized controlled trial								
Study	Randomization	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Funding source		
Marr, 2015	Low risk	Low risk	High risk	Low risk	Some concerns	Some concerns		
Observational studies								
Study	selection of cohort 1	selection of cohort 2	ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	comparability	ascertainment of outcome	follow-up long enough for outcomes to occur	adequacy of follow-up
Marr, 2004	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
Pagano, 2010	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
Raad, 2015	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
Upton, 2007	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk

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Table 3. Certainty in evidence, GRADE summary of findings (both key questions)

Outcome	No of participants (studies), Follow up	Certainty assessment	Relative effect (95% CI)	Anticipated absolute effects	Overall certainty
Mortality outcome for administering combination therapy with mold-active tirazole plus echinocandin compared to mold-active triazole monotherapy when used as **primary therapy** in patients with proven or probable invasive pulmonary aspergillosis	173 patients (3 observational studies) 3 months	risk of bias: very serious due to lack of adjustment for critical confounders, inconsistency: no concern indirectness: no concern imprecision: serious concern (small sample size)	RR 2.13 (1.18-3.83)	98 more deaths per 1,000 patients (182 more to 15 more)	Very low
	277 patients (One RCT) 3 months	risk of bias: not serious. inconsistency: no concern indirectness: no concern imprecision: very serious concern due to small sample size and CI crossing clinically important thresholds	RR 0.75 (0.53-1.04)	98 fewer deaths per 1,000 patients (182 fewer to 15 more)	Low

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	218 patients (probable IPA based on radiographic abnormalities and positive galactomannan (GM) antigen. 6 weeks all-cause mortality	risk of bias: not serious. inconsistency: no concern indirectness: no concern imprecision: very serious concern due to small sample size	RR 0.57 (0.33-0.98)	117 fewer deaths per 1000 patients (183 fewer to 5 fewer)	Low
Mortality outcome for administering combination therapy with mold-active tirazole plus echinocandin compared to mold-active triazole monotherapy when used as **salvage therapy** in patients with proven or probable invasive pulmonary aspergillosis	106 patients (2 observational studies)	risk of bias: serious due to lack of adjustment for critical confounders, inconsistency: no concern indirectness: no concern imprecision: very serious concern due to small sample size and CI crossing clinically important thresholds	RR 1.01 (0.28-3.72)	5 more deaths per 1,000 patients (327 fewer to 1000 more)	Very low
Mortality outcome of systemic antifungal agents when administered as **prophylaxis or empiric** therapy in critically patients who are non-neutropenic and not transplant recipient	1577 (8 RCTs)	risk of bias: some concern due to bias in randomization and missing outcome data inconsistency: no concern indirectness: no concern	1.03 (0.86-1.23)	7 more per 1,000 (31 fewer to 51 more)	Low

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		imprecision: serious concern due to CI crossing clinically important thresholds			

Table 4. Characteristics of studies included in Question 2

Study author and publication year and timing	**Study design**	**Inclusion criteria (Patients)**	**Exclusion criteria (Patients)**	**Intervention**	**Control**	**Duration of therapy**	**Duration of follow-up**	**Outcome**
Antifungal strategy: prophylaxis								

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Ables 2000 [24] October 1994 – December 1996	Single center, double-blind, randomized, placebo-controlled trial	Trauma or surgical patients ≥ 14 years with anticipated ICU stay of >48 hours, with ≥ one additional risk factor within 48 hours of ICU admission (CVC, TPN, MV>24hr, broad spectrum antibiotics).	Documented history of serious adverse reaction(s) to azole drugs, pregnancy, anticipated life expectancy <3 months, severe liver disease, current systemic antifungal use, transfer from another ICU.	Fluconazole 800 mg loading followed by 400mg IV/PO/enteral (adjusted for renal impairment)	Placebo	ICU LOS or until the patient developed an infection due to *Candida* species requiring treatment	Hospitalization	Primary: incidence of severe *Candida* infection Secondary: mortality, hospital length of stay
Albert 2014 [26] August 2010 – July 2012	Multicenter, double-blind, placebo-controlled randomized pilot trial	Non-immunocompromised adult patients admitted to ICU ≥ 96h , clinically suspected VAP with >48 hour of MV and positive respiratory secretions for *Candida* sp.	Positive *Candida* sp. outside lungs.	Anidulafungin 200 mg loading then 100mg IV	Placebo	14 days	The sooner of ICU stay or 28 days after enrolment	Primary: feasibility as judged by enrolment rate Secondary: changes to innate immune responsiveness, organ function, ICU and hospital LOS, acquired infection, acquired resistance

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								to antifungal therapy, duration of MV, ICU 28-day post-randomization and hospital survival reported 28d, 90 day and hospital mortality
Garbino 2002[25] Timing not stated	Single center, double blind, randomized, placebo controlled trial	Adult medical and surgical ICU patients >18 years, MV for ≥ 48 hours and expected to remain on MV for ≥72 hours and receiving selective decontamination of the digestive tract (nonabsorbable syrup consisting of polymyxin B, neomycin, vancomycin)	Life expectancy <7 days after randomization, candidemia at study entry, AIDs, persistence of PT time <50% after 24 hours of vitamin K, neutropenia, pregnancy	Fluconazole 100 mg IV	Placebo	Continued until the earlier of; end of MV; development of fungal infection; serious AE	Not stated – presumed ICU LOS	Primary: severe *Candida* sp. infection Secondary: adverse events, time from study entry to development of severe candida infection and *Candida* sp. colonization

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Ostrosky-Zeichner 2014 [18] August 2007 – March 2010	Multicenter, randomized, double-blind, placebo-controlled trial Patients who developed proven or probably invasive candidiasis were given preemptive therapy	ICU patients, ≥ 18 years of age, non-pregnant, admitted to the ICU during the preceding 3 days (minimum 48h in ICU) and expected to stay for at least 48h, AND meeting the following conditions of the clinical prediction rule: MV, CVC and use of broad spectrum antibiotics AND at least one additional risk factor for IC including TPN or dialysis on any of days 1-3, major surgery, pancreatitis use of systemic steroids or any other	Allergy or intolerance to echinocandin, ANC <500 cells/uL, AIDs, aplastic anemia, chronic granulomatous disease, moderate-severe hepatic insufficiency, pregnancy or lactation, expected survival <24 hours from time of enrollment, previous enrollment in this study, receipt of an investigational agent <10 days prior to study entry.	Caspofungin 70mg Load/50mg IV daily	Placebo	ICU LOS up to 28 days		<u>Primary:</u> incidence of proven/probable invasive candidiasis <u>Secondary:</u> prospectively verify the performance of a clinical prediction rule, evaluate safety, evaluate the effect of a pre-emptive approach, evaluate the effect of prophylaxis and pre-emptive therapy on all-cause mortality and ICU + hospital LOS

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		immunosuppressive agent <7 days before or on ICU admission,						
Pelz 2001 [16] January 1998 – January 1999	Prospective, single center, randomized, placebo controlled trial	Critically ill surgical patients ≥ 18 years with a length of ICU stay of at least 3 days	Pregnancy, receipt of antifungal agents <7 days prior to ICU admission, expected survival <24 hours	Fluconazole PO loading dose of 800 mg followed by maintenance 400mg daily (renally adjusted)	Placebo	ICU LOS, or initiation of empiric antifungals	The earlier of death, initiation of antifungal therapy, diagnosis of a fungal infection or 3 days after ICU discharge	Primary: occurrence of fungal infection during the surgical ICU stay or up to 3 days after ICU discharge.
Antifungal strategy: empiric								

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Knitsch 2015 [19] July 2010 – December 2011	Multicenter, randomized, double-blind, placebo-controlled trial	ICU patients ≥18 years of age requiring surgery for generalized or localized intra-abdominal infection. Patients were included within 48 hours (nosocomial acquired) or 72-120 hours (community acquired) of surgery provide they had an expected ICU LOS ≥48 hours	Pancreatitis, infected intraperitoneal dialysis, solid organ transplantation, severe liver disease, neutropenia, receipt of a systemic antifungal ≤ 14 days before study drug, documented IC at randomization, expected survival <48h	Micafungin IV 100mg daily	Placebo	Up to 6 weeks Stopped earlier if confirmed IC, improvement in surgical condition, alternative antifungal required, death	End of treatment (1-3 days after last dose of study medication)	Primary: Incidence of IC Exploratory: biomarker analysis
Schuster 2008 [17] 1995 - 2000	Multicenter, double-blind, placebo-controlled, randomiz	ICU patients ≥ 18 years with an ICU stay of at least 96 consecutive hours, APACHE II score within 24 hours of randomization of ≥ 16 or more, 4 days of	ALT, AST or bilirubin >5x ULN, ANC <1.0 x10^9 cells/L, AIDS or HIV with CD4 cell count < 0.5 x10^9 cells/L, bone marrow or organ transplantation on	Fluconazole 800mg IV daily	Placebo	2 weeks	4 weeks	Primary outcome (composite): at 4 days post-receipt of the last dose of the study drug: resolution of fever, absence of IFI, no discontinuation

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	ed controlled trial 1995-2000	fever, broad spectrum antibiotics for at least 4 of the preceding 6 days, CVC for at least 24 hours before the study	systemic immunosuppression, ICU admission due to burn injury, receipt of terfenadine, cisapride or any investigational drug <14 days before study enrollment, evidence of IFI <7 days before study entry, life expectancy of <48 hours, previous enrollment in the study.					because of toxicity, non-requirement for additional antifungal therapy Secondary outcomes: ICU and hospital LOS, death at 30 days
Timsit 2016 [20] July 2012 – February 2015	Multicenter, double-blind, placebo-controlled trial 2012 - 2015	Critically ill ICU patients with MV ≥ 5 days, ≥ 1 colonization site positive *Candida sp.*, ≥ 1 organ failure, previous treatment ≥ 4 days using broad-	ANC <500mm^3, previous bone marrow or solid organ transplantation, systemic immunosuppression other than corticosteroids at	Micafungin 100mg daily	Placebo	14 days	90 days	Primary: survival without proven IFI 28 days after randomization Secondary: new, proven IFI, survival at day 28 and day 90,

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		spectrum antibiotics, arterial line or CVC, 1 new finding of ICU-acquired sepsis.	doses <2mg/kg/day of prednisolone, antifungal treatment with an echinocandin for >1 day or with any antifungal agent for >72 hours during the week before inclusion.					organ failure, serum (1-3)-β-D-glucan level evolution, incidence of ventilator-associated bacterial pneumonia

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Table 5. Risk of bias assessment for studies included in Question 2

Study	Randomization	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Funding
Ables 2000	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns (private funding, sponsor's role is not clear)
Albert 2014	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns (private funding, sponsor's role is not clear)
Garbino 2002	Some concerns	Low risk	Some concerns	Low risk	Low risk	Some concerns (private funding, sponsor's role is not clear)
Ostrosky-Zeichner 2014	Some concerns	Low risk	Low risk	Low risk	Low risk	High risk (private funding, sponsor reviewed the results and contributed to the manuscript)
Pelz 2001	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Knitsch 2015	Some concerns	Some concerns	Some concerns	Low risk	Low risk	Some concerns (private funding, sponsor conducted all statistical analysis)

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Schuster 2008	Low risk	Low risk	Low risk	Low risk	Low risk	Some concerns (private funding, sponsor aided in the analysis but not in the interpretation of the data)
Timsit 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

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Figure 1. Flow diagram of literature selection and review for Question 1

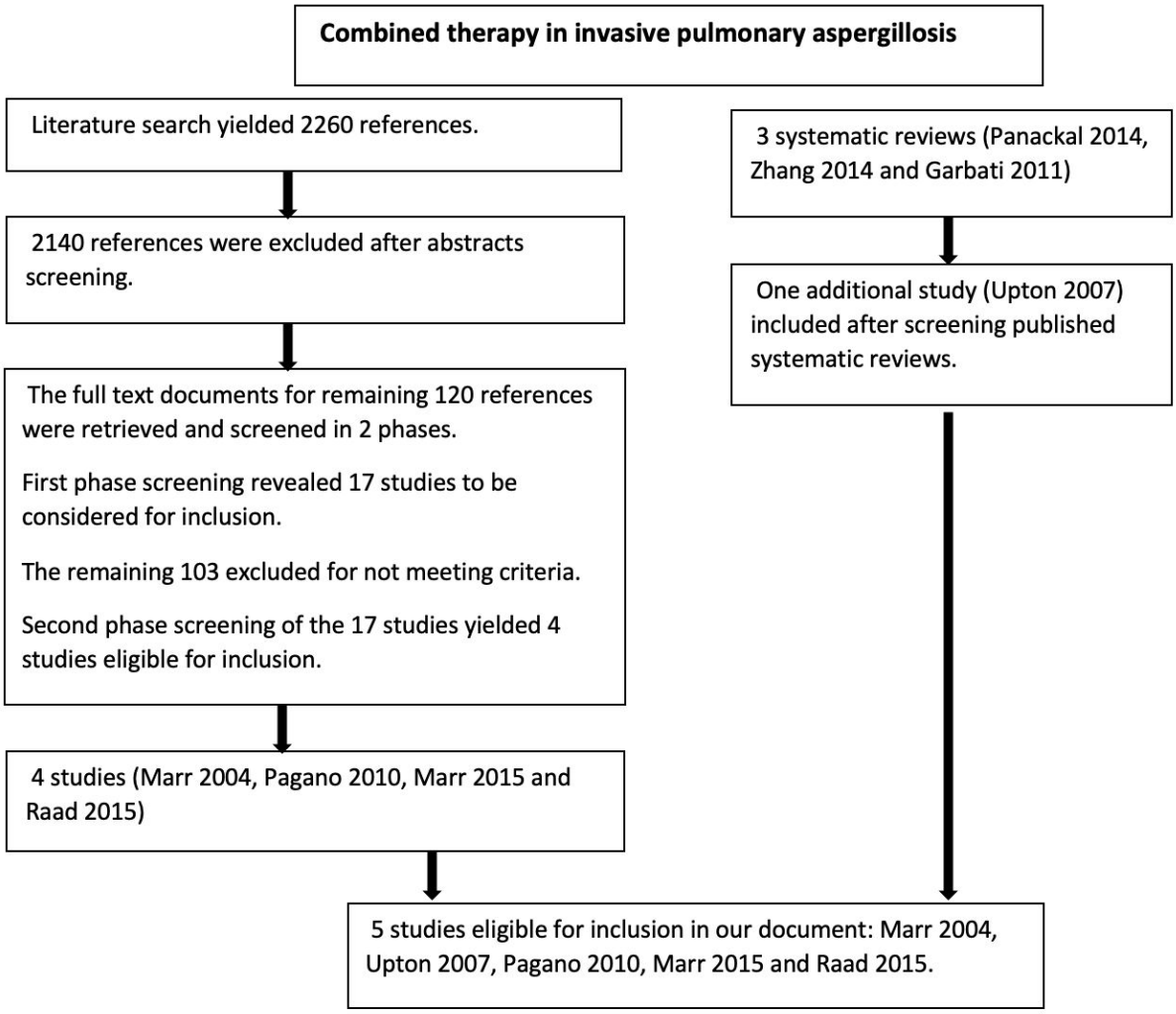

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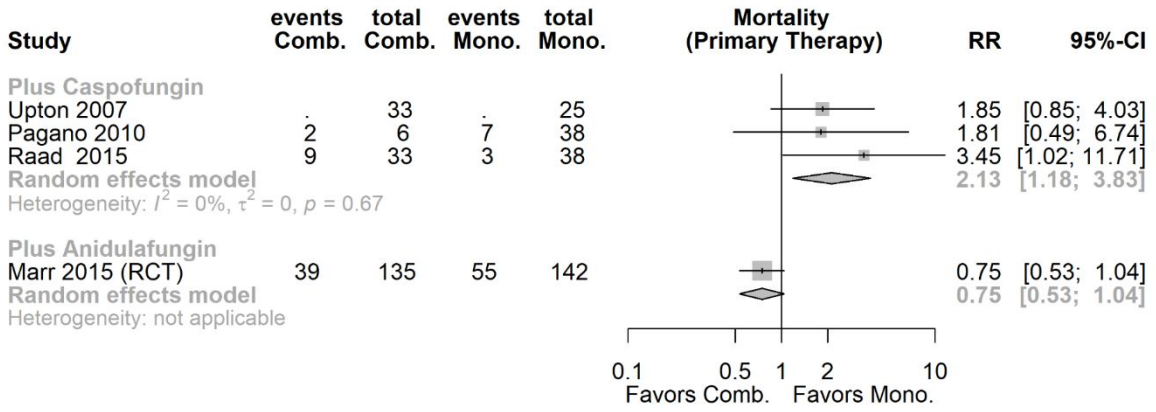
Figure 2. Meta-analysis of mortality following primary therapy in Question 1*



1

*Events numbers for study by Upton 2007 were not reported in the published article and therefore we used the calculated RR to perform the meta-analysis. Studies by Upton 2007 and Raad 2015 reported 3 months mortality and Pagano 2010 reported 4 months mortality. RCT by Marr 2015 reported 3 months mortality.

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Figure 3. Meta-analysis of mortality following salvage therapy in Question 1

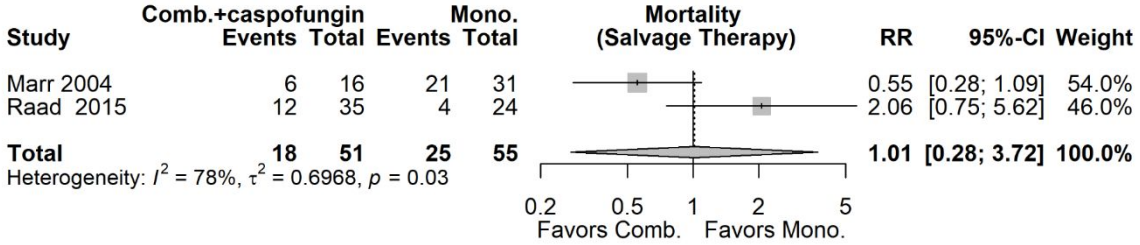

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Figure 4. Flow diagram of literature selection and review for Question 2

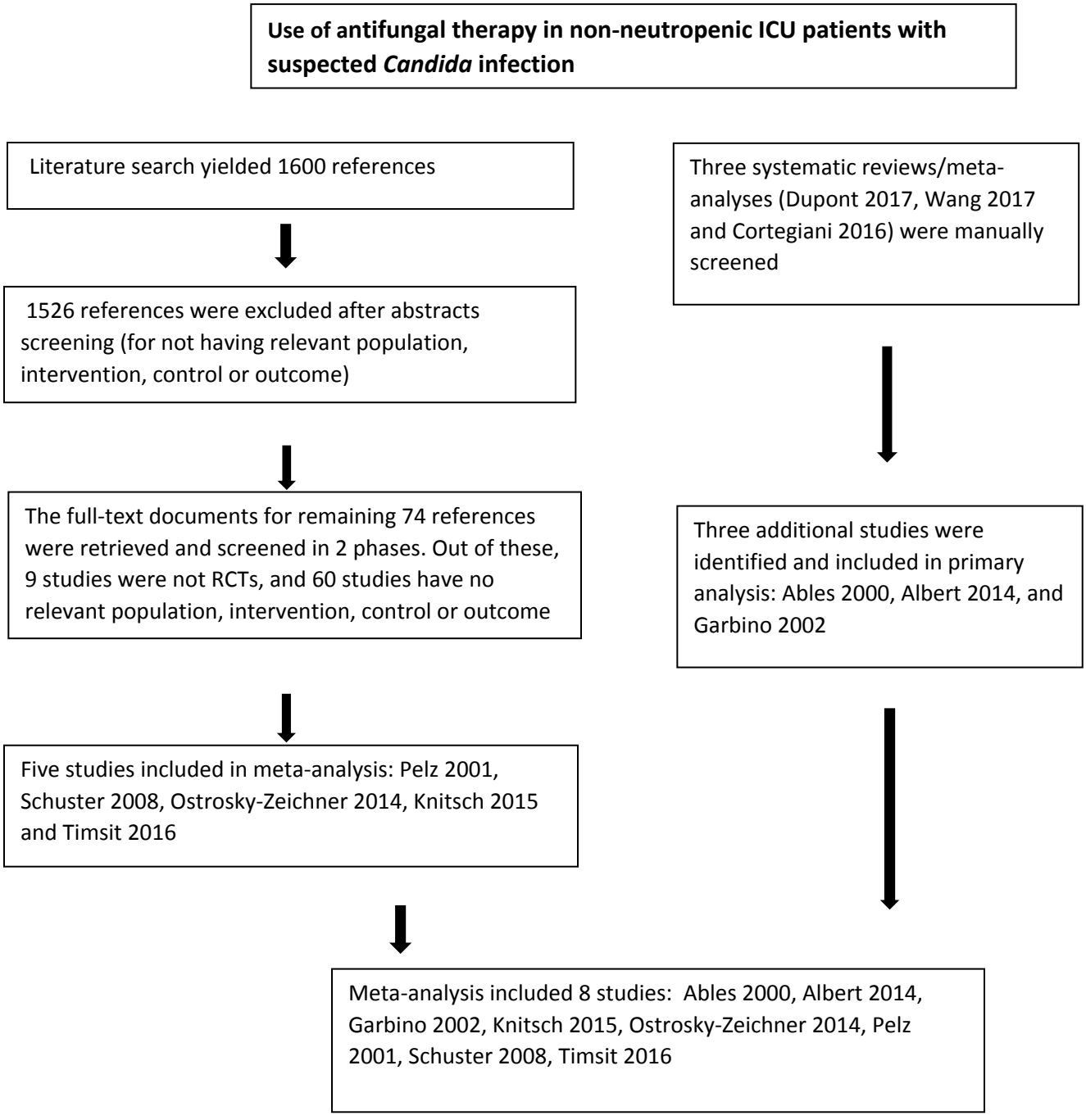

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Figure 5. Meta-analysis of mortality in Question 2 according to strategy of therapy

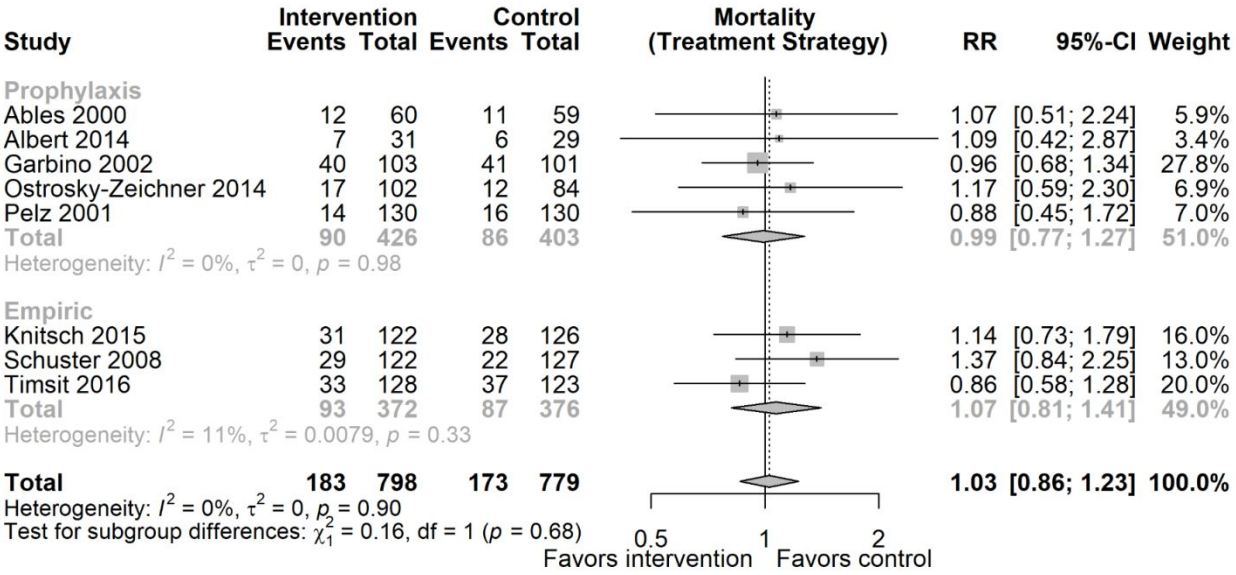

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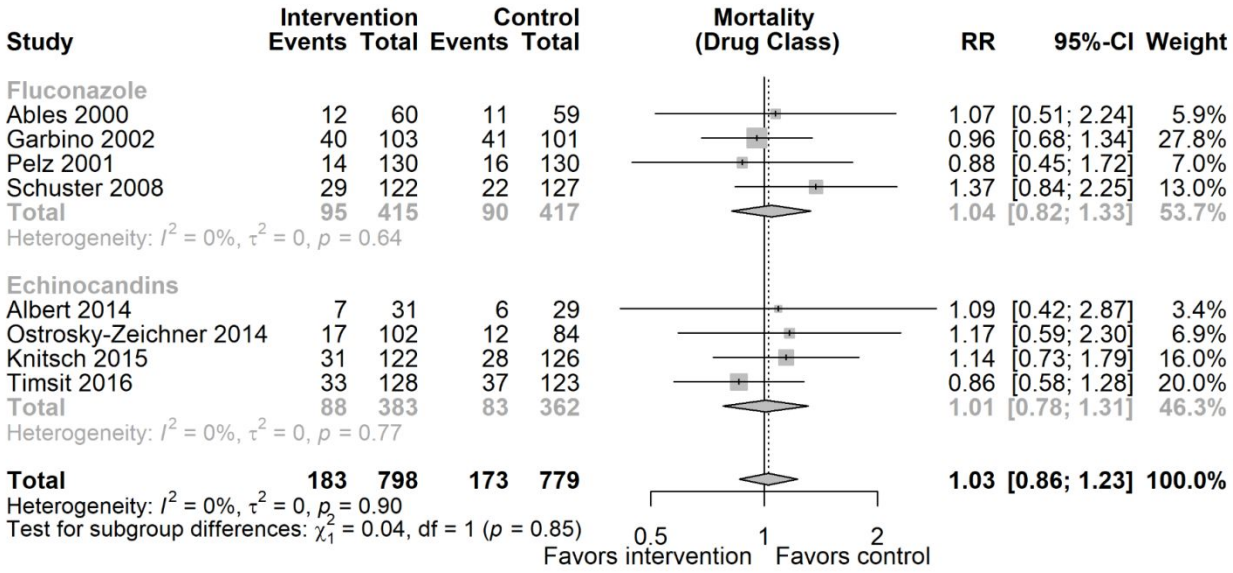
Figure 6. Meta-analysis of mortality in Question 2 according to drug class



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SUPPLEMENTARY MATERIALS

Supplementary Table 1S. result of second phase full texts screening in Question 1

Summary of full-texts screening process for the 17 studies found by our search		
Marr 2004	Include	Voriconazole plus caspofungin vs voriconazole for salvage therapy, retrospective study, outcome was survival and mortality
Singh 2006	Exclude	Voriconazole plus caspofungin vs amphotericin, as primary therapy in transplant recipients, prospective observational study
Kontoyiannis 2009	Exclude	Majority received amphotericin, and no outcome-of-interest
Maertens 2006	Exclude	Open-label, noncomparative, multicenter clinical trial, caspofungin plus triazole vs caspofungin plus amphotericin. comparison not of interest
Maertens 2010	Exclude	Prospective observational study, caspofungin plus azoles or polyenes vs caspofungin monotherapy, uncertain how many received azoles vs polyenes (out of 18 patients) in the combination therapy group
Pagano 2010	Include	Six patients received voriconazole plus caspofungin vs 38 patients received voriconazole, patient's cohort from large prospective registry of patients with AML
Lellek 2011	Exclude	Retrospective study, caspofungin plus posaconazole, non-comparative study, no outcome-of-interest
Steinbach 2012	Exclude	No direct comparison made for outcome-of-interest, reported overall survival rate for all different therapy regimens
Baddley 2013	Exclude	No direct outcome-of-interest, observational study involving large cohort of transplant patients, there were subgroup of 81 patients who received voriconazole plus caspofungin as initial combination therapy, however, mortality for that sub-group was not reported,
Racil 2013	Exclude	No outcome-of-interest reported, large retrospective cohort. Reported overall survival
Liu 2014	Exclude	Same dataset for Marr 2015, reported pharmacokinetic-pharmacodynamic for Marr 2015
Martín-Peña 2014	Exclude	Review article

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Raad 2015	Include	Retrospective study, voriconazole plus caspofungin vs voriconazole, 181 patients with haematological malignancies and IA who received primary or salvage therapy
Marr 2015 (same as Marr 2012	Include	Randomized, double-blind, placebo-controlled multicenter trial. Voriconazole plus anidulafungin vs voriconazole monotherapy, primary outcome was 6-week mortality; secondary outcomes included 12-week mortality
Duma 2017	Exclude	This is a poster. Only 21 patients received intervention-on-interest.
Lee 2019	Exclude	This is a post hoc analysis of the Korean sub-population of Marr 2015. (same data set for Marr 2015)
Zhang 2020	Exclude	No outcome of interest, this is retrospective, voriconazole plus echinocandins for IPA in mechanical ventilation patients

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Supplementary Table 2S. Result of second phase full texts screening in Question 2

Study ID	Include/exclude	Reason for exclusion
Pelz-2001	Include	
Schuster-2008	Include	
Micek-2014	Exclude	Prospective case-series
Ostrosky-Zeichner-2014	Include	
Bruyere-2014	Exclude	Prospective cohort study
Zein-2014	Exclude	Retrospective cohort study
Bailly-2015	Exclude	Prospective cohort study
Knitsch-2015	Include	
Timsit-2016	Include	
Leroy-2016	Exclude	Retrospective study
Cui-2017 International Journal	Exclude	Retrospective study
Cui 2017 BMC	Exclude	Retrospective study
Trifi 2019	Exclude	Retrospective
Sunny 2021	Exclude	Non-randomized, prospective cohort study

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Supplementary Table 3S. Results of primary outcome for studies included in Question 2

Study	Death # in intervention	Total # in intervention	Death # in control	Total # in control	Intervention
Antifungal strategy: Prophylaxis					
Ables 2000	12	60	11	59	Fluconazole 800mg loading/400 IV, PO, enteral daily
Albert 2014	7	31	6	29	Anidulafungin 200/then 100mg IV daily
Garbino 2002	40	103	41	101	Fluconazole 100mg IV and PNV syrup
Ostrosky-Zeichner 2014	24	117	16	102	Caspofungin 70mg Load/50mg IV daily
Pelz 2001	14	130	16	130	Fluconazole PO 800mg Loading/400mg daily
Total	97	441	90	421	
Antifungal strategy: empiric					
Knitsch 2015	31	122	28	126	Micafungin 100mg IV daily
Schuster 2008	29	122	22	127	Fluconazole 800mg IV daily
Timsit 2016	33	128	37	123	Micafungin 100mg IV daily
Total	93	372	87	376	
Overall total	490	813	177	797	

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