THERAPEUTIC ADVANCES in
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Original Research

The top 10 papers on the treatment of invasive fungal infections, 2018–2023

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Abstract

Background: Invasive fungal infections are responsible for a large number of infections in hospitalized patients annually and are responsible for high morbidity and mortality. Familiarity with novel agents or strategies in this area can be challenging.

Objectives: To identify the top 10 manuscripts on the treatment of invasive fungal infections from 2018 to 2023.

Design: Modified Delphi consensus-building technique.

Methods: A three-stage consensus-building approach was used comprised of (1) identifying relevant articles; (2) voting by a panel of experts to establish consensus on the importance of these articles; and (3) finalizing the list of top articles by a small group. Members of the Southeastern Research Group Endeavor network served as content experts. Publications from 2018 to 2023 were evaluated if articles met the following inclusion criteria: (1) published between 2018 and 2023, (2) contained content related to fungal infections, and (3) included an actionable intervention.

Results: A total of 6518 potential publications were assessed. After applying inclusion and exclusion criteria, 82 articles were reviewed. The top 10 publications related to invasive fungal infections, selected by a panel of experts, are summarized in this manuscript and include publications related to the treatment of invasive aspergillosis, candidiasis, and cryptococcosis.

Conclusion: This article highlights the selected publications and may serve as a key resource for teaching and training. Clinicians may also employ these reported interventions to identify new opportunities to optimize antifungal therapeutic strategies within one's institution.

Plain language summary

Top papers in antifungal literature 2018-2023

Fungi live in the environment and in the intestinal tract of humans, and infections caused by fungi can be deadly. Knowing what has been studied in the medical literature can give medical personnel information to best treat these infections. This paper sought to use scientific methods to review and choose the top 10 papers from 2018-2023 that make a difference in treatment of these potentially deadly fungal infections. Infections covered include those caused by yeasts (*Candida* and *Cryptococcus*) and molds (*Aspergillus*). Drugs covered include azole antifungals (isavuconazole, voriconazole, posaconazole, and fluconazole), echinocandins (caspofungin, micafungin), amphotericin, and new drugs (fosmanogepix and rezafungin). Strategies evaluated to improve patient care include dosing changes, empiric therapy choices, and therapeutic drug monitoring. This paper might help medical personnel better manage fungal infections.

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Introduction

In an epidemiologic study from 2014, invasive candidal infections were the fourth-leading cause of bloodstream infections in hospitalized patients.[1,2] Associated morbidity with these infections is high, with prolonged hospitalizations, increased costs of therapy, and some degree of adverse effects associated with most antifungal agents.[3,4] Although there are therapies currently available for invasive mold infections, mortality is high and drug-associated interactions and adverse effects often limit these therapeutic options. Mortality rates associated with invasive fungal infections range from 30% for candidiasis to 60% for invasive mold infections.[3,4]

Ten years later, concerns for invasive fungal infections have only risen as epidemiology shifts to more resistant fungal pathogens.[3–5] Historically, invasive Candida infections were primarily caused by the very treatable *Candida albicans*, but several studies have reported an increasing prevalence of *C. glabrata*, *C. auris*, and other more resistant strains.[1,5] Rare molds have also become increasingly problematic as causes of invasive fungal infections, especially in highly immunocompromized patients.[6] These trends are well documented, and several clinical practice guidelines are available for the management of invasive fungal infections.[7–15] It is also important to note that several newer antifungal agents have been studied in recent years.

The Southeastern Research Group Endeavor (SERGE-45) network is an interprofessional research group composed of infectious-diseases-trained clinicians. SERGE-45 is one of several networks supporting mentored, collaborative research in infectious diseases and antimicrobial stewardship, and it has methodically selected the top antimicrobial stewardship articles for the previous 7 years.[16–22] This manuscript reports the top fungal infection intervention publications from 2018 to 2023 identified from a modified Delphi process.

Methods

Using a modified Delphi technique,[23] a three-stage consensus-building approach was used comprised of (1) identifying relevant articles; (2) voting by a panel of experts to establish consensus of the importance of these articles; and (3) finalizing the list of top articles by a small group. Members of the SERGE-45 network served as content experts.

A literature search was conducted through PubMed and Google Scholar using the term "invasive fungal infections." Publications were evaluated for inclusion if they met the following inclusion criteria: (1) published between 2018 and 2023, (2) content related to fungal infections, and (3) included an intervention. An intervention was defined as a strategy or an initiative that was implemented in practice and resulted in measurable outcomes. Articles had to be performed in human participants and written in English to be considered. Clinical practice guidelines, official statements, review articles, case studies, and articles without an actionable intervention were excluded.

The literature search revealed 6518 potential publications (Figure 1). After applying inclusion and exclusion criteria, 82 articles were identified. Abstracts were screened to ensure that all relevant articles were considered. Two additional articles were identified through a Google Scholar search and reference reviews and those meeting criteria not previously identified were also included for consideration. A total of 80 article citations and abstract links were distributed to members of the SERGE-45 network for ranking via REDCap survey of up to the top 15 articles based on contribution to the literature and relevance to clinical practice.[24] Follow-up email reminders were sent to encourage participation in the voting process. Of note, no conflict-of-interest disclosure was required of participating voters.

Article ranks from the group were averaged, and the top scoring articles were reviewed by K. R. S., H. M. A., and K. E. B. This group discussed rankings and settled disputes on article rankings based on inclusion criteria and diversity of topics included and a final consensus on the top 10

articles was established. Figure 1 is a flowsheet of the article selection process, and Table 1 provides a summary of the selected articles. Included articles are presented in the discussion grouped by subject area and should not be considered to be ranked according to placement.

Results

From the original 82 articles that met inclusion criteria, 10 articles were selected by the expert panel as the top papers describing treatment of invasive fungal infections from 2018 to 2023. Those selected papers are summarized in Table 1 and below. These are not in ranked order but have been organized by infection type for ease of review.

Aspergillus *infections*

Posaconazole versus voriconazole. Voriconazole is generally the preferred treatment option for invasive aspergillosis (IA), but the drug's usefulness can be limited by drug interactions, inter-subject pharmacokinetic variability, and adverse effects.[8] This non-inferiority trial was designed to see how posaconazole compared to voriconazole in terms of efficacy and safety in the primary treatment of IA.[25] Patients were classified according to the EORTC-Mycoses Study Group definitions of proven, probable, or possible definition of IA.[26] After exclusions and randomization, 288 and 287 patients received posaconazole and voriconazole, respectively, in the intent-to-treat (ITT) protocol. The primary efficacy endpoint was all-cause mortality up to day 42 of study drug treatment (ITT). Intravenous or oral dosing was permitted. The treatment dosages were posaconazole 300 mg twice daily for 1 day, then once daily, and voriconazole 6 mg/kg (IV) or 300 mg (oral) twice daily for 1 day, then 4 mg/kg (IV) or 200 mg (oral) twice daily.

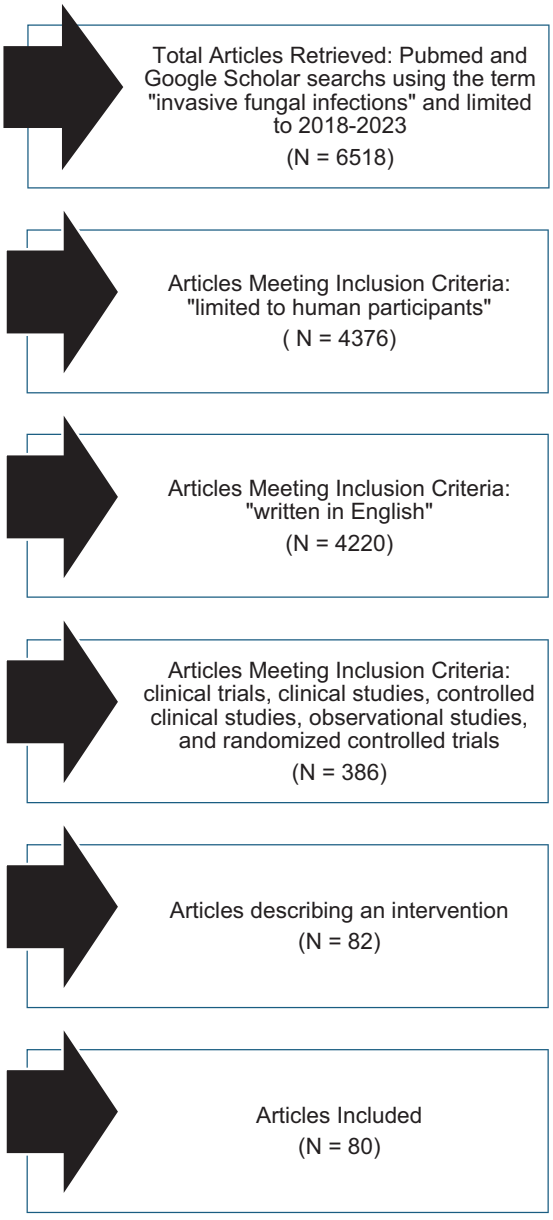

Figure 1. Study selection flow diagram.

The primary outcome of all-cause mortality by day 42 exhibited non-inferiority for posaconazole and lower numerical deaths by day 42 (15% vs 21%) [–5.3%, 95% CI –11.6 to 1.0]. By day 84, death rates were more similar (28% vs 31%) [−2.5%, 95% CI −9.9 to 4.9]. The median time to switch to oral agents was 9 days in each group. Treatment-related adverse events were more common in the voriconazole arm 40% (vs 30% in the posaconazole arm, [−10.2%, 95% CI –17.9 to –2.4]), with eye disorders (e.g., visual field changes) displaying the largest difference.

The most significant limitation of the study was that TDM was not permitted during the study, but a pharmacokinetic analysis was performed on plasma samples after completion of the study. The plasma drug exposure was not reported to have significant associations in terms of efficacy or safety for either drug.[25]

Table 1. Top 10 papers in antifungal literature 2018–2023.

Study citation	Study design	Study location	Intervention summary	Primary and key secondary outcomes
Maertens JA, et al. *Lancet* 2021; 397: 499–509.[25]	Phase III, Multicenter, randomized, prospective, double-blind, double dummy, controlled, non-inferiority trial Used independent adjudication committee Non-inferiority margin set at 10%	Belgium (3 sites), Brazil (1 site), Canada (1 site), China (8 sites), Colombia (3 sites), France (1 site), Germany (3 sites), Hungary (1 site), Israel (3 sites), Italy (3 sites), Mexico (2 sites), Peru (1 site), Russia (3 sites), Singapore (1 site), South Korea (3 sites), Spain (2 sites), Taiwan (1 site), Turkey (3 sites), USA (4 sites)	Posaconazole versus voriconazole for primary treatment of invasive aspergillosis	Primary: • All-cause mortality up to day 42 of study drug treatment in the intent-to-treat population ○ Posaconazole 15% vs voriconazole 21% (–5.3% [95% CI: –11.6 to 1.0]) Secondary: • Global clinical response ○ at week 6: posaconazole 45% vs voriconazole 46% ○ at week 12: posaconazole 42% vs voriconazole 46% ○ Treatment-related adverse events ○ posaconazole 30% vs voriconazole 40% (–10.2% [95% CI: –17.9 to –2.4])
Veringa A, et al. *Int J Antimicrob Agents* 2023; 61: 106711.[28]	Multicenter, prospective, cluster randomized, crossover clinical trial	Netherlands (9 sites) Germany (1 site)	Compared therapeutic drug monitoring (TDM) guided voriconazole dose adjustments with standard treatment for invasive aspergillus	Primary (composite): response to treatment voriconazole treatment • TDM group: 50.9% success • Non-TDM group: 55.0% success discontinuation due to an adverse drug reaction related to voriconazole • 17 patients in TDM group • 18 patients in non-TDM group Secondary: overall mortality 28 days after start of voriconazole treatment • TDM group: 12.0% • Non-TDM group: 10.3% success
Kullberg B, et al. *Clin Infect Dis* 2019; 68: 1981–1989.[29]	Phase III, randomized, double-blind, multinational clinical trial Non-inferiority margin was set at 15%	116 sites in 25 nations including: United States Argentina Australia Belgium Brazil Canada Chile China France Germany Hungary India Israel Italy Lebanon Malaysia Mexico New Zealand Philippines Russian Federation Singapore South Africa Spain Switzerland Thailand	Compared isavuconazole (IV) to caspofungin (IV) for the primary treatment of candidemia or invasive candidiasis	Primary: overall response at the EOIVT • Isavuconazole 60.3% vs caspofungin 71.1% (adjusted diff –10.8%; 95% CI [–19.9 to –1.8]) Secondary: • Overall response at 2 weeks after the end of treatment: isavuconazole 54.8% vs caspofungin 57.2% (–2.7 (–12.2 to 6.8)) • All-cause mortality, day 14: isavuconazole 14.6% vs caspofungin 12.4% (2.5 (–3.8 to 8.9)) • All-cause mortality, day 56: isavuconazole 30.7% vs caspofungin 29.9% (1.4 (–7.1 to 10.0)) • Safety: study-related treatment-emergent adverse effects: isavuconazole 35.5% vs caspofungin 32.3%

(Continued)

Table 1. (Continued)

Study citation	Study design	Study location	Intervention summary	Primary and key secondary outcomes
Garnacho-Montero, et al. *J Crit Care Med* 2018; 46: 384–393.[31]	Retrospective, observational multicenter study of adults with *Candida* bloodstream infection in an ICU	Spain (9 ICUs)	Evaluated initial therapy with fluconazole vs echinocandin for the treatment of candidemia	Primary: all-cause 30-day hospital mortality • Fluconazole 37.4% vs echinocandin 31.9% ($p = 0.380$) Secondary: • 90-day mortality: fluconazole 50.4% vs echinocandin 42.9% ($p = 0.245$) • Recurrence: 4 fluconazole, 1 echinocandin • Propensity-score adjusted analysis: ○ 30-day mortality: echinocandin use protective (OR 0.32 [95% CI 0.16–0.66]), $p = 0.002$) ○ 90-day mortality: echinocandin use protective (OR 0.50 [0.27–0.93], $p = 0.014$)
Benjamin DK Jr, et al. *Pediatr Infect Dis J* 2018; 37: 992–998.[32]	Phase III, randomized, double-blind, multicenter, parallel-group, noninferiority study	United States Brazil Bulgaria Canada Colombia Greece Hungary Israel Philippines Romania Turkey Ukraine	Micafungin (MCA) (10 mg/kg/day) versus Amphotericin B Deoxycholate (AmB-D) (1 mg/kg/day) for a minimum of 21 days and maximum of 28 or 42 days	Primary: Fungal-free survival • 60% in MCA-group infants and 70% in AmB-D group Secondary: • Positive clinical response at the end of the study and 1 week after the last dose of study drug, 61% in MCA group and 70% in AmB-D group • Eradication achieved in 55% MCA group and 80% in AmB-D group • Safety: 90% of MCA- and AmB-D treated infants experienced ⩾1 TEAE
Lin KY, et al. *J Infect* 2018; 77: 242–248.[33]	Prospective, observational study, assessing patients with persistent candidemia treated with echinocandins vs fluconazole	Taiwan	Time-dependent analysis evaluating the impact of definitive therapy (echinocandins versus fluconazole) on mycological eradication and overall survival at 30 days from the index date	Primary: Mycological Eradication and overall survival • 67.3% for echinocandins and 55.6% for fluconazole
Vazquez J, et al. *Antimicrob Agents Chemother* 2023; 68: e0141922.[35]	Multicenter, open-label, single-arm study	South Africa (four sites)	Evaluate the safety and efficacy of fosamanogepix (IV then swapped to oral) for the treatment of candidemia and/or invasive candidiasis cause by *Candida auris*	Primary: • Treatment success[a] at the end of the study treatment (EOST): 8 (88.9%) Secondary: • All-cause mortality through Day 30: 1 (11.1) • Eradication of BSI at EOST: 6 (66.7%) • No study-drug related treatment-emergent adverse effects

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Table 1. (Continued)

Study citation	Study design	Study location	Intervention summary	Primary and key secondary outcomes
Thompson G. et al. *Lancet* 2023; 401: 49–59.[36]	Phase III, Multicenter, double-blind, double-dummy, controlled, randomized non-inferiority trial Utilized independent blinded data review committee Non-inferiority margin set at 20%	USA, Thailand, Spain, Greece, Australia, Belgium, Korea, China, Bulgaria, France, Israel, Italy, Taiwan, Singapore, Colombia	Rezafungin vs caspofungin for treatment of candidemia and invasive candidiasis (ReSTORE)	Primary: • Estimates of all-cause mortality were 24% in the rezafungin arm and 21% in the caspofungin arm (2.4% [95% CI: −9.7 to 14.4]). • The 14 day global cure rates were 59% for rezafungin vs 61% caspofungin (−1.1% [95% CI: −14.9% to 12.7%]). Secondary: • Global cure o At day 5: Rezafungin 56% vs caspofungin 52% o At day 14: Rezafungin 59% vs caspofungin 61% • Mycologic eradication o At day 5: rezafungin 69% vs caspofungin 62% • Study drug-related adverse effects o Rezafungin 16% vs caspofungin 9%
Muilwijk et al. *Antimicrob Agents Chemother* 2020; 64: e00984-20.[39]	Open-label, multicenter, observational pharmacokinetic study in critically ill patients with various degrees of renal function	Netherlands	Blood concentration samples of fluconazole from critically ill patients were evaluated at various timepoints on day 3 and 7 of therapy as well as daily troughs Data were then incorporated into Monte Carlo simulations evaluating various daily doses (100, 200, 400, 800 mg daily) and renal function (120, 60, 20 mL/min and CRRT). A target fAUC/MIC of 100 was evaluated for these regimens	• Among 19 evaluable patients, 11 patients had two consecutive pharmacokinetic curves • Doses of 100 mg and 200 mg daily did not achieve target exposure for any degree of renal function • The 400 mg daily dose was adequate only for patients with estimated GFR between 20 mL/min and 60 mL/min • Doses of 600–800 mg daily were required for estimated GFR > 90 mL/min or CRRT

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Table 1. (Continued)

Study citation	Study design	Study location	Intervention summary	Primary and key secondary outcomes
Jarvis JN, et al. *N Engl J Med* 2022; 386: 1109–1120.[40]	Phase III, open-label, randomized, controlled non-inferiority trial in five countries	Botswana (1 site) Malawi (2 sites) South Africa (2 sites) Uganda (2 sites) Zimbabwe (1 site)	Single dose (10 mg/kg) of liposomal amphotericin B plus 14 days of flucytosine and fluconazole versus amphotericin B deoxycholate (1 mg/kg/day) plus flucytosine for 7 days, followed by fluconazole on days 8 through 14 (control group)	Primary: all-cause mortality at 10 weeks • 24.8% in liposomal amphotericin B group and 28.7% in the control group Secondary: rate of fungal clearance from CSF over 14 days • –0.40 log10 CFU/mL in liposomal amphotericin B group and –0.42 log10 CFU/mL in the control group

[a]Treatment success, survival and clearance of *C. auris* from blood/tissue cultures without additional antifungals.
AmB-D, amphotericin B deoxycholate; AUC, area under the curve; BSI, bloodstream infection; CFU, colony forming units; CI, confidence interval; CRRT, continuous renal replacement therapy; CSF, cerebrospinal fluid; EOIVT, end of intravenous therapy; EOST, end of study treatment; GFR, glomerular filtration rate; ICU, intensive care unit; MCA, micafungin; MIC, minimum inhibitory concentration; TDM, therapeutic drug monitoring.

The newer azole, isavuconazole, was also found to be non-inferior to voriconazole in the treatment of invasive mold infections which included IA.[27] In this phase III, multicenter SECURE trial, mortality (adjusted treatment difference −1% [CI −7.8 to 5.7]) and treatment-emergency adverse effects (96% vs 98%) were similar between isavuconazole and voriconazole, respectively. Posaconazole and isavuconazole now provide alternatives to voriconazole that may offer less interaction or adverse effect potential.

Therapeutic drug monitoring-guided treatment versus standard dosing of voriconazole. Conflicting data exist regarding whether TDM-guided treatment is superior to standard dosing of voriconazole for patients with IA. The article reports on a multicenter clinical trial assessing TDM-guided treatment with standard dosing of voriconazole for IA in patients with hematological malignancies or an allogenic stem cell transplant.[28] Conducted by the Voriconazole ZonMw Study Group, the trial employed a prospective, cluster-randomized, crossover design across multiple medical centers.[28]

Patients meeting specific criteria, including age and diagnosis of IA, were enrolled from Dutch and German centers. Exclusions were made for patients with hypersensitivity or allergies to voriconazole. Diagnostic criteria for IA followed established guidelines, ensuring consistency across participating centers. The primary outcome of the study was a composite endpoint that assessed both treatment response and adverse drug reactions between patients receiving TDM-guided voriconazole dosing and those receiving standard dosing.

A total of 189 patients were enrolled (74 in the non-TDM group and 68 in the TDM group).[28] Treatment failure was seen in 45.0% of non-TDM patients and 49.1% of TDM patients ($p = 0.666$). Adverse events with voriconazole therapy were similar, occurring in 25% of patients receiving TDM-guided dosing and 24% of patients receiving standard dosing ($p = 0.658$). Pharmacokinetic analyses revealed that patients receiving TDM-guided dosing had more optimal (e.g., higher percentage of concentrations in the therapeutic range) and consistent plasma concentrations of voriconazole compared to those receiving standard dosing. Specifically, a higher percentage in the TDM group had median voriconazole troughs between 1 and 6 mg/L (over 80%) as compared to the non-TDM group

(<70%). While there were limitations to this study, including the ability of attending physicians to de-blind patients, small sample size, and difficulty in assessing outpatient response due to different radiological examinations, these findings suggest that TDM-guided treatment did not significantly improve outcomes compared to standard dosing in this patient population.

Candida *infections*

ACTIVE: Isavuconazole versus caspofungin. Candidemia is a severe bloodstream infection responsible for many invasive fungal infections in hospitalized patients. Isavuconazole is a triazole antifungal agent with broad-spectrum activity against various fungal species, while caspofungin is an echinocandin antifungal used as first-line empiric therapy for invasive *Candida* infections. The ACTIVE trial was a phase III, randomized, double-blind, multinational clinical trial that evaluated the efficacy and safety of isavuconazole compared to caspofungin in treating candidemia and other invasive *Candida* infections.[29] A total of 463 patients were enrolled across multiple sites and randomly assigned to receive either isavuconazole or caspofungin. The primary endpoint was the overall success rate at day 42, which was defined as a clinical cure without evidence of microbiological failure. Secondary endpoints included survival at day 42, clinical and microbiological responses at different time points and safety outcomes. The results showed that isavuconazole was inferior to caspofungin in achieving overall success (60.3% vs 71.1%, respectively, adjusted difference −10.8%; 95% CI (−19.9 to −1.8)) at EOIVT, defined as complete or partial clinical response AND mycological eradication or presumed eradication as assessed by the data-review committee.[29] It did, however, demonstrate similar efficacy to caspofungin in terms of mortality, overall response at the end of therapy, and microbiological response. Both treatments were generally well-tolerated, with similar rates of adverse events and serious adverse events. Limitations of this trial include exclusion of pediatric populations, small numbers of patients with neutropenia, limited number with resistant *Candida* species (e.g., *C. glabrata* and *C. krusei*), limiting generalizability to these populations based on the results of this trial. Caution should be advised when using isavuconazole for the treatment of invasive candidiasis.

Antifungal strategy for reducing mortality in critically ill patients. Invasive candidiasis has long been associated with high morbidity and mortality, and this has been particularly true in patients who are critically ill.[30] The Infectious Diseases Society of America (IDSA) invasive candidiasis guidelines suggest an echinocandin as first-line therapy, but limited data are available comparing these to azole antifungals as empiric therapy.[9] In a retrospective, observational multicenter study, initial antifungal therapy with either fluconazole or an echinocandin was evaluated to determine the impact on mortality in a critically ill population.[31] A total of 234 patients (115 fluconazole and 119 echinocandin) were included in the evaluation.[31] The primary outcome in this study was all-cause 30-day hospital mortality, and secondary outcomes included 90-day mortality and the effects of de-escalation on outcomes. Patients receiving fluconazole tended to be older (mean age 65 (52–70) vs 58 (48–69), $p=0.022$) and categorized as less severe (Sequential Organ Failure Assessment (SOFA) score 6 (3–10) vs 8 (4–12), $p=0.054$; Acute Physiology and Chronic Health Evaluation II (APACHE II) score 19 (14–22) vs 21 (16–26), $p=0.012$) than those receiving echinocandins. Of the 119 patients initially receiving an echinocandin, 44 (37%) were de-escalated to fluconazole therapy at median day 5 (3–7). All-cause 30-day hospital mortality was not significantly different between groups in the evaluated patients (fluconazole 37.4% vs echinocandin 31.9%, $p=0.380$), but echinocandin use was a protective factor for 30-day mortality identified in a propensity-score adjusted multivariable analysis (OR 0.32 [95% CI 0.16–0.66], $p=0.002$). Limitations of this study include its retrospective, observational design, small sample size, limited dosing information, and lack of generalizability to populations with neutropenia or hematologic cancers. In addition, patients in the echinoccandin group tended to require higher acuity of care (as defined by APACHE and SOFA scores, septic shock, and mechanical ventilation). Although propensity score matching was used, this discrepancy may indicate that effects of echinocandins may be higher than observed. These results suggest that an echinocandin may be preferred over fluconazole as initial empiric therapy in critically ill patients with suspected invasive candidiasis.[31]

A phase III study of micafungin versus amphotericin B deoxycholate in infants with invasive candidiasis. Invasive candidiasis poses a significant

threat to infants, particularly those in neonatal intensive care units. Traditionally, amphotericin B deoxycholate (AmB-D), has been used, despite its associated adverse effects. Micafungin (MCA) has emerged as a promising alternative due to its efficacy against *Candida* species and favorable safety profile. Research focused on its use in infants has been limited. This phase III study aimed to address this gap by comparing micafungin to AmB-D in infants with invasive candidiasis.[32]

Twenty infants were treated with MCA, and 10 were treated with AmB-D.[32] Infants >2–120 days of life were randomized 2:1 to MCA 10 mg/kg/day or AmB-D 1 mg/kg per day. The primary efficacy outcome was fungal-free survival 1 week after the last dose. The main efficacy measure of fungal-free survival (FFS) at 1-week post-last dose demonstrated that 12 infants (60%; 95% CI: 36%–81%) in the MCA group and seven infants (70%; 95% CI: 35%–93%) in the AmB-D group achieved FFS. Additionally, five infants (25%) in the MCA group and two infants (20%) in the AmB-D group were alive but not fungal-free at this point. Among infants with clinical signs of fungal infection at baseline, 11 infants (61%; 95% CI: 36%–83%) in the MCA group and seven infants (70%; 95% CI: 35%–93%) in the AmB-D group had a positive clinical response at the end of the study. Eleven (55%) and eight (80%) infants in the MCA and AmB-D groups, respectively, achieved eradication at the end of the study and 1 week after the last dose. Two infants (10%) in the MCA group and 2 (20%) in the AmB-D group experienced persistent fungal infections. Emergent fungal infection was observed in 1 (5%) MCA-treated infant, while recurrent infection with the same species occurred in 1 (10%) AmB-D-treated infant. Pharmacokinetic analysis showed that MCA exposure exceeded the target exposure of 170 μg h/mL. Adverse events were similar between groups, with anemia and thrombocytopenia being the most common.[32] Limitations of this study include early termination and a small sample size. In this patient population, to avoid potential adverse effects of amphotericin, micafungin may be considered.

Effectiveness of echinocandins versus fluconazole for the treatment of persistent candidemia: a time-dependent analysis. Current guidelines recommend echinocandins as the first-line therapy for candidemia. Direct comparisons of echinocandins versus fluconazole for persistent candidemia are limited. This prospective observational study focused on hospitalized patients aged 18 years and above diagnosed with candidemia.[33] The study spanned from March 1, 2011, to February 29, 2016, and included patients with persistent candidemia for at least 5 days. Patients with multiple strains of *Candida* isolated, those receiving non-intravenous fluconazole, or those treated as outpatients were excluded. The primary outcome was to compare the effectiveness in terms of mycological eradication and overall survival 30 days from the index date.

A total of 196 patients were included, 64 received echinocandins and 132 received fluconazole. The rate of 30-day mycological eradication was 67.3%, with a median time to eradication of 8 days. The echinocandin group had a higher proportion of infections due to fluconazole non-susceptible *Candida* isolates and *C. glabrata*, but a lower proportion of *C. parapsilosis*. When persistent candidemia was defined as the isolation of the same Candida species from blood cultures for at least 2 days, the analysis revealed that receiving an echinocandin was independently associated with a 56% higher likelihood of achieving 30-day mycological eradication (adjusted hazard ratio (AHR) 1.56; 95% confidence interval (CI) 1.16–2.08). This was also observed when persistent candidemia was defined for 3, 4, and 6 days, with adjusted hazard ratios ranging from 1.44 to 1.61. Additionally, in a sensitivity analysis excluding patients without a negative blood culture follow-up due to death or terminal conditions, receiving an echinocandin still demonstrated a positive impact on mycological eradication, with an adjusted hazard ratio of 1.46 (95% CI 1.02–2.11).[33] Limitations include single-center design and absence of daily follow-up blood cultures. In this study, echinocandins demonstrated a higher likelihood of 30-day eradication. Therefore, they should be considered over fluconazole for persistent candidemia.

Fosmanogepix: A novel antifungal for C. auris*?* Currently, there are limited treatment options for infections caused by *C. auris* that are resistant to the historically available antifungal agents. Fosmanogepix is a first-in-class GWT1 inhibitor that boasts a broad spectrum of activity against *Candida*, *Aspergillus, Fusarium, Scedosporium, Cladosporium*, and other fungal pathogens.[34] In a

phase II, multi-center, single-arm study, fosmanogepix safety and efficacy was evaluated in the treatment of *C. auris*.[35] Adult patients with established diagnoses of either invasive candidiasis or candidemia due to *C. auris* and who had limited treatment options with currently available therapy were included. Nine patients received a loading dose of fosmanogepix 1000 mg intravenously (IV), followed by 600 mg IV daily for 19 ± 5.83 days. Reported minimum inhibitory concentrations were low with fosmanogepix across the board, and 8 of 9 (89%) had treatment success at the EOST. See Table 1.[35] This study is limited by a small population and lack of worldwide generalizability but should fosmanogepix proceed through to phase III trials and secure FDA approval, it may present a valuable addition to the antifungal armamentarium.

ReSTORE: Rezafungin versus caspofungin. This phase III study assessed the utility of the new long-acting echinocandin, rezafungin, as an alternative to caspofungin in the treatment of candidemia and invasive candidiasis.[36] This study complements the findings of the phase II STRIVE trial.[37]

Patients were randomized into two arms. One was intravenous rezafungin dosed at 400 mg on day 1, followed by a 200 mg dose on day 8. Additional doses of 200 mg could be requested on days 15 and 22 if antifungal treatment was still desired. If oral step-down therapy was desired in the rezafungin arm, an oral placebo was used. The other arm received intravenous caspofungin dosed at 70 mg on day 1, then 50 mg daily with the ability to switch to oral fluconazole which was dosed at 200 mg to 800 mg (3 mg/kg or 6 mg/kg) daily based on creatinine clearance. The treatment protocol was for a minimum of 14 days and a maximum of 28 days, with at least 3 days in the intravenous part of therapy. The study had two primary endpoints: global cure at day 14 visit and all-cause mortality up to the day 30 visit. The investigators used a predetermined non-inferiority margin of 20%. Several other secondary endpoints were assessed, including adverse effects and microbiological eradication.

About 70% of patients had candidemia.[36] The median duration of intravenous treatment was 14 days in each arm. Rezafungin was found to be non-inferior for both primary endpoints. Estimates of all-cause mortality were 24% in the rezafungin arm and 21% in the caspofungin arm (2.4% [95% CI: −9.7 to 14.4]). The 14-day global cure rates were 59% for rezafungin vs 61% caspofungin (−1.1% [95% CI: −14.9% to 12.7%]). Secondary endpoints, including safety and mycological analysis, also appeared to be similar. The majority of isolates were *C. albicans* (42.5%) and *C. glabrata* (26.5%). Species were generally balanced, with the exception of *C. parapsilosis*, which was isolated in 17 Caspofungin cases versus only eight cases in the rezafungin arm. Microbiological resistance did not appear to be a problem in the study.[36]

Rezafungin appears to provide similar results to standard therapy but offers the advantage of avoiding multiple doses with limited need for intravenous catheters with its once-weekly dosing. Rezafungin has a low potential for drug interactions, which can be an advantage over other antifungal agents used in the outpatient setting.[38] The most significant limitation of this study was the limited number of patients with infections beyond candidemia which would typically require longer courses, for which long-acting rezafungin's use may be desired.

Suboptimal dosing of fluconazole in critically Ill patients: Time to rethink dosing? Echinocandins are recommended as initial treatment for critically ill patients with invasive candidiasis and candidemia. De-escalation to fluconazole therapy is a common stewardship intervention in select patients. The most recent IDSA guidelines recommend de-escalation from echinocandin therapy to fluconazole in select patients at a dose of 6 mg/kg daily (400 mg) for most strains of *Candida* species and 12 mg/kg daily (800 mg) for *C. glabrata*.[9] Appropriate dosing data within critically ill patients with various degrees of renal function are limited. Muilwijk et al. evaluated the impact of renal function including continuous renal replacement therapy (CRRT) on critically ill patient pharmacokinetics.[39] This was accomplished through an open-label, multicenter, observational study.[39] Blood samples were obtained from 19 patients on days 3 and 7 during therapy. A nonlinear mixed-effects model was created with subsequent Monte Carlo simulations from a previous cohort (1706) incorporated. The target area under the curve (AUC) was 400 mg h/L to achieve an fAUC/MIC ratio of

100 aligning with the European Committee on Antimicrobial Susceptibility Testing recommendations. Dosing regimens (100, 200, 400, and 800 mg daily) and renal function (estimated glomerular filtration rate (GFR) of 120, 60, 20 mL/min, CRRT) were used to determine exposure.

Doses of 100 mg and 200 mg daily were inadequate to meet the fAUC/MIC pharmacokinetic target of 100 irrespective of renal function.[39] The currently recommended guideline maintenance dose for most patients (400 mg daily with normal renal function) was only adequate with an estimated GFR between 20 and 60 mL/min. For patients with estimated GFR > 90 mL/min or CRRT, 600–800 mg daily doses are necessary. Limitations of this study include a low number of patients used for simulations, minimal documented *C. glabrata* isolates ($n = 1$), and lack of clinical outcome data. While confirmatory studies including outcomes would be helpful, it is reasonable to consider using higher doses of fluconazole when de-escalating from echinocandins due to their excellent safety profile and the significant mortality associated with invasive candidiasis.

Cryptococcus

Single-dose liposomal amphotericin B treatment for cryptococcal meningitis. The AMBITION trial was a phase III, open-label, randomized controlled non-inferiority trial conducted across multiple centers in sub-Saharan Africa.[40] The study aimed to compare single, high-dose L-AmB treatment to a seven-day amphotericin B deoxycholate-based regimen for HIV-associated cryptococcal meningitis (CM). The primary outcome measure was all-cause mortality within the first 10 weeks post-randomization. Secondary outcome measures included early fungicidal activity, incidence of adverse events, pharmacokinetic parameters, health service costs, and disability levels at 10 weeks. Adult participants with HIV were randomized to receive either intravenous L-AmB 10 mg/kg on day 1 given with 14 days of oral fluconazole 1200 mg/day and oral flucytosine 100 mg/kg/day (intervention) or intravenous amphotericin B deoxycholate 1 mg/kg/day for 7 days given with 7 days of oral flucytosine 100 mg/kg/day followed by 7 days of oral fluconazole 1200 mg/day (control). After the two-week induction phase, all participants then received oral fluconazole 800 mg/day to complete 10 weeks of therapy and 200 mg/day thereafter.[40]

A total of 814 patients were included in the ITT population. The trial demonstrated non-inferiority of the single-dose L-AmB regimen compared to the standard regimen in terms of all-cause mortality within the first 10 weeks post-randomization.[40] Additionally, similar rates of cryptococcal relapse and pharmacokinetic parameters between the two treatment groups were observed. Both treatment regimens were generally well-tolerated, though there was a lower incidence of adverse events observed in high-dose L-AmB arm ($p < 0.001$). Although a single large dose of liposomal amphotericin will be more costly than amphotericin deoxycholate, the expense of multiple days of IV therapy and associated costs may also be reduced with single-dose therapy. Of note, although results were similar between arms, the mortality rate in both groups (24.5% vs 28.5%) was high, and better treatments for HIV-associated CM are still needed.[40] The findings of the AMBITION trial suggest that the single-dose L-AmB regimen offers a promising alternative for the management of CM in resource-limited settings, potentially reducing treatment duration while maintaining efficacy and safety.

Discussion

Significant advancements have been made these past 5 years in the management of invasive fungal infections. First, robust diagnostic tools for fungal infections are still lacking, but several new rapid diagnostic and molecular-based tools are now available.[41–43] Next, stewardship of antifungal agents and diagnostic tests has become more prevalent, hopefully preserving the longstanding antifungals that have been the cornerstone of antifungal therapy for the past decade.[44–46] Finally, several novel antifungals and antifungal classes have been introduced in the past 5 years.[34,47,48]

Of the new antifungal agents in trials, three are FDA-approved, including ibrexafungerp, rezafungin, and oteseconazole.[49–51] Ibrexafungerp is a first-in-class triterpenoid that is related to the echinocandins, and oteseconazole is a tetrazole related to the triazole antifungals.[34] In phase II and phase III clinical trials, fosmanogepix and olorofim represent new classes with novel

mechanisms of action and broad spectrums of activity. Should these agents be approved, they will provide much-needed alternative options for difficult-to-treat invasive fungal infections, including those caused by rare mold species.[34,48]

The studies selected as the top 10 papers on the treatment of invasive fungal infections by ID clinicians in this modified Delphi process are not without limitations. While 6 of the 10 included studies were randomized controlled trials, the other four included a multi-center single-arm open-label prospective study, a prospective observational study, an open-label crossover study, and a retrospective observational study. Several studies were limited by small sample sizes, either overall or for special populations such as those with neutropenia. Limited information was assessed in these trials for resistant pathogens, limiting generalizability in those cases. Finally, not all studies included TDM, which is essential for drugs like voriconazole to maximize efficacy while minimizing toxicities.

The future management of invasive fungal infections is bright. Our hope is that there will continue to be advancements in diagnosis, introductions of novel therapies, and liberal application of antifungal stewardship to preserve the antifungal agents currently available until these new agents have supporting outcome data for routine use.

Conclusion

Invasive fungal infections are frequently responsible for infections in hospitalized patients and are responsible for high morbidity and mortality. The most impactful articles selected by ID clinicians included evaluations of treatments for aspergillosis, candidiasis, and cryptococcosis. In evaluations of IA, studies demonstrated non-inferiority of posaconazole and isavuconazole versus voriconazole, and stressed the importance of TDM when using voriconazole. In evaluations for invasive candidiasis, studies have demonstrated the improved efficacy of echinocandin use versus azoles, including isavuconazole. In infants, micafungin has proven to be an effective and safe alternative to amphotericin B. In new and upcoming antifungals, rezafungin demonstrated similar results as standard-of-care, and fosmanogepix may provide a new option for difficult-to-treat resistant infections. In the treatment of CM, a one-time, high dose of liposomal amphotericin B proved non-inferior to 14 days of induction therapy with amphotericin B deoxycholate plus flucytosine followed by high-dose fluconazole. As advancements are made in diagnostics, novel therapies are introduced, and antifungal stewardship gains popularity, clinicians should stay abreast of the current literature and guidelines to continue providing state-of-the-art care in the treatment of invasive fungal infections.

Declarations

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Consent for publication

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Author contributions

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