

# **Antifungal Therapy Guidelines for Pediatric Acute Leukemia Patients Infected with Candida and Aspergillus Species**

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**An Analysis of Discrepancies  
between Published and  
Hospital-based Guidance**

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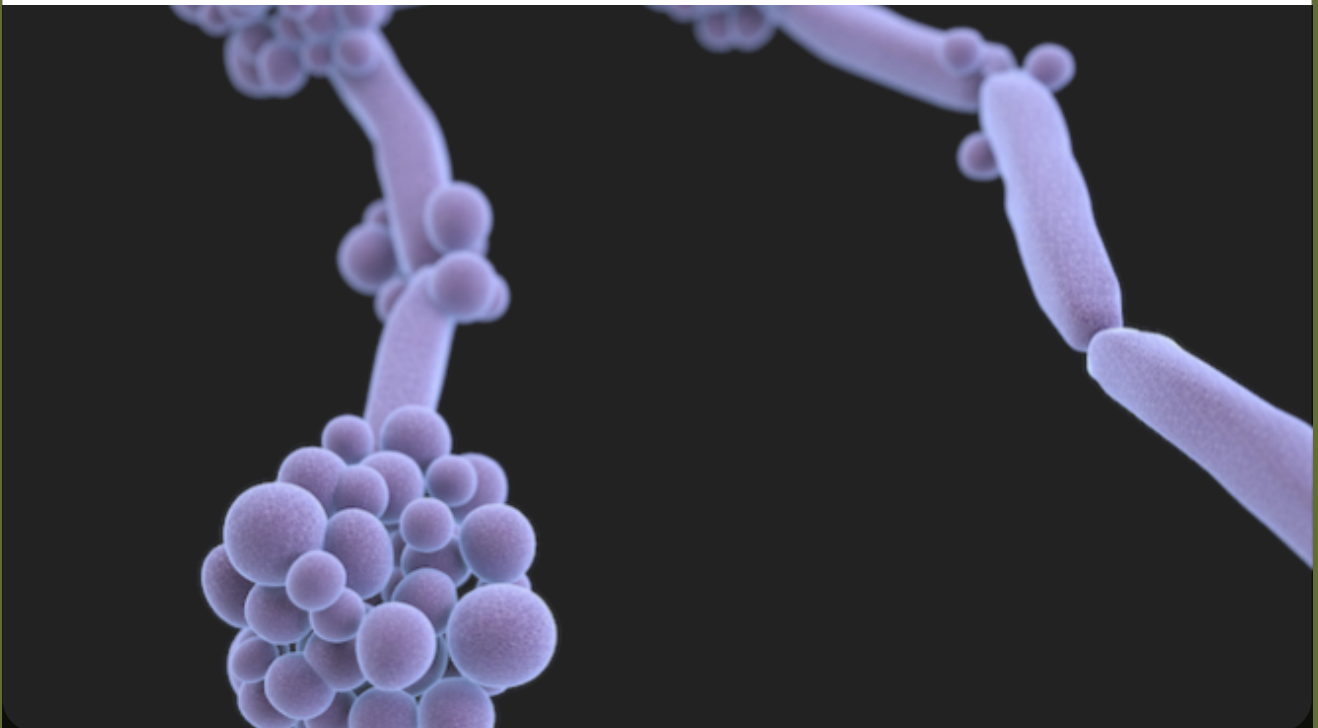
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# Executive Summary

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The most recent published antifungal guidelines for pediatric acute leukemia patients recommend treating *Candida* infections with echinocandins and treating *Aspergillus* infections with voriconazole, with liposomal amphotericin B as an acceptable alternative treatment for both. US hospital-based guidelines agree with the most recent published guidelines; however, international hospital-based guidelines do not.



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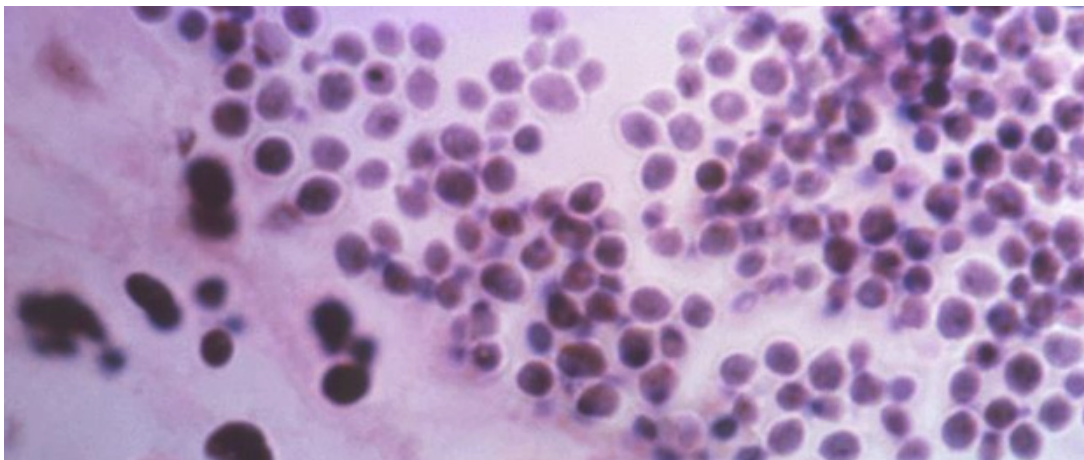
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# Issue Overview

*Candida* spp. and *Aspergillus* spp. are the leading causes of invasive fungal infection (IFI) in pediatric acute leukemia patients worldwide. They are a major cause of morbidity among these patients, with high mortality rates (10% to 50% for *Candida* infections and 25% to 80% for *Aspergillus* infections). Additionally, these infections are difficult to diagnose and cure.

Pediatric antifungal drug and dosage guidelines help providers combat these infections, but hospital-based guidelines may not always use the most up-to-date published data.

We compared published and hospital-based guidelines to determine any discrepancies between the most up-to-date guidelines on pediatric antifungal use for suspected and confirmed invasive fungal infections for children with leukemia and what is recommended in hospitals in the United States and internationally.



# Methods

We reviewed 9 guidelines or consensus statements published by professional groups in the peer-reviewed literature, 5 international hospital-based guidelines, and 10 US hospital-based guidelines for recommendations applicable to pediatric acute leukemia patients.

We then compiled a summary of recommended antifungal drugs and dosages using 5 of the professional society guidelines published in the literature, 3 of the international guidelines, and 4 of the US guidelines.





# Findings: Published Candida Treatment Recommendations

The current published guidelines recommend treating *Candida* infections initially with echinocandins. There are currently more data available on caspofungin and micafungin than there on anidulafungin, with guidelines giving caspofungin and micafungin a stronger recommendation. The strongest alternative recommendation is liposomal amphotericin B. Voriconazole (accompanied by therapeutic drug monitoring) and fluconazole are also acceptable alternatives. Standardized treatment durations are not specified, and clinicians are instructed to administer therapy until 2 weeks after the infection is cleared.

More complicated invasive *Candida* infections have their own specific recommendations based on the complication itself. Endocarditis can be treated with either echinocandins or amphotericin B, meningoencephalitis should be treated with liposomal amphotericin B (possibly in combination with flucytosine), and hepatosplenic candidiasis can be treated with either echinocandins or liposomal amphotericin B, followed by fluconazole.

**Table 1: Candida Antifungal Dosage Recommendations**

<i>YEAR OF PUBLICATION</i>	<i>CASPOFUNGIN*</i>	<i>MICAFUNGIN</i>	<i>LIPOSOMAL AMPHOTERICIN B</i>
<b>2007</b>	50 mg/m <sup>2</sup> daily	1-4 mg/kg/day	1-5 mg/kg/day
<b>2019</b>	50 mg/m <sup>2</sup> daily**	2-4 mg/kg/day***	3 mg/kg/day (IV)
<b>2021</b>	50 mg/m <sup>2</sup> daily**	2-4 mg/kg/day***	3 mg/kg/day (IV)

\*Caspofungin is dosed based on surface area (mg/m<sup>2</sup>)

\*\*Loading dose: 70 mg/m<sup>2</sup>

\*\*\*if weight > 50 kg, then 100–200 mg/kg/day



# Findings: International Hospital-based Candida Treatment Recommendations

Internationally, there is no clear agreement on the primary antifungal of choice. The NHS University Hospital in Bristol, England, recommends treating a probable systemic *Candida* infection with oral fluconazole.

NHS Greater Glasgow and Clyde in Scotland recommends treating a *Candida* infection with liposomal amphotericin B, and lists caspofungin as an acceptable alternative.

Children's Health Queensland Hospital and Health Service in Australia recommends caspofungin or micafungin as first-line therapy, with voriconazole or liposomal amphotericin B as alternatives. If the patient has a complicated urinary tract infection, Children's Health Queensland recommends fluconazole as the first-line drug. NHS Greater Glasgow and Clyde and Children's Health Queensland agree that, for patients with a central nervous system infection, voriconazole is the recommended drug.





# Findings: US Hospital-based Candida Treatment Recommendations

US hospitals tend to recommend micafungin as the primary antifungal of choice over caspofungin.

UC Davis (California), Children's Minnesota, and C.S. Mott Children's Hospital (Michigan) recommend micafungin as first-line therapy for *Candida* infections, while UCSF Benioff Children's Hospital (California) recommends caspofungin.

C.S. Mott and UCSF Benioff list liposomal amphotericin B as an acceptable alternative, and UCSF Benioff also lists fluconazole and voriconazole as acceptable alternatives, depending on the specific *Candida* species identified.



# Findings: Published *Aspergillus* Treatment Recommendations

The current published guidelines recommend treating *Aspergillus* infections with voriconazole, accompanied by therapeutic drug monitoring. Voriconazole can have toxic side effects, with kidney injury a particular concern, and monitoring the trough levels of this antifungal may optimize the therapy while minimizing the potential for toxicity.

Liposomal amphotericin B is an alternative recommendation. Combination therapy is not recommended.

Table 2. *Aspergillus* Antifungal Dosage Recommendations

<b>YEAR OF PUBLICATION</b>	<b>VORICONAZOLE (2-12 YO OR 12-14 YO WEIGHING &lt; 50 KG)</b>	<b>VORICONAZOLE (15+ YO OR 12-14 YO WEIGHING &gt; 50 KG)</b>	<b>LIPOSOMAL AMPHOTERICIN B</b>
<b>2007</b>	4 mg/kg twice daily*	4 mg/kg twice daily*	1-5 mg/kg/day
<b>2019</b>	8 mg/kg twice daily (IV) 9 mg/kg twice daily (oral)	4 mg/kg twice daily (IV) 200 mg twice daily (oral)	3 mg/kg/day (IV)
<b>2019</b>	8 mg/kg twice daily (IV) 9 mg/kg twice daily (oral)	4 mg/kg twice daily (IV) 200 mg twice daily (oral)	3 mg/kg/day (IV)
<b>2021</b>	8 mg/kg twice daily (IV) 9 mg/kg twice daily (oral)	4 mg/kg twice daily (IV) 200 mg twice daily (oral)	3 mg/kg/day
<b>2022</b>	8 mg/kg twice daily (IV) 9 mg/kg twice daily (oral)	4 mg/kg twice daily (IV) 200 mg twice daily (oral)	--

\*on day 1, 6 mg/kg twice daily

# Findings: International Hospital-based *Aspergillus* Treatment Recommendations

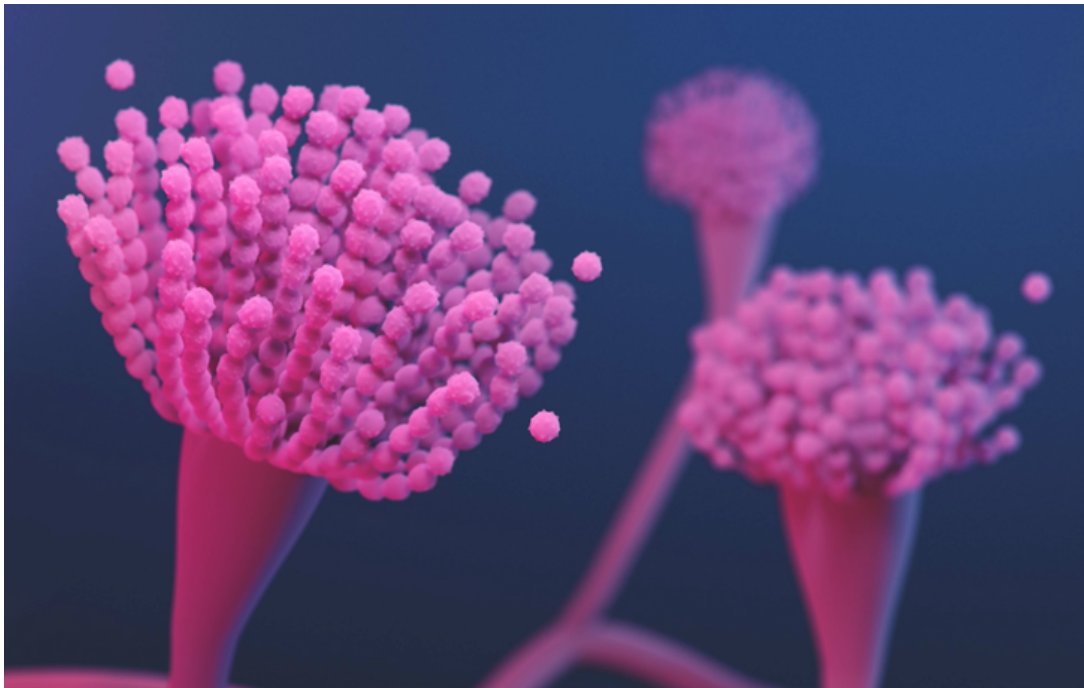
Internationally, there is disagreement over whether voriconazole or liposomal amphotericin B is the preferred first-line drug for invasive *Aspergillus* infections. The NHS University Hospital in Bristol recommends treating an *Aspergillus* infection empirically with liposomal amphotericin B as a first-line drug. Voriconazole with therapeutic drug monitoring is the second-line therapeutic approach and should be combined with caspofungin until adequate blood levels of voriconazole are achieved, at which point caspofungin treatment can be halted.

NHS Greater Glasgow and Clyde recommends liposomal amphotericin B as the first-line drug, with fluconazole or voriconazole with therapeutic drug monitoring as acceptable alternatives. Posaconazole is the second-line drug, although posaconazole is not currently approved in children under 13 years of age.

Children's Health Queensland Hospital and Health Service recommends voriconazole with therapeutic drug monitoring as the first-line approach, with liposomal amphotericin B as an acceptable alternative.

# Findings: US Hospital-based Aspergillus Treatment Recommendations

In the United States, all hospitals investigated in this comparison recommend voriconazole as the preferred first-line drug. UCSF Benioff also lists liposomal amphotericin B as an acceptable alternative.



# Conclusions

The most recent published data on the first-line therapy for invasive fungal infections in children with leukemia recommend that *Candida* infections be treated with an echinocandin—either caspofungin or micafungin—and that *Aspergillus* infections be treated with voriconazole accompanied by therapeutic drug monitoring. Liposomal amphotericin B is an acceptable alternative treatment for both types of infections but is not the first choice.

Internationally, only Children's Health Queensland Hospital and Health Service in Australia follows these recommendations. This is likely because this facility is heavily involved in the academic research behind the most recent published data.

The other two international hospitals investigated in this comparison recommend fluconazole and liposomal amphotericin B for *Candida* infections and liposomal amphotericin B for *Aspergillus* infections, contrary to the most recent published data. This indicates a large discrepancy among first-line antifungal prescriptions internationally.

# Further Discussion and Future Research Directions

## **Pediatric-specific data**

A serious lack of pediatric data concerning antifungals and acute leukemia has led to the possibly inappropriate use of adult data to inform pediatric guidelines. Additional research is necessary to determine the optimal dosages and durations of antifungal therapies for immunocompromised pediatric patients.

## **Public availability of guidelines**

Nationally, many US hospitals did not have publicly available antifungal guidelines. US hospitals should consider making their antifungal guidelines publicly available to increase data transparency and assist in future pediatric antifungal research.

## **Guideline concordance with published data**

Two international hospitals based in Bristol (England) and Glasgow and Clyde (Scotland) have current antifungal guidelines that do not agree with the most recent published data. Additional comparisons should be done between UK hospital-based guidelines and the most recent published data to determine if this is a trend in this region.



## **Disclaimer**

The information presented in this issue brief is intended to provide an understanding of the landscape of recommendations for treatment of suspected or confirmed invasive fungal infections in children with leukemia. It is not intended to provide clinical advice or guidance, and it does not include an analysis of studies or clinical experience that may offer greater insight into individual and nuanced prescribing decisions in these complex scenarios.

## **Note on antifungal prophylaxis**

This comparison did not investigate current guidelines for antifungal prophylaxis. This comparison is solely about treatment recommendations for confirmed fungal infection (and probable/empirical treatment where indicated in the text).

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