Pediatric Invasive Aspergillosis

William J. Steinbach, MD

Key Words: aspergillosis, antifungal, galactomannan

Pediatric Invasive Aspergillosis

I invasive aspergillosis (IA) remains an infectious disease that causes numerous subspecialists, young and old alike, to cower with fear and lose sleep at night. The more seasoned pediatricians see those nondescript scattered pulmonary nodules on a CT and remember the thief that has stolen so many of their oncologic success stories during eras where they tried every antifungal therapy permutation, including several that were not antifungals at all. The more-junior specialists are amazed at our seeming ineptitude when confronted by such a devastating killer, marveling at how, despite all the advances in medicine today, we still cannot diagnose this disease in a timely fashion nor consistently treat it. Although the terror remains the same, the face of the demon has changed. This brief primer will highlight some of the important concepts for the current management of IA.

DIAGNOSIS

IA patients suffer from the shortcoming that there is no easy diagnostic methodology for either accuracy or timeliness. For years, the mainstream diagnostic approach—CT replacing the often useless plain radiograph in the last 2 decades. Even in the CT realm, differences abound, with high resolution CT with lung windows yielding more information than a quick thick-sliced scan. In Europe where, early diagnosis and pre-emptive therapy is better emphasized, many centers use twice-weekly diagnostic tools.1 Those tools have migrated from the CT in high risk patients to twice weekly screening with serum galactomannan (GM) (Platelia, BioRad). GM is a released polysaccharide, and although it is technically not a single molecule, one should remember that it is a part of the living Aspergillus cell wall. GM is not found on other fungi, so its detection is quite specific for IA. The GM assay is a commercially available double-sandwich ELISA, noninvasive serologic assay. A robust infection will yield an elevated GM in the right patient population, but defining that correct patient population has not been easy. Patients with hematologic malignancies or those undergoing hematopoietic stem cell transplantation are the best populations for this assay, whereas it does not work as well in solid organ transplant recipients. A special pediatric population to note is those with primary immunodeficiency, especially those with chronic granulomatous disease, for whom the assay often yields false-negative results.2 For several years, it was thought that the GM assay was not useful in children because of an unacceptably elevated false-positive rate, but 2 more recent studies have shown that it works well in pediatric patients.3,4 If in doubt, biopsy and culture still remain the gold standards.

ANTIFUNGAL TREATMENT

Antifungal treatment used to be simpler. For decades, the therapeutic mainstay was amphotericin B deoxycholate (AmB), which was an afterthought of an ineffective antifungal amphotericin A. AmB therapy was at best one-third effective, with older reports consistently demonstrating the majority of patients succumbing to IA. Itraconazole in the early 1990s, and various lipid formulation flavors of AmB in the mid-1990s, offered some improvement. Itraconazole heralded an erratically absorbed oral alternative to AmB, which was later improved with an oral solution to remove the capsular formulation’s inconsistencies, and the lipid vehicles surrounding the parent AmB guaranteed less acute and chronic toxicity. Although there were some success stories, including a clear bias whereby patients receiving itraconazole were healthy enough for an oral agent and, not surprisingly, did better overall when compared with the intravenous toxic standard, IA was far from mastered. In the late 1990s, we saw the birth of the second (or third, depending on how technically accurate one cares to be) generation of triazole antifungals. In 2002, a large trial showed a clear response benefit for voriconazole versus AmB against IA.5 Although some argued that the real test would have been voriconazole against a lipid product, these were not licensed at the time of trial design. A subsequent analysis of other licensed therapy used in the 2002 trial—antifungals employed by worried investigators who were allowed to switch agents mid-trial—proved that for this disease the triazole therapy, especially when used first, was best.6 The recent Infectious Diseases Society of America guidelines provide more background on this concept7 and highlight the importance of initiating therapy with a triazole.
antifungal. One key question surrounds the optimal therapy for recalcitrant disease if this initial agent fails, termed as “salvage therapy.” Here, firm data are sparse, and options include switching antifungal classes (such as an echinocandin or an AmB-based agent), or combination therapy with drugs which are active against multiple cellular targets. Although the debate here rages forward, what is very clear is the importance of immune reconstitution. Recovery of immune function, through decreased immunosuppression coupled with administration of exogenous stimulating factors or possibly donated granulocytes, is key to disease resolution. 8

Although voriconazole is a derivative of fluconazole, posaconazole is another licensed triazole and a chemical successor of itraconazole. This little fact changes some fundamental pharmacokinetic principles. Oral voriconazole is best given on an empty stomach because its bioavailability drops significantly in the presence of food. Posaconazole, currently only available as an oral solution, requires a fatty meal. Herein lies the challenge with posaconazole—the art of coercing neutropenic children with mucositis into ingesting a cheeseburger before taking one of their plethora of medications that day. Posaconazole should, and anecdotally has, worked as well as voriconazole for the treatment of IA. However, the only real experience with posaconazole and IA is a historical control study. 9

PEDIATRIC ANTIFUNGAL DOsing AND DRUG INTERACTIONS

The pharmacokinetics of voriconazole in children are fundamentally different than in adult patients. 10 In adults the dosing is nonlinear, whereas in pediatric patients it is linear and therefore larger doses are required to achieve similar serum concentrations. The optimal dosing for children is to begin with 7 mg/kg/dose twice daily, but even that may not be an appropriate amount for a specific patient. Much has been written regarding the utility of therapeutic drug monitoring (serum levels) of voriconazole in the management of IA, but these are neither as straight-forward nor as well-studied as aminoglycoside levels. However, they do have a role in complicated patients. The caveat is that voriconazole levels have good intrapatient correlation, wherein a single patient’s serum levels can change based on the dose administered, but making population generalizations is very difficult. To add to the fire, there are clinical trial data to document patients who, despite a known undetectable level, had proven resolution of IA disease. The general consensus is that levels should ideally be at least above the MIC - generally 0.5 or 1.0 μg/mL.

While every agent has potential problematic drug interactions, 1 large relevant confounder in pediatrics is the vinca alkaloid vincristine used concomitantly with either voriconazole or posaconazole. Although not a black box warning with the triazoles (like sirolimus), these antifungals can potentially dangerously elevate vincristine to irreversibly toxic levels. One possible solution is avoidance of the azole antifungal, because altering a known effective childhood cancer protocol based on a theoretical drug interaction is not good medicine. Generally, this means switching to another antifungal class, an AmB product or an echinocandin, for the duration of vincristine therapy. In cases of more severe or recalcitrant IA, a balance needs to be maintained between the antineoplastic drug and the antifungal therapy competing for serum time. One must decide which deadly disease is moving fastest and needs to be attacked most aggressively.

TREATMENT DURATION

Treatment duration was historically based on the concept of instilling a magical total quantity of AmB into the bloodstream and then the treatment ended. We know now that this is not correct, and each patient deserves proper individual attention. As a rule, therapy should not be short. Treatment should continue at least until clinical resolution of any symptoms and remarkable radiologic improvement is seen; generally, this equates to at least 3 months. If the child remains immunosuppressed or will be again in the short term, then continuing antifungal therapy throughout that period is warranted.

REFERENCES