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Lectures

The Problem of Fungal Infections in Immunosuppressed Children

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Fungi have emerged as important pathogens in immunocompromised children. At the National Cancer Institute, approximately 40% of children undergoing cancer treatment who succumb during periods of prolonged granulocytopenia will have evidence of invasive fungal disease at postmortem examination. While most of these patients have refractory malignancies, in some cases fungal infection has contributed to the death of patients undergoing primary cancer treatment. The predominant fungal pathogens which occur in immunocompromised children include *Candida* and *Aspergillus*. Less commonly, infections with the *Phycomycetes*, *Cryptococcus*, *Trichosporon* or *Fusarium* result in serious infection.

Both the host and the environment contribute to the risk and incidence of infection. For example, certain fungal infections arise from the patient's endogenous flora (e.g., *Candida sp*) as a consequence of cytotoxic and immunosuppressive therapies along with antibiotic selection. Other fungal organisms (e.g., *Aspergillus*) are acquired from exogenous sources (e.g., spores generated from hospital construction). Geographic variation in the fungal pathogens (e.g., *Cryptococcus*, *Histoplasma*, *Coccidioides*) also alter the patterns of infection. Similarly, the degree of host compromise may predispose the patient to certain types of fungal infection. For example, the child with T-cell deficiencies (severe combined immune deficiency, DiGeorge Syndrome) are at risk for candidal infection, as are children with adrenal insufficiency and the syndrome of chronic mucocutaneous candidiasis.

One of the major difficulties with an invasive fungal infection is the difficulty in diagnosing it accurately. It is often problematic to determine how colonization with a particular fungal pathogen *per se* equates with infection. Moreover, sites of active infection may be difficult to define, either because of their inaccessibility (e.g., pulmonary processes) or because of the poor *in vitro* growth characteristics of the organism. In spite of considerable research effort, virtually all of the antigen-detection assays are limited by a high rate of false negative results. This necessitates that the clinician be aware of the syndromes most likely to be caused by invasive fungal infections and to be prepared to intervene promptly (and frequently empirically) in their treatment.

Unfortunately, the therapeutic agents available to treat and prevent invasive fungal infections remain suboptimal. Amphotericin B is still the gold standard of therapy but suffers from an extensive array of side-effects and from a limited efficacy in patients with persistent neutropenia (especially when the offending organism is *Aspergillus*). Recently, encouraging results have been obtained when amphotericin B has been encapsulated into liposomes and clinical trials using unilamellar and multilamellar liposome-encapsulated amphotericin B are in progress. The imidazole antifungal agents (ketoconazole, clotrimazole, miconazole) have had demonstrable efficacy in immunocompromised children with superficial infection (e.g., oral mucositis, chronic mucocutaneous candidiasis, esophagitis) but have had limited efficacy for patients with invasive infection. In a randomized trial that we recently performed at the NCI comparing oral ketoconazole to intravenous amphotericin B for patients with persistent fever and neutropenia, we observed that whenever an invasive fungal infection emerged in a patient receiving ketoconazole, it invariably progressed, and that the only improvements which occurred took place when the patient was crossed over to amphotericin B. Alternatively, it is clear that amphotericin B is far from a panacea since, as noted, it also has a high failure rate in treating *Aspergillus* or *Mucor* infections, particularly in patients who remain persistently neutropenic. Although there is little conclusive supporting data (except for *Cryptococcal* meningitis), some centers have suggested that an improved outcome can be attained by combining amphotericin B with flucytosine.

One of the most important guiding principles is to institute antifungal therapy as early as possible in the patient's treatment course if the clinical setting is compatible with invasive fungal disease. Situations in which we have observed a benefit for this strategy include patients with symptomatic esophagitis, patients with new pulmonary infiltrates which have appeared during antibiotic treatment and prolonged neutropenia, neutropenic patients with "bull's-eye" lesions on abdominal ultrasound or CT scan which are compatible with hepatic candidiasis, patients with persistent granulocytopenia (≥ 1 week) and fever. Prompt intervention with

antifungal therapy can be successful in each of these settings although extended treatment courses are sometimes necessary.

Antifungal agents have also been used topically and orally to try to prevent colonization or invasion by potential pathogens. While some success in controlling infection with *Candida sp* has been observed, no beneficial effect on *Aspergillus* has been attained. In centers where a prohibitive incidence of *Aspergillus* infection exists, specialized air filtration systems (e.g., HEPA filters or laminar air flow rooms) can be used to limit the number of *Aspergillus* spores in the air and to reduce colonization and subsequent infection.

In summary, fungal infections are a major diagnostic and therapeutic problem for the pediatrician involved in the care of immunosuppressed children. Improved diagnostic techniques and more effective therapeutic agents are of critical importance if the limitations that fungi place on current treatment strategies are to be overcome.

Selected REFERENCES

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Do the Vaccines Cause Adverse Reactions?

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A critical question on any vaccination is the harm potentially induced to the vaccinee. A number of various signs and symptoms have been attributed to immunizations, but usually the suggested causal relationship has been sequential only. However, *post hoc est non propter hoc*.

A vaccination project for elimination of measles, mumps and rubella (MMR) from Finland was started in November 1982. Potential adverse reactions were studied in twins by using the placebo controlled double blind and cross-over fashion. Parents of the twins born during one year were asked for participation. If an agreement was reached, A-twin received the vaccine coded as A, and B-twin received B. Another injection was administered after three weeks; twin A received vaccine A, and twin B vaccine B. At this time both children had received the live MMR vaccine once and placebo once. A questionnaire presenting 16 specific queries was given to the parents at each time. In addition, the vaccinators (public health nurses) filled their own forms.

At the stage when data of 870 children (435 twin pairs) at the age of 14 months to 6 years had been analyzed, and only the question was answered whether or not a particular sign or symptom was observed within 21 days after vaccination, no statistical significance was reached in any reaction whatsoever between the vaccinees and the placebo controls. Respiratory symptoms, for example, were reported in 17% and 17% after the first injection no matter whether the MMR vaccine or placebo was used. Practically with the same frequency were reported also erythema at the injection site, generalized eczema, irritability, exhaustion, fever, gastroenteritis, and conjunctivitis.

The conclusion is that although statistical differences between the two groups might be observed when the reactions are analyzed day-by-day, the vast majority of the so called vaccination reactions were not caused by MMR. It is probable that this finding holds true in many other immunizations, too.