The changing face of childhood meningitis

Canadian pediatricians and family physicians will likely remember 1993 as the year when infections caused by Haemophilus influenzae type b (Hib) virtually disappeared. This remarkable development reflects the outstanding efficacy of universal infant vaccination programs initiated in all provinces during 1992. Their effect on Hib disease was swift: by the third quarter of 1993, the Canadian Paediatric Society’s Immunization Monitoring Program, ACTive (IMPACT) network (1) reported a 90% decline in preventable cases at the 10 participating pediatric centres, compared with the same period in 1992. The actual number of preventable cases encountered in the third quarter of 1993 was only three. These data underscore the actual improvement over baseline conditions because other Hib vaccines used since 1985 had some impact on illness rates. Currently used Hib vaccines have an excellent safety record and rarely fail to protect after completion of the three-dose primary series.

The direct benefits of Hib disease eradication include an overall decrease in childhood meningitis cases of approximately 70% (2), along with virtual elimination of epiglottitis cases, and a substantial decrease in cases of septic arthritis, cellulitis, pneumonia and bacteremia. The indirect benefits include a refocusing of investigative effort on the second tier of serious bacterial pathogens affecting children, catalysed by the many technological insights learned from Hib and by the joy of conquering a serious pathogen.

The spotlight has already shifted. A renewed effort to control pneumococcal infections in children is well under way. Pneumococci are the leading cause of bacteremia and, with control of Hib, are now the number one cause of meningitis. Compared with Hib meningitis, pneumococcal cases are six times more likely to end fatally (19% case fatality) (2). In a Canadian case series (3) 56% of survivors had neurological sequelae. The recent increase in prevalence of pneumococci resistant to penicillin and multiple other antibiotics (4) has added a note of urgency to the development of improved vaccines suitable for use in infants. Multivalent, polysaccharide-protein conjugate vaccines look promising for use in infants to prevent otitis media and pneumococci, as well as invasive infections including meningitis.

One wonders if the recent, aggressive approach to controlling meningococcal outbreaks with community-wide vaccination programs is not conditioned in part by the success with Hib, with a concomitant decrease in tolerance for life-threatening infections.

If the sun has set on Hib, it has clearly risen on group B streptococcal (GBS) infections. Major programs for peripartum chemoprophylaxis have been advocated (5), although many practical issues remain to be resolved. Detection of GBS-colonized women before delivery poses challenges, especially where culture facilities are limited or women have little or no prenatal care. Additionally, the cost of cultures and ensuring that results are available in the case room when needed are problematic. Only a small proportion of GBS-colonized women will deliver infants at high risk for invasive infection, but algorithms that attempt to restrict chemoprophylaxis according to existing risk factors work imperfectly. Late-onset GBS cases are most likely to present with meningitis and may not be prevented by chemoprophylaxis because the source of infection is often nonmaternal. The better long term solution will likely prove to be maternal immunization, using polysaccharide-protein conjugate vaccines (6). Such vaccines are under development, replacing candidate polysaccharide vaccines that proved to be insufficiently immunogenic.

Progress can have unfortunate effects as well. Just as dexamethasone treatment was becoming widely used for Hib meningitis, the target disappeared. Its usefulness in cases caused by pneumococci or meningococci is unproved. No data are available regarding its use in babies with GBS or other causes of neonatal meningitis. The low frequency of meningitis caused by these
second-tier pathogens will make it difficult to reevaluate the usefulness of dexamethasone adjunctive treatment, leaving clinicians uncertain whether to use it.

REFERENCES


Systemic antifungal drugs: Are we making any progress?

The incidence of opportunistic fungal infection is increasing worldwide, and invasive fungal infections have become an important problem in patients with profound immunosuppression. Increased use of potent cytotoxic drugs and broad-spectrum antibacterial agents, as well as the AIDS pandemic, have been the main contributors in modifying the current epidemiological and clinical pictures of serious fungal infections. For years amphotericin B was the only antifungal drug available. Its administration was, however, plagued by important side effects and toxicities. Clinical tolerance is often achieved only through premedication with antipyretics, diphenhydramine or hydrocortisone. Electrolyte imbalance and renal toxicity are frequently observed. Finally, amphotericin B is often administered for long periods of time at high sustained doses, particularly in invasive infections, and can only be administered intravenously. It is therefore not surprising that alternatives have been sought during the past two decades, particularly to develop wide spectrum, nontoxic, well tolerated and easy to administer antifungal drugs.

Flucytosine was licensed in the early ‘70s. Its spectrum of activity is narrow, including only strains of Candida species and Cryptococcus neoformans, while most other fungi are resistant or vary in their susceptibilities (1). Despite excellent absorption after oral administration, and good diffusion and tissue penetration, flucytosine has two important problems: emergence of resistance and serious toxicities. Drug resistance arising during flucytosine monotherapy is usually profound and accompanied by clinical deterioration (2). This emergence of secondary resistance led to recommendations to use flucytosine in combination with amphotericin B (2-3). Toxicities associated with flucytosine, ie, bone marrow aplasia and gastrointestinal toxicities, are common. Their presence correlates with high flucytosine serum levels (4). The elimination of flucytosine is mainly renal, and amphotericin B combined with flucytosine can cause sufficient renal impairment to decrease the elimination and increase the serum concentration of the latter, thus causing flucytosine-related toxicities. Leukopenia and diarrhea are also commonly associated with the use of flucytosine. In immunocompromised hosts, such as AIDS patients, these phenomena are commonly observed.