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Ciprofloxacin Prophylaxis in Children With Acute Leukemia in an Era of Increasing Antibiotic Resistance

To the Editors:

We read with great interest the results of the randomized placebo-controlled trial from Laoprasopwattana and coworkers[1] regarding the effectiveness of ciproflaxacin prophylaxis for preventing fever in neutropenic children with acute leukemia or lymphoma. In this study, there was a 23% reduction of febrile episodes in patients receiving ciprofloxacin, with a consequent decrease in the number of patients who needed to be treated to prevent 1 febrile episode to 4. In a similar, multicenter study comparing amoxicillin–clavulanate with placebo in a homologous patient population,[2] we observed a 21% reduction of febrile events, with a number needed to be treated of 5. What becomes apparent from both studies is that for every 100 neutropenic patients receiving prophylaxis, 75–80 of them are treated unnecessarily to prevent the remaining 20–25 from developing fever and neutropenia. If we consider that the incidence of Gram-negative bacteremia, the most feared complication because of high mortality, generally represents no more than 10–15% of all febrile neutropenic episodes,[3] we estimate that we would administer unnecessarily prophylaxis in 96–97 patients to prevent Gram-negative bacteremia in 3–4 patients. This number could still be considered as acceptable, if antibiotic resistance was not an emerging problem. In the Laoprasopwattana study, the proportion of ciprofloxacin resistant Gram-negatives colonizing patients after 2 weeks of intervention was 95%, whereas it was 27% in those randomized to receive placebo.[1] To the contrary, in our institution where ciprofloxacin is not administered for prophylaxis, resistance to ciprofloxacin is 17% (25/145) of Gram-negative organisms causing bacteremia in children with cancer during an 8-year period (2004 to 2011). We consider this proportion as worrisome and worth strictly monitoring.[4] The prolonged use of fluoroquinolone prophylaxis is associated with appearance of resistant strains,[4,5] with the emergence of bacteria displaying cross-resistance to β-lactams, and aminoglycosides. This limits its use for empirical therapy, at least in low-risk conditions. Moreover, there is no proof of its efficacy in repeated episodes of neutropenia.

We believe that now is the time when antibacterial prophylaxis in neutropenic children with cancer should be abandoned at least during chemotherapeutic regimens.

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The authors have no funding or conflicts of interest to disclose.

ISSN: 0891-3668/13/3205-0581
DOI: 10.1097/INF.0b013e318286f91f

First Case of Severe Enterovirus 71 Infection in Portugal

To the Editors:

In December 2011, a 17-month-old boy was admitted to a pediatric intensive care unit in Lisbon, Portugal, because of rapidly progressive acute flaccid paralysis, rhombencephalitis and coma. He had been diagnosed with hand-foot-mouth disease 3 days before admission. Leukocyte counts, C-reactive protein and serum glucose values were elevated. He was treated with acyclovir, ceftriaxone and ciprofloxacin. Due to this clinical severity, intravenous immunoglobulin and a pulse of methylprednisolone were administered.

After 4 cardiac arrests, hypotension and pulmonary edema, he was managed with high frequency oscillatory ventilation, nitric oxide and inotropic support for 4 days. Cerebrospinal fluid cytochemical analysis was normal. Immunoelectrophoresis revealed intrathecal IgG production and an increased permeability pattern. Magnetic resonance imaging showed lesions in the medulla oblongata, pons, dentate nuclei of the cerebellum and spinal cord, suggesting enterovirus rhombencephalitis. An enterovirus was identified in the stool by reverse transcription-polymerase chain reaction, despite negative cerebrospinal fluid, as

The work was done in Hospital Dona Estefânia, CHLC, in the Pediatric Intensive Care Unit.
The authors have no funding or conflicts of interest to disclose.

ISSN: 0891-3668/13/3205-0581
DOI: 10.1097/INF.0b013e31828689ab

expected during enterovirus central nervous system infection, especially in severe cases.[1] It was identified as C2 EV71, by sequencing of the partial nucleotide sequence of viral protein 1.[1] No index case was found.

His condition evolved to spastic tetraparesia and tracheostomy because of an absent gag reflex, with cavitation of the brainstem and cervical spinal cord lesions and diffuse brain stem and encephalic atrophy.

EV71 neurologic disease includes acute flaccid paralysis, meningitis and rhombencephalitis. Cardiopulmonary complications, like neurogenic pulmonary edema, and cardiac collapse occur in a subset of children with rhombencephalitis, mostly in those younger than 5 years, associated with high mortality rate.[1] Among survivors, neurodevelopmental sequelae are frequent. Prognostic factors are progressively being found, including central nervous system involvement, leukocytosis, hypotension and hyperglycemia, all of which were found in our case.

Since 1969, several epidemics have been reported in the Asia-Pacific region. C2 EV71 was responsible for large outbreaks in Taiwan (1998) and Australia (1999). In the last 10 years, reported cases in Europe have been sporadic and mild, mainly C1 and C2 EV71. This is the first known case in Portugal and the most severe EV71 infection described in Europe in the last decade, since the 2 fatal cases in United Kingdom and France.[2] The C2 strain in this case is related to strains circulating in other European countries and the Asian-Pacific region.

EV71 infection therapy is mainly supportive. Epidemiologic studies in China implicated glucocorticoids, which block the innate immune response, as a risk factor for critical and fatal EV71 infections.[3] However, children with critical EV71 infection have a high incidence of adrenal insufficiency, which can affect their prognosis. Glucocorticoids may be considered when this condition is identified or highly suspected.[3] In our case, it was initially impossible to exclude acute disseminated encephalomyelitis. Therefore, glucocorticoid was used. Vaccine is the best option for controlling the disease.[4]

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