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Does Fluconazole Prophylaxis Reduce Death or Invasive Candida Infection in Extremely Preterm Infants?

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COMMENTARY

Invasive candida infection in preterm infants is associated with a case-fatality rate of approximately 30% (1) and long-term neurodevelopmental impairment is common among survivors (2). Prior studies have identified fluconazole prophylaxis as an effective strategy to reduce the incidence of invasive candidiasis (3, 4), particularly among preterm infants weighing <1000g at birth (5). However, concerns regarding short- and long-term safety of antifungal prophylaxis and lack of a clear benefit on mortality have remained unresolved (5), and some studies have suggested an increased risk of cholestasis related to fluconazole prophylaxis (6).

In a multicenter randomized trial in the US (7), investigators evaluated the efficacy and safety of fluconazole prophylaxis among the most immature preterm infants, those weighing <750g at birth. The study showed no effect of fluconazole prophylaxis on the composite outcome of death or invasive candidiasis. However, fluconazole prophylaxis did decrease the incidence of invasive candidiasis.

How are we to explain the lack of an effect on mortality despite a significant reduction in invasive fungal disease? It is possible, as the authors explain, that fluconazole prophylaxis does not have an effect on mortality, despite the high case-fatality rate associated with infection. Infants with invasive candidiasis may also suffer from other co-morbid complications of prematurity that have an effect on mortality that would not be expected to be modified by fluconazole prophylaxis. Alternatively, the effect of fluconazole prophylaxis on death from invasive candidiasis may be too small to be detected by this study. Assuming a reduction in the absolute risk of invasive candidiasis of 7% in this study and a 30% case-fatality rate (1), the risk difference in candida-related mortality would be expected to be around 2%, a difference this study was not powered to detect.

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URL to the full review on the EBNEO web site:

<https://ebneo.org/2015/03/does-fluconazole-prophylaxis-reduce-the-incidence-of-death-or-invasive-candida-infection-in-extremely-preterm-infants/>

Conflicts of interest

None

The authors' selection of their composite primary outcome of death or invasive candidiasis in the trial is reasonable, both because of the hypothesized effect of fluconazole on reducing mortality from invasive candidiasis as well as a method to account for mortality as a competing event in this high-risk population (8). In addition, the authors are correct to focus their conclusion that "these findings do not support the universal use of prophylactic fluconazole" based on the results of the primary composite outcome, rather than the individual components. Although long-term follow-up rates were relatively low, there was no differential loss to follow-up between treatment groups. The lack of an effect of fluconazole prophylaxis on long-term neurocognitive outcomes in this study is consistent with prior studies (9), despite the potential adverse effects of invasive candida infection on neurodevelopment (2).

What is less clear is how this study will influence the use of fluconazole prophylaxis in clinical practice. Taking into account the other prior randomized trials, we can confidently conclude that fluconazole prophylaxis effectively reduces invasive candidiasis. This trial also supports its favorable safety profile for use among this population. However, until additional studies are completed, this therapy cannot be recommended to clinicians seeking to improve survival without neurodevelopmental impairment among their most immature infants.

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