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Efficacy and Safety of Azithromycin for Typhoid Fever

I have some concerns about the interpretation of data in the paper by Aggarwal and colleagues on efficacy and safety of azithromycin for uncomplicated typhoid fever [1]. While many children in the study sample had typhoid fever, evidence is unconvincing that all of them had the specific disease. The inclusion criteria included at least 4 days of fever with clinical features suggestive of typhoid fever, such as abdominal pain (present in 69%), diarrhea or constipation (61%), splenomegaly (27%) and hepatomegaly (73%). While the sensitivity of such a spectrum would be high to include typhoid fever, the specificity would be quite low, except for splenomegaly. This suspicion is strongly supported by the very low blood culture yield (17 children, 15.5%). Moreover, other diagnostic possibilities were not excluded or apparently even considered.

If the diagnosis is not firm, the drug trial is on slippery grounds. Azithromycin is well known to be safe. As for efficacy, azithromycin is active against several pathogens and as pointed out above, such agents could have been the cause of fever in some children. Its efficacy evaluation against typhoid fever in this study is not valid since the case definition was not stringent enough. Moreover, children seen with fever on the fourth day, with only mild discomfort and no localizing signs may well be left alone with symptomatic support and close monitoring; their recovery cannot be attributed to the drug therapy. Many children with uncomplicated fever have surprised pediatricians by their recovery without antibiotic treatment, while their blood cultures have yielded *Salmonella typhi*. The data on the 17 culture-proven cases, of whom 16 completed the study – their response and final outcome are essential to consider the efficacy of the drug, but they are not specifically mentioned. The report says that 5 of them "required add-on antibiotics" [1], suggesting treatment failure in one-third.

Three questions arise. One, what are the indications to start an antibiotic in children with fever of less than one week and without specific diagnosis? Second, what are the criteria to diagnose typhoid fever when blood culture result is negative and when blood culture was not attempted? Third, what are the criteria to choose azithromycin in typhoid fever in preference to other inexpensive oral drugs? These questions have no answer in the paper. The IAP Task Force's guideline on treatment of enteric fever seems to have been ignored by the investigators; it includes azithromycin as an 'alternative' agent for treating uncomplicated typhoid fever [2]. However, the IAP Task Force did not provide minimum diagnostic criteria – clinical and laboratory – for typhoid fever, but apparently alludes that blood culture is essential [2].

In short, the present study cannot be taken as a precedent to diagnose typhoid fever without defined criteria. The rationale to choose azithromycin as the first drug to be given when typhoid fever in 'suspected' or even 'diagnosed' needs further clarification. Perhaps azithromycicn is justified when no cause for fever is available but the child is ill, the cause is suspected to be infection which could include a variety of agents including *S typhi*.

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Hyperglycemia in the PICU : Tread with Caution

The article "Treating Hyperglycemia in the Critically Ill Child Is there Enough Evidence?"[1] was indeed an eye opener. In our regular care of the critically ill pediatric patient, we commonly encounter hyperglycemia which is, many a times, self-limiting. This is especially true of the immediate post-operative period following neurosurgery, gut surgery or cardiac surgery. While we do not have precise data, our observations seem to suggest that post-operative hyperglycemia is transient, self-limiting and not necessarily indicative of a poor outcome. The author has reviewed studies of adults with critical illnesses, severe sepsis, myocardial infarction, stroke and trauma as well as children with critical illnesses, bronchiolitis, meningococcal sepsis and septic shock. The entire review contains only a single reference regarding children undergoing heart surgery. Patients undergoing elective and even emergency surgery may have much less multiorgan dysfunction, unlike the critically ill child. While the author emphasizes that the risk of hypoglycemia is minimal, though this may be true in PICU's with tight monitoring of blood glucose, there is a distinct risk of life threatening hypoglycemia in smaller and peripheral set-ups with the use of insulin in the face of a spontaneously and rapidly correcting blood glucose in certain patients. Trying to achieve rigorous normoglycemia in this post-operative group of transient hyperglycemia would seem unjustified. While the epilogue does seem to give a more balanced approach, the tone of the actual article as well as the key messages may send out a wrong message

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