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AUTHORS' REPLY

We thank the authors for showing interest in our article. The clarifications to the concerns raised are as follows:

1. In the 'proven' category of invasive fungal infections, none of the isolate was *Aspergillus*. Fungi isolated from blood were *Candida albicans*, *Candida tropicalis*, and *Trichosporon spp.*
2. Out of 11 isolates from sputum, *A. fumigates* was positive in seven and *A. flavus* was the species in four patients. The antimicrobial sensitivity details are not available.
3. The authors rightly stated that current literature argues against cross-reactivity of Galactomannan (GM) antigen test and the new EDTA-containing piperacillin/tazobactam formulation. However, in low- and middle-income countries where generic

formulations are widely used, it remains a valid concern. A recent study had shown that the rate of false positive serum GM antigen test was as high as 56% in patients who received generic preparation [1]. With standard brands, the association is no longer applicable, but false positive can still be there with generic medicines [2].

4. We agree that pulmonary leukostasis may lead to a false impression of a fungal nodule or ground-glass opacities on computed tomograph (CT) scan. In our study, three patients had hyperleukocytosis but none of them had evidence of fungal infection on CT scan.
5. We did not perform bronchoalveolar lavage (BAL) after recovery as baseline information on BAL was not available. We agree that GM antigen testing from BAL is more sensitive as well as specific for invasive fungal infections.

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Therapeutic Hypothermia using Phase changing Material in Indian Neonates

This refers to the large multicentric trial conducted in India, and recently published in *Indian Pediatrics* [1]. I have few concerns related to this paper. To begin with, the ambient temperature in the neonatal intensive care unit (NICU) in any of the centers was not mentioned in the study, which is very important for the Phase changing material (PCM) to work effectively [2]. The time taken to reach the target temperature was longer (120 minutes) but the fluctuation was less (0.39) in this study as compared to other large trials. The mean age of initiation of cooling

(2.9 hours) was impressive as average time taken to reach hospital in out-born babies in Indian scenario ranges from 2-5.6 hours [3], and less than 30% of babies reach within 6 hours of life [4]. It would be worth knowing the number of inborn and out-born babies in each center. Three out of 103 babies with mild encephalopathy were cooled when they were not eligible for the intervention.

The discussion of the study mentions that it had only 10% (results showed nearly 19%) of babies with severe encephalopathy as compared to 60% in TOBY trial [5], which is a huge difference as we know that babies with severe insult have multiorgan dysfunction creating doubts about authors' claims of PCM to be safe and feasible. Lastly, the study was partly funded by a manufacturer of PCM, which could have possibly, but not necessarily, influenced the interpretation of study results. It also raises the question when the results mention that PCM is

comparable to servo-controlled equipment in maintaining target temperature, when this study has not directly compared to this intervention with servo-controlled devices.

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AUTHORS' REPLY

We thank the author for his comments related to our study [1]. The ambient temperature in the neonatal intensive care units (NICUs) was not systematically measured in the study. However, all the NICUs were air-conditioned where the ambient temperature is maintained in the range of 24-28°C.

The mean (SD) age of initiation of therapeutic hypothermia (TH) in our study was 2.9 (1.9) hours. We do not have data on the proportion of out born infants included in the study and on the number of infants who could not be cooled due to admission after 6 hours of life. However, most of the study infants were inborn and we included only those outborn babies who reached within 6 hours after birth. It is our experience that in the last few years, more babies with asphyxia are being referred earlier and are reaching us within 6 hours as referring hospitals are becoming aware of the fact that cooling is being offered in our institutions. It is interesting that 76% of infants cooled in the HELIX feasibility trial were out-born infants [2].

Though the protocol recruited only those with

moderate to severe encephalopathy, three babies were noted to have only mild encephalopathy during data analyses. Such trial deviates are also seen in the other major trials on TH, and is well-documented phenomenon in literature [3].

Nineteen (18.4%) infants had severe encephalopathy in our study. The figure of 10% in the discussion is a typographic error. The fluctuation of the temperature during cooling phase (0.39°C) in our study was less when compared to the fluctuations reported by the TOBY (0.5°C) [4] and NICHD (0.45°C) [5] trials using servo-controlled equipment. The good temperature control and few complications seen in this study suggest that cooling is safe and feasible in a NICU setting in India. We agree with the authors that the results of our study cannot be directly compared to those of NICHD and TOBY trials due to the difference in the proportion of infants with severe encephalopathy. However, this should not influence the safety and feasibility of TH, which was the focus of our study.

Though the study was partly funded by the device manufacturer, they had no input in study design, data accrual and analysis, or manuscript preparation.

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