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Probiotic prophylaxis to prevent ventilator-associated pneumonia (VAP) in children on mechanical ventilation: an open-label randomized controlled trial—response to comments by Saptharishi et al.

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Dear Editor,

Thank you for giving us an opportunity to clarify the issues raised by the readers of your esteemed journal. We thank Saptharishi et al. [1] for their keen interest in our study and their thoughtful comments.

We agree with Saptharishi et al. [1] that the criteria we used for ventilator associated pneumonia (VAP) were modified and could have led to over-diagnosis of VAP in a few of our patients, especially the children admitted with community acquired pneumonia. However, in these patients a diagnosis of VAP was made in cases of fever and new or persisting radiographic infiltrate beyond 72 h in conjunction with either radiographic evidence of pulmonary abscess formation (i.e., cavitations within pre-existing pulmonary infiltrates) or increase in leukocytosis of at least 25 % from the baseline count and/or positive blood/pleural fluid culture cultures being identical to the organisms recovered from cultures of respiratory secretions (tracheal aspirates). Blood and pleural fluid cultures were obtained within a period of 48 h before or after the clinical suspicion of VAP [2]. Differentiating "persistent" from "progressive" infiltrates is a subjective exercise and as such the sensitivity and specificity of chest radiograph in diagnosing VAP are poor [3]. In fact the latest Centers for Disease Control and Prevention (CDC) guidelines for VAP have excluded chest radiography because of subjectivity and lack of accuracy [4]. Hence minor deviations in the definition used by us especially with regard to radiography would not have significantly altered the results. Future studies should ideally use the new CDC definitions.

We also agree with the observation of Saptharishi et al. [1] that quantitative cultures would have definitely increased the accuracy of VAP diagnosis and some of our VAP diagnosis could have been actually tracheal colonization or ventilator associated tracheobronchitis (VAT). These are the organisms likely to cause pneumonia in a patient on mechanical ventilation. Studies have proved that probiotics reduce the nasal and oropharyngeal colonization of the pathogenic bacteria [5]. The microbiological profile of the VAP and colonization was not presented in the published manuscript because of space constraints. We will be happy to provide the data if requested.

Established 'VAP bundles' and other standard infection control practices (such as hand hygiene, oral care, tracheal suctioning protocols, positioning, sedo-analgesia protocols, etc.) were common to all the PICU patients. The compliance to VAP care bundles was ensured by frequent monitoring by an infection control nurse, a member of the infection control committee at our institution (JIPMER) and regular presentation of this data at audit meetings. The compliance to these practices was not collected as part of the study but is available as part of regular ICU audits for performance measures.

Saptharishi et al. [1] have also mentioned about adjusting for age in the analysis. According to Kahan et al., failure to adjust for the variable used for stratified randomization can result in *P* values that are too large and confidence intervals that are too wide; this leads to a decrease in power and a reduction in type I error rate, which could potentially lead to an incorrect conclusion that the treatment has no benefit [6]. Hence not adjusting for age in our analysis could have led to more conservative estimates of intervention effect. We had adjusted for age in the multivariate analysis by including it as one of the variables in the analysis. In addition to age, variables used in the regression analysis were use of probiotics, requirement of more than two intubations, requirement of indwelling central venous catheter for more than 7 days, and duration of ventilation at the end of 7 days (time for which probiotics were administered). Only variables which were significant on univariate analysis were included for the multivariate analysis model.

The number of children who had genetic syndromes was not a major proportion to be included in the analysis. Steroid use was one of the exclusion criteria for the study; this was mentioned in the section of methodology. However, data on transport out of PICU was not collected.

We do agree with Saptharishi et al. [1] that presentation of some of the data in Tables 1 and 2 as median (interquartile range) would have improved the clarity regarding the true distribution of the data without affecting any of the study results.

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the

ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments. This article does not contain any studies with animals performed by any of the authors.

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