imipenem, meropenem, cotrimoxazole, cefoperazone/ sulbactum, ticarcillin/ clavulinic acid and tigecycline.

Penicillin was the standard drug of choice for treating pneumococcal infections for many years until the emergence of resistance to penicillin [3], which compelled the use of alternative antibiotics. Among the 20 microbiologically identified pneumococcal isolates in pediatric patients from our laboratory, cefotaxime and ceftriaxone non-susceptible pneumococci accounted for 5 (25%) cases. Some of these cases also showed levofloxacin resistance (37.5%). Thus, it can be implied that the overall prevalence of resistance to beta-lactam agents amongst pneumococcal species mirrors the rise in resistance documented worldwide [4].

Staphylococcus aureus is an important cause of both community-acquired as well as hospital-associated infections. The incidence of methicillin resistant *S. aureus* (MRSA) varies from 25 per cent in Western part of India to 50 per cent in Southern India [5]. In 175 confirmed cases of infections due to *Staphylococcus aureus*, prevalence of MRSA was 133 (76%). No resistance was reported towards vancomycin, teicoplanin, linezolid and tigecycline. β-lactams are superior for the treatment of MSSA bacteremia and endocarditis. With MRSA isolates being widespread, it is necessary to de-escalate to β-lactams once the cultures reveal a MSSA isolate. Glycopeptides and linezolid need to be used only against MRSA isolates.

In conclusion, high level of resistance to the first line drugs probably reflects their overuse or irrational use in the treatment of unrelated infections. This calls for more studies and mandates a review of first line therapeutic strategies.

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Treatment of Neonatal Seizures: Levetiracetam *vs* Phenobarbitone

We read the recent study by Vykuntaraju, *et al*. [1] with great interest. Phenobarbitone, the currently used first line antiepileptic drug in neonatal seizures, has been associated with increased neuronal apoptosis in animal models and cognitive impairment in humans. This well conducted randomized controlled trial comparing levetiracetam to pheonobarbitone addressed a relevant question. A few queries; however, emerge:

1) Sample size was calculated considering the proportion of outcomes in levetiracetam group to be 77% [2]. However, the reference study [2] had a higher proportion of premature babies, and electrographic seizure resolution was documented, which was not the case in present study [1]. Hence, a larger sample size might have been required. Also, same sample size cannot be used to calculate both safety as well as efficacy, as has been done in this study.
2) Baseline characteristics in both groups demonstrated hypoxic ischemic encephalopathy (HIE) as the predominant etiology; HIE stages, however, have not been specified. HIE stage 2 could show better response than stage 3. Subclassification could have avoided any unintentional bias.
3) Levetiracetam has been approved for use in children aged more than 4 and adults by the US Food and Drug Administration as an adjuvant drug. Hence, neonatal

use as an off-label drug [3] may pose an ethical dilemma.

4) Neonates have lower plasma clearance and higher volume of distribution; hence, longer half-life of levetiracetam as compared to adults [4]. Most studies in small population groups, have been insufficient to understand the pharmacokinetics and advocate routine use in neonates.This confusion is amplified by various studies where doses as low as 10 mg/kg/day and as high as 80 mg/kg/day have been used. Appropriate neonatal dose needs to be established through phase II trials.

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AUTHOR'S REPLY

We thank the readers for critically evaluating our research study [1]. The queries raised are addressed below:

1. The sample size required was calculated based on difference in proportion of outcomes between the two groups as 31% (levetiracetam 77% and phenobarbitone 36%), and this data was taken from a systematic review on the efficacy of levetiracetam in neonatal seizures [2]. The sample size was calculated based on efficacy and not based on adverse events/safety as efficacy was our primary outcome. We agree that electrographic seizure resolution was not documented and the sample size was inadequate for the outcomes related to various adverse effects; this has already been mentioned as a limitation of the study [1].
2. Hypoxic ischemic encephalopathy (HIE) staging was done and no statistical difference in outcome was noted between HIE stage II *vs*. HIE stage III (11 HIE stage II *vs*. 9 HIE stage III in levetiracetam group and 13 HIE stage II *vs*. 11 HIE stage III in phenobarbitone group).
3. In 2012, FDA approved levetiracetam for use as adjunctive therapy for partial onset seizures in infants and children one month of age and older [3]. In 2013, levetiracetam gained monotherapy indications with new level I, II, and III evidence for use in adult partial onset seizures, adult tonic-clonic seizures and children with benign childhood epilepsy with Centro temporal spikes [4]. Despite lack of studies supporting its use at that time, a 2007 survey demonstrated 47% of pediatric neurologists recommend levetiracetam, off-label for the treatment of neonatal seizures [5].
4. We acknowledge that dose of levetiracetam is not established and we have chosen based on evidence available from off-label use and our experience. In our study, no adverse events were noted with 20 mg/kg. We agree that trials comparing different dose regimens have to be conducted in future.

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