EDITORIAL

Management of Children with Severe Acute Malnutrition in India: We Know Enough to Act, and We Should Act Now

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The fourth round of National Family Health Survey (NFHS-4) conducted in 2015-16 provides an intriguing and disturbing trend on malnutrition in India. Over a ten year period since 2005-06, the proportion of under-five children suffering from Severe Acute Malnutrition (SAM), as measured by Weight-for-height Z score (WHZ) <–3, based on the WHO standards has increased from an already high proportion of 6.4% to 7.5% [1]. It is well established that malnutrition increases the risk of death in a dose-dependent fashion. For children with WHZ <–3, the mortality risk is 10 times higher than non-wasted children, and for those with WHZ <–4, it increases to 20 times! There is a reasonable homogeneity in these risk estimates across countries and over time periods [2].

In a paper published in this edition of *Indian Pediatrics*, Sachdev and colleagues [3] followed up a cohort of 409 severely wasted children identified as part of a cross-sectional survey in Meerut district of Uttar Pradesh; the median follow-up duration was 7.4 months. There were 11 deaths, with a case fatality of 2.7%. At follow-up, 30% of the survivors were still severely wasted and 31% had recovered spontaneously. The authors call for confirmation of the low case fatality and spontaneous recovery rates in Indian children. Comparing the findings with those from African studies and with a recently concluded multicenter trial in India [4], they raise a concern on the benefits of investing in community management of SAM in India.

We suggest exercising caution in interpreting these estimates. First, the small sample size precludes reliable estimates of mortality. Further, children with severe illnesses and physical deformities were excluded from the assessment. This could have excluded several SAM children with complications, who were likely to have much higher mortality. The fact that severe wasting rate (2.2%) in the study was less than half of that reported by NFHS-4 for rural Meerut District (4.9%) suggests that this may be a possibility [5]. The follow-up was conducted once over a varying period, which might have led to missing out on the long-term impact of severe wasting on mortality. Finally, the study did not include children below 6 months of age, which would have led to underestimates of the risk, given the high vulnerability of this group.

However, it is also plausible that risk of mortality among severely wasted children has decreased over years as suggested by the authors. Does that diminish the public health importance of the problem in India? Applying NFHS-4 estimates of SAM to the under-five child population, we have over 1 crore SAM children in the country. Using the estimates of case fatality of 2.7% provided in this paper, there would be more than 270,000 child deaths due to SAM. So, should we be worried? Do we require urgent action? We strongly believe that the answer to both these questions is a resounding and sobering yes. It is important to review the options available to address this problem, and to implement them with full sincerity and urgency.

Do we have effective interventions to improve outcomes among SAM children in India?

Based on the review of available evidence from several studies in Africa and South Asia, large scale program experience and consensus among the experts, Indian Academy of Pediatrics (IAP) recommended an integrated management of SAM comprising of in-patient management of children with complications and out-patient management of those with no complications, which included judicious use of therapeutic food. Since there was not enough evidence on effectiveness of Ready to Use Therapeutic Foods (RUTF) in Indian settings, it was recommended to generate Indian data, to identify an effective and safe therapeutic food that is "acceptable to the children and meets WHO/UNICEF specifications" [6].

Since then, a large multi-centric trial in India tested the effectiveness of an approach combining community-

based detection, early use of antibiotics, identification and prompt management of illnesses and provision of therapeutic food, on recovery of children with SAM in India [4]. The trial compared commercially available RUTF and locally manufactured RUTF with energy rich home foods augmented with micronutrients. The recovery rates were highest for children who received locally manufactured RUTF (56%), followed by those who received commercial RUTF (47.5%), and then by those who received augmented home foods (42.8%). The study was not designed or powered to estimate the impact on mortality, but overall five out of the 906 enrolled SAM children across the three arms died during the study period, indicating a low case fatality. While this study does suggest that a community-based approach is an effective and safe option for management of SAM in India, an important concern stays. In this study, when children were followed-up 16 weeks after completion of treatment, one-third of them were again found to be severely wasted. While more studies and innovative solutions from India would be required to better understand the reasons for this slipping, evidence from South Asia and Africa may provide some solutions.

One of the earliest and most elegant studies on community management of SAM, from Bangladesh, followed up recovered children every two weeks for a period of one year – providing dietary advice and recognition and referral of illnesses for appropriate treatment. Early identification of illness and prompt management led to negligible relapse rates [7]. In another trial in Africa, therapeutic food was continued for a few weeks even after the child had recovered as per anthropometric assessment [8]. Both these studies highlight the importance of continued care beyond the recovery.

Call for action

The origin of malnutrition and that of severe malnutrition lie in social and economic conditions of the families and communities in which children live, the autonomy which women enjoy, and the resources they have to act in best interests of their children [9]. A long-term solution to preventing SAM lies in correcting the social, economic and gender inequities, and in providing a nurturing environment to all children. In the short term, it is an ethical imperative that we reverse the highly vulnerable situation we have failed to prevent them from slipping into. We know that a set of interventions, delivered in an integrated manner in the community and in health facilities, can prevent many of these deaths – the exact estimates may vary. Beyond survival, in our field areas in Southern Rajasthan, we see a significant impact of management of SAM children on activity levels and interest of the children in surroundings – *aankh ki chamak* "brightness of the eyes", as mothers tell us.

Waiting for correction of social and economic inequities and for generation of more effective solutions, and not taking any action based on available knowledge will be irresponsible. We should act on what we know to light up the lives and brighten the eyes of millions of severely malnourished children in India.

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EDITORIAL

Levamisole: Standard or Intensive Therapy?

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Nephrotic syndrome has an estimated prevalence of 12-16 children per 100000 child population [1]. Almost one-half of these patients have frequent relapses or steroid dependence, which require management to prevent complications due to relapses as well as toxicity of corticosteroid therapy [2]. The initial management of patients with frequent relapses is with long-term prednisolone, which while effective, is associated with risks of steroid toxicity, particularly impaired growth and bone mineralization, and visual and metabolic complications. The use of steroid-sparing agents that enable reduction or cessation of corticosteroid therapy is therefore recommended [3,4]. Medications accepted for this purpose include levamisole, cyclophosphamide, mycophenolate mofetil (MMF), calcineurin inhibitors and rituximab. Evidence for their use is based on retrospective or prospective case series, few randomized placebo-controlled studies and even fewer comparative trials [5]. Guidelines from professional organizations recommend the use of steroid-sparing agents, but the order of therapy is not defined [3,4].

For more than three decades, levamisole has been considered effective and safe for preventing relapses of steroid-sensitive nephrotic syndrome [2-4]. The medication is available in Asia and marketed in few countries in Europe, but not in North- and South-Americas, and Africa. Data from multiple case series and meta-analysis of trials confirm that 1-2 year therapy with levamisole is steroid-sparing and results in about 50% reduction in relapses [5]. Despite clinical effectiveness, there is a limited evidence to explain the mechanisms of levamisole action. Some studies suggest that therapy results in upregulation of specific cytokines, including interleukin (IL)-8, IL-24 and those involving Th1-lymphocytes [6]. Glucocorticoid receptor expression and signaling on podocytes may be modulated by levamisole, and contribute to the response [7].

Two recent trials (available as conference abstracts) emphasize the efficacy of levamisole in relapsing nephrotic syndrome [8,9]. A study from our center compared the efficacy of alternate-day therapy with levamisole (n=73) to daily MMF (n=76) in reducing the frequency of relapses [8]. Over next 12 months, there were similar number of relapses in the two groups; relative relapse rate 1.27 relapses/person-year (95%CI 0.94, 1.74; P=0.12). The respective relapse rates were significantly reduced compared to the year preceding randomization in both levamisole (mean difference 2.1 relapses/person-year) and MMF (mean difference 2.4 relapses/person-year) (both P<0.0001) groups. The second is a double-blind placebo-controlled study that evaluated the efficacy of one year levamisole versus placebo therapy in 99 patients [9]. During follow-up, the time to relapse was increased in patients receiving levamisole compared to placebo (hazard ratio 0.22; 95% CI 0.11, 0.43; P=0.001). After 12-month treatment, 6% patients receiving placebo and 26% receiving levamisole were in remission (P=0.012). Moderate neutropenia, which reversed on discontinuation of treatment, occurred in 8%. Other side effects of prolonged therapy included elevation of transaminases and rare occurrence of small vessel vasculitis.

In this issue of *Indian Pediatrics,* Samuel, *et al.* [10] report a retrospective experience with levamisole in 95 patients with frequently-relapsing (n=62) and steroid-dependent (n=33) nephrotic syndrome. Therapy with alternate-day levamisole (2-2.5 mg/kg) was effective in 70 (73.7%). Out of 25 patients where alternate-day therapy with levamisole was not successful, a switch to daily levamisole administration at similar doses resulted in additional success in 14 patients. Therapy with standard alternate-day and the novel daily-therapy thus resulted in an overall benefit in 84 (88.4%) patients. Similar to others, results were better in the frequent relapsers than those with steroid-dependence [5,8,9]. No side effects were observed, although there is a possibility of under-reporting in the retrospective review. The effect of therapy was not sustained; one-half of patients showed frequent relapses on stopping levamisole.

The above observations are interesting and similar to recent reports that show promising results of daily therapy, should administration of alternate-day levamisole fail [11]. However, the literature is limited , and includes retrospective and prospective case series with significant risk of selection, performance and detection-bias; all of which might result in overestimation of effect-size by 20-35%. A placebo-controlled, multicenter double-blind randomized trial, stratified for steroid dependence, is required to examine if daily administration of levamisole is superior to alternate-day therapy. Given the observed effect, the study would require 130 patients per arm at 90% power, two-tailed alpha error of 5% and assumed attrition of ~10%. A careful prospective monitoring for adverse events would be necessary.

A note of caution! Five decades ago, the ISKDC empirically recommended 8 weeks of prednisone treatment for the initial episode of nephrotic syndrome; this increased to 12 weeks based on a randomized study by the APN [12]. Over the next 25 years, multiple open-label randomized studies (some with significant bias) showed that further prolongation of therapy was even better, resulting in meta-analysis based guidelines for ~7-month initial therapy, despite risks of steroid toxicity [13]. Over the past 4 years, the wheel has come 'full circle' with four high-quality multicenter double-blind trials affirming that 8-12 week initial therapy was enough with prolongation having no long-term benefits [14,15].

We need not follow the same path for levamisole. Multiple randomized trials affirm the satisfactory role of levamisole, administered on alternate days, as a steroid-sparing agent in patients with relapsing nephrotic syndrome. Until results from placebo-controlled studies confirm the benefits and safety of daily over alternate-day levamisole therapy, we suggest that pediatricians continue to follow standard guidelines for treatment.

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