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N-Acetyl Cysteine in Non-Acetaminophen Pediatric Acute Liver Failure: Recent evidence !

We read with interest the current consensus statement on management of acute liver failure in infants and children [1]. Pediatric acute liver failure (ALF) is a devastating disease in which previously healthy children rapidly lose hepatic function due to a variety of causes and become critically ill within days. Management is largely supportive and only few conditions are amenable to directed therapy, such as acute acetaminophen toxicity. N-acetyl cysteine (NAC) replenishes mitochondrial and cytosolic glutathione stores and is the treatment of choice for acute acetaminophen toxicity. Studies in the past have shown some role of NAC in non-acetaminophen ALF [2,3].

The writing committee stated that there is increasing evidence for use of NAC infusion in non-acetaminophen causes of ALF [1]. They recommended routine use of NAC in the dose of 100 mg/kg/day in all cases of ALF irrespective of the etiology. This was based on a retrospective single site review involving 170 children done by Kortsalioudaki, *et al.* [2]. In this study NAC was associated with a shorter length of hospital stay, higher incidence of native liver recovery without transplantation, and better survival after transplantation.

However, a recent well designed placebo controlled trial conducted by the Pediatric Acute Liver Failure Study Group does not support the broad use of NAC in non-acetaminophen Pediatric ALF [4]. This multi-centre trial included 184 children under the age of 18 years. The study group found that NAC did not improve 1-year survival in children with non-acetaminophen ALF. One-year liver transplant free survival was significantly lower in the NAC-treated group, especially among children less than 2 years of age with HE grade 0-1. This study emphasized the importance of conducting prospective pediatric drug trials.

With the availability of new evidence in recent literature, indiscriminate use of NAC in all cases of pediatric ALF is not justified.

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Should N-acetylcysteine be used in Treatment of Non-acetaminophen Pediatric Acute Liver Failure?

In a recently published consensus statement on management of acute liver failure, the authors have recommended the use of N-acetylcysteine in the treatment of children with non-acetaminophen pediatric acute liver failure [1]. Intravenous N-acetyleysteine (NAC) was incorporated into the general management of acute liver failure following a small uncontrolled study suggesting improved cardiovascular hemodynamics and oxygen transport in liver failure in adults [2]. In pediatric population, NAC became popular after a retrospective

single-center review from Kortsalioudaki, *et al*. [3] which affirmed its beneficial effect in acute liver failure. Based on these data, the consensus among pediatric hepatologists over the years has been to use this inexpensive medication in liver failure.

However, a recently published, decade long, multi-centric, randomized placebo controlled study to test the widespread assumption of usefulness of intravenous NAC in non-acetaminophen pediatric liver failure by Squires, *et al*. [4] does not support broad use of NAC in this condition. The study by Squires, *et al*. in itself is unique with regard to its design and the results and perhaps is the only prospective study in children which tries to give an insight to the role of NAC in non-acetaminophen pediatric liver failure. More prospective studies are still warranted before we can establish the role of NAC in treatment of non-acetaminophen pediatric acute liver failure.

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Reversible Skin Hyperpigmentation in Imerslund-Grasbeck Syndrome

A 2-year-old girl presented with progressive hyperpigmentation of both the distal interphalangeal joints of fingers and toes along with palmar and plantar hyperpigmentation of both hands and feet for the last one year with no other associated symptoms. Clinically, her weight (13.5 kg), height (91 cm) and developmental assessment were appropriate for age. Her other systemic examination but for her skin pigmentation were all normal. Investigations were not contributory, other then a low vitamin B_{12} level (84.2 pg/mL) and mild megaloblastic picture in bone marrow. A diagnosis of Imerslund-Grasbeck syndrome (IGS) was considered and was treated with intramuscular injection of 1000 µg methylcobalamin daily for 7 days, followed by weekly injections for 1 month and then oral doses of 1000 µg daily. With therapy, there was a significant change in 10 days time and there was total resolution of skin lesion in a month's time. She was advised to have lifelong daily therapy with 1000 µg oral methylcobalamin.

Hyperpigmentation due to vitamin B_{12} deficiency appears only in patients whose skin is normally pigmented, hence may not be a feature in Caucasians, whereas it is more common in darker-skinned patients. In Indian children, isolated mucocutaneous lesions could be one of the earliest signs of B_{12} deficiency [1] that may predate other systemic manifestations. IGS should be considered in any individual with macrocytic anemia, reduced serum B_{12} levels and proteinuria. This child with IGS had only skin manifestation on presentation, probably with time haematological manifestations could have surfaced, as evidenced by the marrow revealing megaloblastic changes despite other haematological indices being normal. Life-long treatment with vitamin B_{12} is necessary for IGS, which alleviates hematologic, gastrointestinal and CNS symptoms except proteinuria [2]. High oral doses of B_{12} (1000 µg and 2000 µg) is safe, acceptable and as effective as intramuscular administration [3,4]. Oral treatment is based on the finding that in larger doses, sufficient amounts are absorbed even in the absence of intrinsic factor.

Available literature suggests that, pigmentary changes remain unresponsive with vitamin B_{12} replacement in IGS as was observed in two Chinese siblings [5]. This child with vitamin B_{12} replacement had complete resolution of skin pigmentation but her proteinuria persisted even on follow up for 3 years.

To conclude, a diagnosis of vitamin B_{12} deficiency has to be considered in any case of isolated skin hyperpigmentation.