the participants in their study because it was set in rural Democratic Republic of Congo. All of the limitations are appropriately accounted for in the analysis and discussion.

Dietary supplementation not only has an impact to prevent malnutrition, but also impacted development in children. The report is provocative and raises the question about what intervention or combination of interventions are likely to be most optimal in LMIC. Is this the Holy Grail to optimize nutrition in children in LMIC? The next generation depends on identifying the appropriate implementation of programs to decrease prevalence of malnutrition to the rates set in the millennium development goals. More evaluation in real settings such as that described by Addo et al will provide the data that will assist with policy development and implementation by governments and agencies. Malnutrition rates remain alarming high and wasting still impacts the lives of far too many young children. ■

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Paracetamol (Acetaminophen) for Patent Ductus Arteriosus: Where Do We Stand?

The patent ductus arteriosus (PDA) closes spontaneously by the end of the first postnatal week in most preterm infants ≥28 weeks of gestation.[1] In contrast, 50%-70% of infants <28 weeks of gestation persist in having a moderate-to-large PDA shunt for weeks after birth.[1] Indomethacin and ibuprofen are currently the only drugs labeled for treatment of the PDA. Paracetamol (acetaminophen) also seems to be an effective agent for inducing PDA closure.[2] Although its mechanism of action has not been fully elucidated, paracetamol's vasoconstrictive effects seem to be mediated through inhibition of the peroxidase moiety of prostaglandin H2 synthetase.[3] With its presumed superior safety profile, paracetamol has the potential to be an excellent substitute for the 2 currently labeled drugs.

See related article, p 79

PDA Patent ductus arteriosus
RCT Randomized controlled trial

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In this volume of *The Journal*, Kumar et al report the results of a randomized, controlled, head-to-head, noninferiority trial testing the hypothesis that enteral paracetamol is noninferior to enteral ibuprofen in closing moderate-to-large PDA shunts in preterm neonates of <32 weeks of gestation.[4] Using an a priori noninferiority margin of 15%, they found that enteral paracetamol was noninferior to enteral ibuprofen in closing the PDA.[4] This study adds additional information to the 7 other randomized, controlled trials (RCTs) that have compared enteral paracetamol with enteral ibuprofen.[5-11] So, are we now at the point where we can finally say that enteral paracetamol is as effective as enteral ibuprofen and, by extension, as effective as indomethacin, because meta-analyses have also concluded that ibuprofen is comparable with indomethacin?[12]

To answer that question, we need to examine in greater detail several features of the current study's design. Noninferiority trials are most often used in cases where a conventional RCT, designed to show that a new treatment is superior to a placebo, is considered unethical. The new treatment is rather compared with a proven standard treatment, with the goal of showing that the new treatment is not unacceptably worse than the standard, especially if the new treatment has other potential benefits. Noninferiority trials are specifically powered to answer the question of good enough efficacy, where good enough is defined by a margin of noninferiority, determined a priori from studies that compare the standard treatment with a placebo; it is designed to maintain at least a certain amount of the standard treatment's proven superiority over no treatment/placebo, while specifically improving on the placebo itself. When comparing the new treatment with the standard treatment, the results are determined to either fall within the region defined by the specified margin (in which case the new treatment is judged to be good enough and noninferiority is concluded) or not (in which case the null hypothesis of inferiority cannot be rejected). However, noninferiority trials have their own limitations in both design and interpretation. Narrow margins require large study numbers. Conversely, wide margins run the risk of inflation of type I error and erroneous acceptance of an inferior treatment. In addition, the margin of noninferiority is calculated under the assumption that we know the benefit of the standard treatment over placebo, to be certain that the new treatment improves on no treatment at all. This last assumption is not always so straightforward, especially when considering closure of the PDA where many unknowns are at work.

Ductus closure after birth depends on the balance between competitive pathways that regulate ductus smooth muscle constriction and ductus smooth muscle relaxation. The factors that regulate this balance change markedly with advancing gestation.[13-16] Prostaglandin-mediated vasodilation seems to be the primary vasodilator pathway affecting the fetal and neonatal ductus during the first 48 hours after birth. The infant's gestational age, as well as the infant's race/ethnicity, ancestral background, growth restriction, and exposure to antenatal betamethasone are all important modifiers of prostaglandins' effects and play a significant role in determining the rate of drug-induced closure during the first days after birth.[16-19] Unfortunately, most of the drug-comparison trials (like the trial by Kumar et al) have studied populations that include relatively few infants below 28 weeks of gestation.[4] These extremely low gestational age infants are the most resistant to pharmacologic ductus closure and seem to respond differently when compared with more mature infants. For example, ibuprofen seems to produce a similar rate of ductus closure as indomethacin in studies where the average gestational age is 28 weeks or greater.[12] In contrast, when the study population is restricted to infants born before 28 weeks' gestation, ibuprofen seems to be less effective than indomethacin in producing persistent ductus closure.[20] We have similar concerns regarding the RCTs comparing paracetamol with ibuprofen and indomethacin. Although paracetamol seems to be as effective in these trials as ibuprofen and indomethacin, none of the RCTs (including the trial by Kumar et al) restricted the study populations to those born before 28 weeks of gestation.[2,4-11,21-25] To address this concern, a recent multicenter RCT compared the efficacy of the 3 drugs in infants delivered exclusively before 28 weeks of gestation who still had a moderate-to-large PDA at the end of the first week.[26] The trial found that infants treated with indomethacin had the greatest rate of constriction among the 3 drugs tested: when compared with the rate of spontaneous PDA constriction (which was 20%) during the 7-10 days after enrollment, the relative risk of indomethacin-induced closure was 3.21 (95% CI, 2.05-5.01), followed by ibuprofen at 2.03 (95% CI, 1.05-3.91), and acetaminophen at 1.33 (95% CI, 0.55-3.24).[26] It should be noted that, even in the infants studied by Kumar et al, the rate of ductus closure after paracetamol appeared to be less robust than after ibuprofen.[4] Although the ultimate rate of PDA closure after 1 or 2 courses of paracetamol was similar to the rate of closure after ibuprofen, the rate of PDA reopening was higher after paracetamol and more neonates who were treated initially with paracetamol required a second course of the drug. These findings are consistent with in vitro and in vivo preclinical studies which found paracetamol to be less effective than the other cyclo-oxygenase inhibitors in very immature animals.[3,27]

It is also important to note that, because other nonprostaglandin-mediated vasodilator pathways emerge after birth, the role of prostaglandins in maintaining ductus patency becomes less important.[28,29] As a result, the effectiveness of all 3 drugs—paracetamol, ibuprofen, and indomethacin (which act primarily through prostaglandin inhibition)—wanes with advancing postnatal age.[30]

The infant's postnatal age is also likely to affect the pharmacokinetics and the pharmacodynamics of the drugs used to close the ductus. However, few pharmacokinetic or pharmacodynamic studies have been undertaken to determine the best dose, frequency, duration and route of administration of paracetamol for effective PDA closure.[3,26,31,32] Only 2 small trials have compared the effects of intravenous with enteral paracetamol administration; unfortunately, each had opposing results.[3,31] Similarly, the range of effective

paracetamol serum concentrations is still in doubt. Bin-Nun et al found that serum concentrations of 20 mg/L or greater predicted ductus constriction; in contrast, Liebowitz et al found no difference in paracetamol concentrations between infants who constricted their ductus and those who did not.[26,32] Future pharmacodynamics trials will be needed to determine if serum paracetamol concentrations can predict ductus constriction and whether these concentrations can be achieved safely by increasing enteral or intravenous dosing.

Probably the most important variable in evaluating drug effectiveness in any PDA drug treatment trial is the background rate of spontaneous ductus closure in the study population. This factor is especially true for noninferiority trials where the margin of noninferiority is calculated based on the benefit of the standard treatment over nontreatment/placebo to make sure that the new treatment actually does improve on no treatment at all. Studies that include a large number of infants in which the PDA is likely to close spontaneously by the end of the drug treatment period (without any drug treatment) run the risk of biasing the study outcome toward rejecting the null hypothesis, and concluding that the new drug is noninferior to the standard (even though the new drug may really be inferior). This problem is significant when examining studies where the average gestational age is greater than 28 weeks because the rate of spontaneous closure during the study period is likely to be as high as 70%-80%.[23] The rate of spontaneous constriction is considerably lower among infants born before 28 weeks of gestation, but still is around 54% in infants born between 26 and 27 weeks, and 26% in infants born at 25 weeks of gestation or less.[33] The rate of spontaneous constriction also varies widely between study centers, even when criteria are standardized for determining the size of the ductus shunt and the age of the study population. Among the 17 centers in the PDA-TOLERATE trial, the incidence of spontaneous constriction at the end of the first week ranged from 21% to 77% in infants born between 26 and 27 weeks of gestation, and from 8% to 50% in infants born at 25 weeks of gestation or less.[33] This center-specific incidence of spontaneous ductus constriction brings up an obvious caveat: in head-to-head comparative studies, like the one of Kumar et al, evaluation of the study results is difficult when a placebo group is not included and the rate of spontaneous closure is unknown in the study population.[4] In drug comparison studies, it should come as no surprise when a study site that has a very high incidence of spontaneous ductus closure reports that it finds no difference between the drugs in the rate of ductus closure; most of the infants at that site would have closed their ductus with or without drug treatment anyway!

The current interest in paracetamol for PDA constriction is based on the thought that, if effective, paracetamol might have fewer side effects than indomethacin or ibuprofen. Unfortunately, information about paracetamol's long-term effects in this population is lacking. Recently, concern has been raised about paracetamol's presumed superior safety profile based on reports of neurocognitive impairment after prenatal exposure and of hypotension following intravenous administration.[34,35] This concern underscores the need for appropriate pharmacodynamic and follow-up studies examining both the route and dose of paracetamol, as well as the population being studied, before we can conclude which is the most effective and safest drug to use when PDA treatment is needed. ■

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