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References

1. Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. Inflamm Bowel Dis 2011;17:423-39.
2. Adamiak T, Walkiewicz-Jedrzejczak D, Fish D, Brown C, Tung J, Khan K, et al. Incidence, clinical characteristics, and natural history of pediatric IBD in Wisconsin: a population-based epidemiological study. Inflamm Bowel Dis 2013;19:1218-23.
3. Vernier-Massouille G, Balde M, Salleron J, Turck D, Dupas JL, Mouterde O, et al. Natural history of pediatric Crohn's disease: a population-based cohort study. Gastroenterology 2008;135:1106-13.
4. Walters TD, Kim MO, Denson LA, Griffiths AM, Dubinsky M, Markowitz J, et al. Increased effectiveness of early therapy with anti-tumor necrosis factor-alpha vs an immunomodulator in children with Crohn's disease. Gastroenterology 2014;146:383-91.
5. Mackner LM, Greenley RN, Szigethy E, Herzer M, Deer K, Hommel KA. Psychosocial issues in pediatric inflammatory bowel disease: report of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr 2013;56:449-58.
6. Greenley RN, Hommel KA, Nebel J, Raboin T, Li SH, Simpson P, et al. A meta-analytic review of the psychosocial adjustment of youth with inflammatory bowel disease. J Pediatr Psychol 2010;35:857-69.
7. Mackner LM, Bickmeier RM, Crandall WV. Academic achievement, attendance, and school-related quality of life in pediatric inflammatory bowel disease. J Dev Behav Pediatr 2012;33:106-11.
8. Cohen BL, Zoega H, Shah SA, Leleiko N, Lidofsky S, Bright R, et al. Fatigue is highly associated with poor health-related quality of life, disability, and depression in newly-diagnosed patients with inflammatory bowel disease, independent of disease activity. Aliment Pharmacol Ther 2014;39:811-22.
9. van der Valk ME, Mangen MJ, Leenders M, Dijkstra G, van Bodegraven AA, Fidder HH, et al. Risk factors of work disability in patients with inflammatory bowel disease—a Dutch nationwide web-based survey: work disability in inflammatory bowel disease. J Crohns Colitis 2014;8:590-7.
10. Singh H, Nugent Z, Brownell M, Targownik LE, Roos LL, Bernstein CN. Academic performance among children with inflammatory bowel disease: a population-based study. J Pediatr 2015;166:1128-33.

Meconium Stained Newborns: Ethics for Evidence in Resuscitation

The name meconium aspiration syndrome (MAS) for the immediate respiratory distress associated with meconium stained amniotic fluid (MSAF) in a newborn highlights the beliefs of obstetricians and neonatologists about the etiology of MAS. For decades, airway obstruction was assessed to be a major component of MAS and, consequently, suction maneuvers directed to remove meconium from the airways were recommended to decrease the frequency and severity of MAS. The background behind those policies and recommendations were the results of a few observational studies with designs that would currently be considered inappropriate to prove causality.[1-3] In particular, there is a lack of correlation between the presence of meconium in the trachea and clinical symptoms of severe MAS.[4]

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More recently, two large randomized trials demonstrated that suctioning meconium from the airway, either before or after birth, does not improve the prognosis of infants born through MSAF. The study of prenatal oro- and nasopharyngeal suction by Vain et al included all infants with MSAF, whereas the trial of endotracheal intubation and suction by Wiswell et al randomized only infants who were vigorous at birth.[5,6]

Following recommendations of the Neonatal Resuscitation Program, when infants with MSAF are born depressed, most neonatologists continue suctioning of the airway before initiating positive pressure ventilation (PPV).[7] However, the International Consensus on Cardiopulmonary Resuscitation 2010 recommendations acknowledge a lack of evidence for this procedure.[8]

As with many routine practices that remain unproven, the procedure appears to make sense. We know that there is meconium in the amniotic fluid and, therefore, in the airway. We introduce the endotracheal tube, while the in-

MAS	Meconium aspiration syndrome
MSAF	Meconium stained amniotic fluid
PPV	Positive pressure ventilation
RCT	Randomized control trial

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fant is not breathing; why then not clear the airway from meconium before starting PPV? Several questions arise: Is clearing some meconium that could be located in the larynx and trachea enough to prevent or ameliorate MAS? The performance of endotracheal intubation takes time even in well trained hands. To be more efficient in eliminating meconium, we were taught to use the endotracheal tube as the suction device while withdrawing it from the airway, and to repeat the maneuver 2 or 3 times before initiating PPV.[3] Delaying the onset of PPV and eventually the administration of oxygen in potentially asphyxiated infants could lead to unnecessary hypoxia, increase acidosis and hypercapnia, and potentially intensify pulmonary hypertension.

The study by Chettri et al published in this issue of *The Journal* should therefore be welcomed by the perinatal community.[9] The authors should be congratulated for being brave enough to evaluate in a single center randomized control trial (RCT) a procedure that albeit unproven, is considered standard of care by most neonatal groups. The study is small and has several other drawbacks. First, the process of enrollment, randomization, and treatment assignment can be questioned because the allocation of the intervention was performed prior to subject qualification. However, the process described by the authors makes selection bias unlikely. Second, the circumstances in which the informed consent process was carried out raise concerns as to its validity.

Nevertheless, 122 depressed infants born with MSAF were "randomly" exposed to either intubation and suction followed by PPV or to no suction and immediate PPV. Moreover, another similar study performed in India was recently presented at the 2014 Pediatric Academic Societies meeting: 175 non-breathing infants born through MSAF were similarly randomized.[10] Most importantly, in both studies there were no differences reported in any clinical outcome between groups.

These results spark several interesting and controversial questions and issues: Are these 2 studies sufficient to confirm that the procedure should not be performed? In our opinion, not yet. The history of neonatology is full of examples of small studies demonstrating an effect or an association that cannot be sustained after 1 or more large RCTs are performed.[11-13] Both studies have to be considered as pilots acknowledging that the risk of a type II error is high.

However, as some authors point out, the best possible information can be preferable to no information for questions where low statistical power should be much less of an issue for both institutional review boards and editors than the potential for under-reporting of systematic bias.[14,15] The lack of evidence acknowledged by experts, together with the results of these recent trials, highlight the need for more definitive studies.[8-10] To carry out a large multicenter RCT exploring the effect of endotracheal intubation and suction in non-breathing meconium stained infants would face several major difficulties. In our view, the most important would be those related to the methodological aspects and the validity of the informed consent process.

Recently, these specific topics were the focus of a published debate among several experts discussing the issue of waiving consent and other alternatives such as antenatal consent.[16] As described in a previous editorial in *The Journal*, consent should be free, voluntary, sufficiently informed, and should include the description of alternatives to participating in research. Time should be provided for reflection, and consenting parents must be competent to give consent.[17] Can parents under the stress of labor complicated by MSAF be competent to give consent? Can an ethically valid informed consent be obtained during labor in pregnancies complicated by MSAF? In our opinion, the answer to both questions is no.

In fact, the trials demonstrating the lack of effect of both intubation and suctioning for vigorous infants with MSAF and of the prenatal oral and naso-pharyngeal suctioning were performed under a waiver of informed consent.[5,6] These studies were relevant in that they resulted in the elimination of the recommendation to perform both procedures with no reports of a subsequent increase in MAS or other complications.[18] Proponents of a waiver of consent strategy for a trial such as this argue that the requirement of an antenatal consent would be misguided based on methodological, practical, and ethical grounds.[16] When consent is deemed mandatory, even for research in emergency situations, the risks are that both inclusion and representativeness of the population might be compromised.[19,20]

The strategy of prenatal consent for every woman admitted to the hospital for delivery as candidates for a neonatal trial is also questionable, can unnecessarily expose parents to stress, and was associated with the least level of comfort in a survey.[21,22] As done previously in neonatal resuscitation research, other modalities of randomization such as a cluster controlled trial could be considered to avoid conflicts with assignment and potentially allow other informed consent modalities such as a continuous process or an "opt-out" strategy.[23-25] Finally, some consideration should be given to designing a study of this sort as a non-inferiority trial.

Returning to the clinical aspects, in some infants born through MSAF, chest radiographs show severe involvement and potential obstruction of the airway (some areas of atelectasis and other areas with emphysema). However, many of those infants are almost asymptomatic. Other newborns show minimal radiographic involvement but they develop severe respiratory distress.[26] It is likely that the degree of asphyxia and pulmonary hypertension are more related to the severity of the disease than the degree of obstruction of the airway.[4,27] Although obstruction of the lower airways may contribute to MAS, all efforts to clear the airway have been so far unsuccessful for improving the prognosis. Several research studies have suggested that inflammation and surfactant inhibition caused by meconium may also be involved