the Kaiser HMO system may limit the generalizability of their results. It is possible that the observed risks are underestimates of those that would be observed in a less-advantaged population.

In conclusion, Petrini et al7 have provided important new information about the long-term prognosis of infants born at late preterm gestational ages. Pediatricians and other providers of care to late preterm infants should be more vigilant for potential neurocognitive problems in their follow-up of such infants. But this new information should also give us cause for concern about ovulation stimulation and multiple embryo transfer, and particularly about the rising rate of labor induction. We need to pose the question of whether more frequent induction might be doing more harm than good. Future observational studies with clinically detailed databases from HMOs and other health care systems should attempt to fill gaps with respect to additional potentially confounding factors—particularly pregnancy complications, labor induction, and other underlying maternal and fetal causes of preterm birth. It may be, however, that the issue of how much labor induction is too much can be adequately addressed only with a randomized trial of labor induction at 34 to 36 weeks for specific maternal or fetal indications. In the meantime, obstetricians, pediatricians, and other care providers should inform pregnant women of the long-term risks associated with late preterm birth and should take those risks into account when making decisions about ovulation stimulation, multiple embryo transfer, and labor induction.

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High-Flow Nasal Cannula: A Kinder, Gentler CPAP?

In this issue of The Journal, Lampland et al describe their observations comparing high-flow nasal cannula (HFNC) with traditional ventilator-derived continuous positive airway pressure (CPAP) for preterm infants. They reported that pressure increased with flow in their in vitro system and that the presence of a leak as low as 30% reduced such pressures to <3 cm H2O. They also noted an increasing RR in the infants receiving high flow nasal cannula (HFNC), as flow decreased from 6 lpm to 2 lpm.

Although the use of HFNC may seem like an attractive approach that would conceivably avoid trauma to the nose by using the smaller nasal cannula compared with most nasal CPAP interfaces, there are a number of concerns, including desiccation of the nasal mucosa with associated bleeding2 and airway obstruction3 when using non-humidified HFNC. However, as we have pointed out previously,4 the use of HFNC to deliver CPAP is problematic because the users generally have no knowledge of the actual level of CPAP delivered to the infant, and current delivery systems may not prevent excessive pressure delivery to the infants’ airway, which may result in significant lung overexpansion.5 Sreenan et al pointed out that adequate pressure delivery required maintenance of “a good seal in the oral cavity,”6 consistent with earlier observations that there is a dramatic fall in pressure from cannula to pharynx that is aggravated when the mouth is open, as shown for CPAP.7 Sreenan et al studied HFNC with as much as 2.5 lpm to produce CPAP of 6 cm H2O, as measured by equivalent esophageal pressures (4.5-4.6 cm H2O), and reported that 6 hours of such treatment was equivalent to 6 hours of traditional CPAP for the treatment of apnea in 28-week-old infants at 30 weeks post-conception.
tion age. Their calculations would indicate that a flow of 1.6 lpm in an infant weighing 1000 gm and 1.3 lpm for an infant weighing 500 gm with similar cannula would produce 6 cm H2O CPAP.

Lampland et al used a nasal prong and humidified delivery system to deliver HFNC. Even with flows of 6 lpm and with infants’ mouths closed, this study did not produce an esophageal pressure equivalent to that seen with 6 cm H2O of conventional CPAP. Their measured end expiratory esophageal pressures (EEEP) using a fluid-filled catheter were lower than those reported by Sreenan et al using an esophageal balloon. These methods may not produce identical results, and both are difficult to use in a clinical environment.

The authors demonstrated a trend of increasing EEEP with each liter increase in nasal cannula flow that was not significantly different from each separate flow measure or the EEEP seen with NCPAP at 6 cm H2O. Their Figure demonstrated that with increasing NC flow there was an increase in EEEP, but it was never equivalent to the 3.4 cm H2O at 6 cm H2O reported in their Table 1. They also noted very large variation in the EEEPs, suggesting that these measures are not clinically useful. Their mean EEEP was always <2 cm H2O for all flows <6 lpm, and for flows <3 lpm, they reported EEEPs <1 cm H2O. They did not find pressures similar to those reported by Sreenan et al (4.5 cm H2O at 6 cm H2O NCPAP), and this may reflect different measuring systems, nasal cannula size, and the duration of the measurements.

The use of a pressure-regulated source of CPAP, such as a ventilator or underwater seal, ensures that within narrow limits the delivered pressure will not exceed the set pressure, irrespective of the state of the airway. Even the use of nasal cannula oxygen with room air and flows as high as 2 lpm is of some concern. The American Association of Respiratory Care 2002 Clinical Practice Guideline stated that maximum flow for nasal cannula in newborn infants should not exceed 2 lpm, a flow that may be excessive for the extremely low birth weight infant. Locke et al previously demonstrated that with flows of 2 lpm it was possible to deliver 12 cm H2O CPAP, dependent on infant and cannula size, and subsequently demonstrated that HFNC are associated with significantly higher upstream pressures. There are increasing reports that use HFNC as a form of respiratory support in preterm and term newborn infants with flows as high as 6 lpm, and these reports do not document the level of CPAP or overall patient benefit.

Although it is unclear what the optimal level of CPAP is for any individual infant, earlier studies in infants with respiratory distress syndrome have suggested that this value is close to 8 cm H2O, with significant interpatient variability.

The airway pressure delivered using a high-flow gas source will vary with the presence of leaks within the airway. When these are always constant, the actual pressure may be predictable. However, such conditions seldom exist in the preterm infant. Thus, when the infant closes the mouth and there are dried secretions around the nares that essentially occlude the nose around the catheter tips, the flow will continue to increase the pressure until either the airway opens or the air under pressure can escape somewhere else. One would hope that that the natural airway orifices would be the first to give!

There are few routine clinical evaluations that can detect an over-expanded lung, and even daily chest radiography may not provide timely information about such a problem before the occurrence of an air leak. It is somewhat reassuring that retrospective reviews of the use of HFNC with flows as high as 8 lpm have not demonstrated significant morbidity, except for the observation of increased gram-negative infections. However, it would be more reassuring if the caregivers actually measured the esophageal pressure with their typical devices and a range of flows to ensure that they are not potentially over-distending the lung. It may be that the use of HFNC with very low effective pressures may be an advantage compared with CPAP, because infants may not require such treatment, and the potential benefit of HFNC is that it reduces infants’ exposure to measurable CPAP levels. It would appear that the use of nasal cannula with a pressure-regulated supply could reduce the likelihood of inadvertent over-distension, and at the same time, such devices will reduce the likelihood of providing significant CPAP to infants who no longer need such therapy. We agree with Lampland et al on the need for a properly powered prospective randomized trial comparing HFNC with known pressure delivery (if possible) and current methods of delivering CPAP and which evaluates important outcomes to properly determine the safe and effective use of HFNC.

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Infection, Inflammation, and the Downward Spiral of Cystic Fibrosis Lung Disease

Clinicians caring for children with cystic fibrosis (CF) are often found explaining the disease process to their patients’ families—and to themselves—as a “vicious cycle” of airway obstruction, infection, and inflammation wherein each of these 3 components contributes to both the overall progression of lung disease and the negative impact of the other 2 processes. Phenomenologically this makes perfect sense, because all 3 elements are easily demonstrated early in CF by a variety of methods and approaches. Pathogenetically, however, the waters remain muddied—which came first? Is this important? If early intervention is key to the “vicious cycle” question, the final answer remains elusive. As we are now in the era of widespread newborn screening for CF, the opportunity for preventive therapy has at least theoretically arrived. If the initiating insult in CF is obstruction due to airway surface fluid volume depletion and impaired mucociliary clearance, rehydration and airway clearance therapies are warranted as soon as possible after diagnosis.1-3 This is the current paradigm of CF pulmonary pathogenesis. However, antimicrobial or antiinflammatory therapy would be immediately indicated if these processes precede or accompany impaired clearance and obstructive lesions.4-8 Although studies of infants and young children with CF have yielded important insights to the “vicious cycle” question, the final answer remains elusive.

In this issue of The Journal, Sagel et al9 give results from the largest reported cohort of young children assessed for 2 components of the CF vicious cycle, infection and inflammation. These young children between 6 months and 6 years of age (mean, ~3 years) were selected for study on the basis of positive oropharyngeal (OP) cultures for Pseudomonas aeruginosa (PA) within the preceding year and at screening. Bronchoalveolar lavage was then performed within 3 weeks to evaluate infection by means of quantitative bacterial cultures and inflammatory markers such as neutrophil counts, neutrophil elastase, and proinflammatory cytokines. This study in CF analyzes effects of lower airway infection with several bacterial species on local inflammation and clinical status, and compares inflammatory responses to PA and Staphylococcus aureus (SA). The results suggest that lower airways infection at least in part drives the inflammatory process, in that inflammation was clearly linked to positive bronchoalveolar lavage culture, in a manner specific for and dependent on the bacterial pathogen, so that both PA and SA increase inflammation in an additive fashion that is related to bacterial density when both are present. PA infection also correlated with poorer clinical scores. The presence of a positive OP culture did not necessarily predict lower airway infection and attendant inflammation, confirming the primarily negative predictive usefulness of OP cultures, the backbone of current microbial surveillance in CF.10

Before considering the implications, it is useful to point out the limitations of the study design. First, many CF physicians intervene with antibiotic therapy for positive PA OP cultures; indeed, a large multicenter study is in progress in the United States to evaluate the safety and efficacy of several different approaches to early PA “eradication” therapy.11 Some physicians also apply an aggressive antibiotic approach to positive SA OP cultures.12 The study of Sagel et al9 does not allow an assessment of such interventions as treatment, and monitoring strate-

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**See related article, p 183**

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**Table 1**

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