

## Hazards of systemic steroids for ventilator-dependent preterm infants: What would a parent want?

Keith J. Barrington

Survival rates for very premature infants are improving, and even those born alive at 24 weeks' gestation now have a better than 50% chance of survival.<sup>1</sup> Furthermore, most very premature infants experience normal neurodevelopmental progress. Nonetheless, about 30% of survivors have neurodevelopmental disabilities, and in about half of these, the disabilities are severe, including cerebral palsy and global developmental delay.<sup>2</sup> Sadly, at least some of these problems may be associated with the life-saving intensive care needed by many infants born at less than 28 weeks' gestation. Such care often includes assisted ventilation, a treatment that may lead to acute lung injury followed by chronic lung disease and persistent respiratory problems in as many as a third of survivors.<sup>3</sup>

The early stages of lung injury include a florid inflammatory response. Recognition of this response led to trials of systemic steroids, in the hope that the inflammation would be dampened and pulmonary outcomes improved. Many case series reporting dramatic short-term improvements in gas exchange and lung mechanics were published in the late 1970s and 1980s. However, the use of steroids leads to abnormal brain development in newborn animal models,<sup>4</sup> and concerns were raised as long as 25 years ago that these drugs might also cause brain injury in newborn human infants and lead to increases in cerebral palsy and developmental delay. Given the already fairly high prevalence of neurodevelopmental problems in surviving babies, careful investigation of neurodevelopmental outcomes after administration of steroids to treat or prevent lung injury should have preceded their general adoption. Unfortunately, such investigations were not undertaken. Instead, researchers began randomized controlled trials of systemic steroids for infants with early or established chronic lung injury, all of them concentrating on short-term pulmonary outcomes; the first such study was published in 1983.<sup>5</sup>

To date, about 40 randomized controlled trials have been completed, but do they provide good evidence of substantial clinical benefit? The best evidence available, summarized in 3 systematic reviews,<sup>6-8</sup> has confirmed the initial clinical impression, that systemic glucocorticoids generally reduce oxygen requirements and allow earlier extubation, thus shortening the duration of assisted ventilation. Trials of "moderately early" steroid use (at 7 to 14 days of age) appear to show the greatest potential benefit. Steroids given at this postnatal age reduce the duration of oxygen therapy and consequently the proportion of children who are oxygen de-

pendent at 36 weeks corrected age, a common indicator of the severity of lung injury. It also appears that administration of steroids at this postnatal age also delays death, which leads to a reduction in the number of deaths before 28 days; however, the overall risk of dying before discharge from hospital is not significantly affected.<sup>6-8</sup> Steroids do not appear to affect the proportion of children who are discharged on oxygen. In another systematic review, in which the same studies were subdivided differently, Doyle and Davis<sup>9</sup> were also unable to demonstrate an improvement in the mortality rate for any particular group.

Given the lack of convincing evidence of a permanent benefit of steroids, are they at least safe? Unfortunately, the answer to that question is No. Growth impairment during therapy is nearly universal. Other frequent and serious short-term side effects include gastrointestinal perforation (in up to 12% of patients),<sup>10</sup> gastrointestinal hemorrhage (in 12%), infection (in 35%), hypertension (in 7%), hyperglycemia (in 32%) and cardiac hypertrophy (in 19%).<sup>6-8</sup>

The first study of any size to report long-term neurodevelopmental follow-up<sup>11</sup> was not published until more than 10 years after the first controlled trial appeared in print and was probably falsely reassuring, in part because the rate of treatment with steroids for control infants was 40%. In fact, most studies have allowed crossover treatment of control patients after a short delay and have reported rates of steroid treatment of controls as high as 62%. With such significant contamination of the randomization schedules, long-term follow-up has been largely uninformative about the effects of glucocorticoids on neurologic outcome, cognitive development or even pulmonary health.

Within the past 2 years the situation has begun to change, and 8 trials have now reported long-term neurologic and developmental follow-up after neonatal steroid treatment given in pharmacologic doses.<sup>11-18</sup> Four<sup>12-14,17</sup> of these 8 trials (with contamination rates between 0%<sup>12</sup> and 26%<sup>13</sup>) have shown statistically and clinically significant increases in rates of cerebral palsy (overall relative risk, as derived from these 4 studies, 2.89, 95% confidence interval 1.96-4.27). They also showed probable increases in rates of total neurodevelopmental disability (overall relative risk 1.66, 95% confidence interval 1.26-2.19). In 2 trials (one with only 20 babies<sup>15</sup> and the other with 40% crossover<sup>11</sup>) there was a nonsignificant increase in the rate of cerebral palsy. The last trial presented follow-up information for only 5 controls and showed no significant effect.<sup>16</sup> The

postnatal age at which the drugs are given appears unimportant: Shinwell and associates<sup>13</sup> gave the drugs at less than 36 hours after birth, whereas O'Shea and colleagues<sup>12</sup> administered them at 15 to 25 days of age, yet both groups of investigators reported increases in rates of cerebral palsy. Overall, the rate of cerebral palsy increases from about 1 in 6 to about 1 in 3. The proportion of babies with any neurologic or developmental abnormality increases from about 1 in 4 to about 1 in 3.

Despite the lack of convincing evidence of benefit and the serious complications reported, steroids are now widely used to treat lung injury in premature infants. The multicentre Canadian Neonatal Network has collected data for 1085 infants with extremely low birth weight (less than 1000 g) who survived to 28 days (Shoo K. Lee, University of British Columbia: personal communication, November 2000). By that age, 415 (38%) of them had received postnatal steroids, and it is likely that more received steroids after 28 days. Similar rates of steroid use are evident from the reports of the Vermont Oxford Network, a database representing 325 intensive care units from all over the world.<sup>19</sup>

How could a therapy that appears to be so harmful have become so widely used? The reasonable suspicions that steroids may interfere with development of the central nervous system should have mandated neurodevelopmental follow-up in all of the studies and should have prevented the haphazard contamination of randomized studies by treatment of controls with steroids. However, it is much easier to design studies with short-term physiologic endpoints such as gas exchange (since such studies usually have smaller sample sizes, lower budgets and easier recruitment) than to ask the question to which families would probably want an answer: "If my baby receives steroids, will he or she be better off a year from now or 2 years from now or even 5 years from now?" Surely these are the kinds of questions to which we too should want the answers. If we are to provide the best medical care, we must integrate our clinical experience with appropriate and relevant scientific evidence and the wishes of families.

So what should be the indications for pharmacologic doses of systemic steroids in ventilator-dependent premature infants? Given the adverse long-term results and the short-term improvements in lung function, I suggest that only infants with a high risk of dying because of the severity of their chronic lung disease be considered for this therapy, that treatment of such infants should preferably occur only within randomized controlled trials and that this treatment should occur only after full disclosure to the parents of the potential risks of the therapy.

In the hustle and bustle of a busy intensive care unit, many treatments are commenced without direct consultation with the parents. Starting antibiotics and performing radiography are done so frequently and have such low complication rates that asking for explicit consent would be unreasonably onerous. However, because starting systemic steroids at pharmacologic doses appears to be a toxic ther-

apy with doubtful long-term benefits, no premature infant should receive such treatment unless the parents have been asked, "What do you want for your baby?" and have been given the information they need to make a decision.

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Dr. Barrington is Director of Neonatology, Royal Victoria Hospital, and Associate Professor in the Department of Pediatrics, McGill University, Montreal, Que.

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**Correspondence to:** Dr. Keith Barrington, Hôpital Royal Victoria, 687, avenue des Pins Ouest, Montréal QC H3C 1A1; fax 514 843-1741; kbarri@po-box.mcgill.ca