

## CLINICAL ISSUES: INFANCY AND CHILDHOOD

### Less Aggressive Treatment of Neonatal Jaundice and Reports of Kernicterus: Lessons About Practice Guidelines

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**Abstract.** The publication of guidelines calling for less aggressive treatment of jaundice in newborns has been followed by a reappearance of case reports of kernicterus. These case reports illustrate important issues for writers and consumers of practice guidelines. One issue is the particular salience of identified patients with bad outcomes, and their potentially disproportionate influence on decision-makers. A second issue is whether, when good evidence of treatment benefit is lacking, policymakers should recommend what has traditionally been done, recommend less treatment, or not make recommendations at all. Finally, the cases raise the question of whether treatment guidelines should be more conservative than their authors actually believe is necessary, to take into account the likelihood that they will not be closely followed.

We believe that case reports can serve as an important early warning system, but policymakers should be aware of their potentially disproportionate influence. In the long run, patients and clinicians will be best served by guidelines that summarize and acknowledge the limitations of existing evidence, that allow a wide range of treatment options when evidence is weak, and that recommend what the guideline authors actually believe should be done. In the short run a period of readjustment may be required, however, as clinicians become accustomed to guidelines written to be followed, rather than bent. *Pediatrics* 2000;105:242-245; *neonatal jaundice, bilirubin, kernicterus, practice guidelines.*

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ABBREVIATION. TSB, total serum bilirubin.

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In 1992, we wrote an article suggesting a “kinder, gentler approach” to the evaluation and treatment of jaundice in the term newborn.<sup>1</sup> We suggested that much of the then-recommended treatment of jaundiced newborns was unnecessary, and that fewer laboratory tests and higher treatment thresholds were more consistent with available evidence. The article received a mixed response from

neonatal jaundice experts.<sup>2-9</sup> Some<sup>7-9</sup> expressed the concern that the new recommendations might lead to an increase in kernicterus. Nonetheless, a practice parameter published 2 years later by a committee of the American Academy of Pediatrics<sup>10</sup> recommended a similar approach.

Shortly thereafter case reports of newborns who developed apparent kernicterus began to appear.<sup>11-15</sup> Although early postpartum discharge received much of the blame for these cases, some authors suggested that because the guidelines advocated a less aggressive approach to the treatment of neonatal jaundice they may also have contributed to these kernicterus cases.<sup>13-15</sup>

These case reports raise several questions that are relevant to producers and consumers of clinical practice guidelines in general. How should case reports influence health policy? How should guidelines be written in the face of insufficient evidence? Finally, should guidelines be more conservative than their authors actually believe is necessary, to take into account the likelihood that they will not be closely followed? We discuss these issues below.

#### WHAT SHOULD BE THE IMPACT OF CASE REPORTS ON HEALTH POLICY?

Brown and Johnson,<sup>15</sup> combining their own cases with recent reports of others, identified 41 cases of kernicterus occurring in the United States in the last 20 years. Of these, 31 occurred after 1990, representing what they believe to be a dramatic increase. The degree to which this increase in case reports represents a true increase in kernicterus, however, is unknown. At least some of the apparent increase may be attributable to increased interest and reporting, stimulated by their and others' concern about the dangers of early postpartum discharge or less aggressive jaundice treatment. Without a uniform case definition and a constant level of surveillance it is impossible to quantify, or even to be entirely confident of any increase in the incidence of kernicterus. Nonetheless, case reports can provide an early warning system for a change in practice that might be hazardous, and are worth examining carefully in an effort to determine the root cause of any adverse outcome. Was the guideline followed? Were there particular characteristics of the patient that might explain the bad outcome?

At this writing, details of many of the cases have

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not been published. However, one striking finding is that the bilirubin levels of these infants, generally  $>30$  mg/dL, were much higher than current recommended treatment thresholds. This suggests that the problem is not that treatment thresholds in the new guidelines are too high, but that infants with high bilirubin levels are not always being identified and treated according to the guidelines.

Although case reports can be useful, they may have a disproportionate influence on policymakers and the public. One reason for this is that known, identifiable victims are more salient than unidentifiable prevented casualties. Clinicians who have observed cases of apparent kernicterus can describe the case histories of these infants in vivid detail. Such clinicians may be overrepresented on committees preparing jaundice guidelines. On the other hand, the identities and stories of those whose lives were saved by not receiving an exchange transfusion are not known, and any memory of specific infants who suffered exchange transfusion disasters in the past are likely fading, as exchange transfusions have become a rarity.<sup>16</sup> Past and projected exchange transfusion casualties are therefore less conspicuous and likely to have less impact on decisions.<sup>17</sup>

What are left to balance the vivid case reports of kernicterus are the much more mundane but less severe drawbacks of close follow-up and intervention in jaundiced infants. But figuring out how to balance these two very different types of risks is difficult. Kernicterus is so awful that it is hard to say how many blood tests, how much separation of mothers and infants for phototherapy, how many hospital days and outpatient visits, or how much money it is worth to prevent 1 case. It is clear, however, that part of the answer will depend on the individual circumstances and as well as parental preferences—how close they are to the hospital, whether they have insurance, social support at home, and so on.

Financial considerations can be particularly difficult. Americans have a difficult time saying no to interventions that have even a very small absolute benefit, even when they are not cost-effective.<sup>18</sup> Because the potential identified victims, those taking care of them, and more to the point, those writing guidelines are not likely to feel directly positively impacted by money being saved, there is understandable reluctance to accept even a minuscule risk of identifiable tragic outcomes in return for dollar savings that are invisible.

How many dollars might be saved by the new guidelines? In the Northern California Kaiser Permanente Medical Care Program in 1995–1996 about 10% of 51 387 term infants had a total serum bilirubin (TSB) level of  $\geq 15$  mg/dL, 2% had a TSB level  $\geq 20$  mg/dL,<sup>19</sup> and only about 2% received phototherapy. Because previous recommendations would have called for phototherapy for all those with TSB  $\geq 15$  mg/dL, a ballpark estimate is about 8% fewer infants receiving phototherapy than traditionally recommended. If similar changes occurred in the entire US birth cohort (4 million

births per year), this would mean 320 000 fewer infants receiving phototherapy. Even using a low estimate of \$600 per infant for phototherapy, this translates to savings of almost \$200 million.

If phototherapy were done according to traditional guidelines, and reduced by 90% the number of infants with TSB  $\geq 20$  mg/dL, this would still leave .2% of infants (8000 nationally) at a level at which traditional guidelines<sup>20</sup> and many current practitioners<sup>21</sup> would implement exchange transfusion, compared with the observed rate in this cohort of only .004%. Again, using a low estimate of a .1% risk of death and a 2% risk of serious sequelae from exchange transfusion,<sup>22</sup> this translates into 8 fewer exchange transfusion deaths and 160 fewer serious exchange transfusion sequelae per year from less aggressive treatment. Because most of the case reports of kernicterus had TSB levels well above those at which new guidelines recommend intervention, this suggests that following guidelines could lead to benefits from doing fewer exchange transfusions and less phototherapy without a concomitant increase in the risk of kernicterus.

#### HOW SHOULD GUIDELINES BE WRITTEN WHEN EVIDENCE IS INSUFFICIENT?

What is the best approach to widely prevalent practices for which there is insufficient existing evidence of benefit? The maxim *primum non nocere* (first do no harm) is a good one, but how should it be applied in this context? One interpretation is that one should not propose guidelines that might be harmful. A less aggressive treatment guideline could do harm if an existing treatment, despite lack of evidence, really were beneficial, and were utilized less often. In the case of neonatal jaundice, we (and the American Academy of Pediatrics) judged this possibility to be unlikely, because available evidence suggests that if there is any risk of kernicterus in term, well infants with bilirubin levels of 20 to 25 mg/dL, it is less than the risk of exchange transfusion.<sup>1,23–25</sup> As will be discussed below, however, such a guideline could also do harm if it led to a relaxation of treatment beyond what was explicitly recommended.

An alternative interpretation is that one should not use *treatments*, eg, exchange transfusion or phototherapy, that could do (net) harm. In this interpretation, one needs good evidence that a treatment is beneficial *before* using it, and especially before publishing a guideline recommending it. This is the philosophical approach of the US Preventive Health Services Task Force.<sup>26</sup> It seems particularly important for *preventive* interventions, which often will require that many people who are not ill be treated for each one that benefits. The possibility of doing harm is, of course, magnified when an intervention is applied to large numbers of people who start out well.

Which interpretation is correct? We believe that both are, and that in the end the choice must rest with clinicians and their patients. The best that writers of guidelines can do is to summarize exist-

ing evidence accurately and distinguish between recommendations that are based on sound evidence and those based on tradition, tenuous extrapolations, or guesses from pathophysiology. As discussed below, it is possible that acknowledging such uncertainty around traditional practices may be harmful, but if one really believes in evidence-based guidelines, it is hard to see any acceptable alternative.

### SHOULD GUIDELINES BE MORE CONSERVATIVE THAN THEIR AUTHORS ACTUALLY BELIEVE IS NECESSARY?

Neonatal jaundice is one of many clinical entities for which a wide range of practices is consistent with the relatively meager available evidence.<sup>21</sup> In such situations, there are at least 2 reasons for guidelines written by professional societies to err on the side of recommending doing too much, rather than doing too little. First, authors of guidelines may fear that if a range of treatment options is provided, care managers whose goal is to minimize spending might authorize only the least expensive approach.<sup>27</sup> To make sure the more aggressive or expensive treatment option is reimbursed for those that want it, they may recommend it for everyone.

Second, clinicians may bend guidelines they believe generally to be too conservative or too much trouble to follow.<sup>28</sup> This raises the question: should guidelines state what clinicians are actually supposed to do, or should the guidelines recommend more treatment than is actually necessary, under the assumption that they will not be closely followed?

As an analogy, consider a stretch of road with a posted (traditional) speed limit of 25 miles per hour, but on which it is safe (and common) to go up to 45 miles per hour. Along come the evidence-based speed limit people, and (compromising between their desire to be evidence-based and their desire not to be too radical) raise the speed limit to 35 miles per hour. If someone then has an accident going 55 miles per hour, are the evidence-based speed limit people at least partly to blame? One argument states that speed limits should always be set well *below* the maximum speed at which it is actually safe to travel, because people often exceed the speed limit. The opposing argument is that setting the speed limit too low forces people either to drive unnecessarily slowly or to break the law, and erodes the credibility with motorists of those setting speed limits.

There are multiple similar examples in medicine. Should physicians recommend annual mammographic or Pap-smear screening to increase the chances that everyone will be screened at least every 2 to 3 years? Should they prescribe penicillin 3 or 4 times a day for strep throat, to make sure it is actually given at least twice?

It is tempting for those writing guidelines to err on the side of "safety," writing guidelines that are quite conservative. That way, in case of a bad outcome, those writing the guideline will not feel responsible. However, there is something paternalis-

tic about this approach that seems inconsistent with evidence-based medicine. Just as patients may not always choose to follow their physician's advice, so might clinicians, when informed of available evidence, choose not to follow a practice guideline. We believe that in the long run, by being honest about available evidence and the range of practices consistent with it, writers of guidelines can earn the trust of clinicians, and in the end have a greater influence on practice.

### CONCLUSIONS

Practice guidelines are likely here to stay, and for many pediatric problems good evidence on which to base them is a long way off. We suggest that in the meantime, writers of guidelines should examine case reports closely, but be cognizant of their scientific limitations. When evidence is insufficient, guidelines should summarize available evidence and its limitations and offer a range of acceptable practices. Finally, if guidelines are to be evidence-based, they must recommend what the evidence actually supports, rather than being overly conservative in an effort to second-guess third-party payers or clinicians.

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