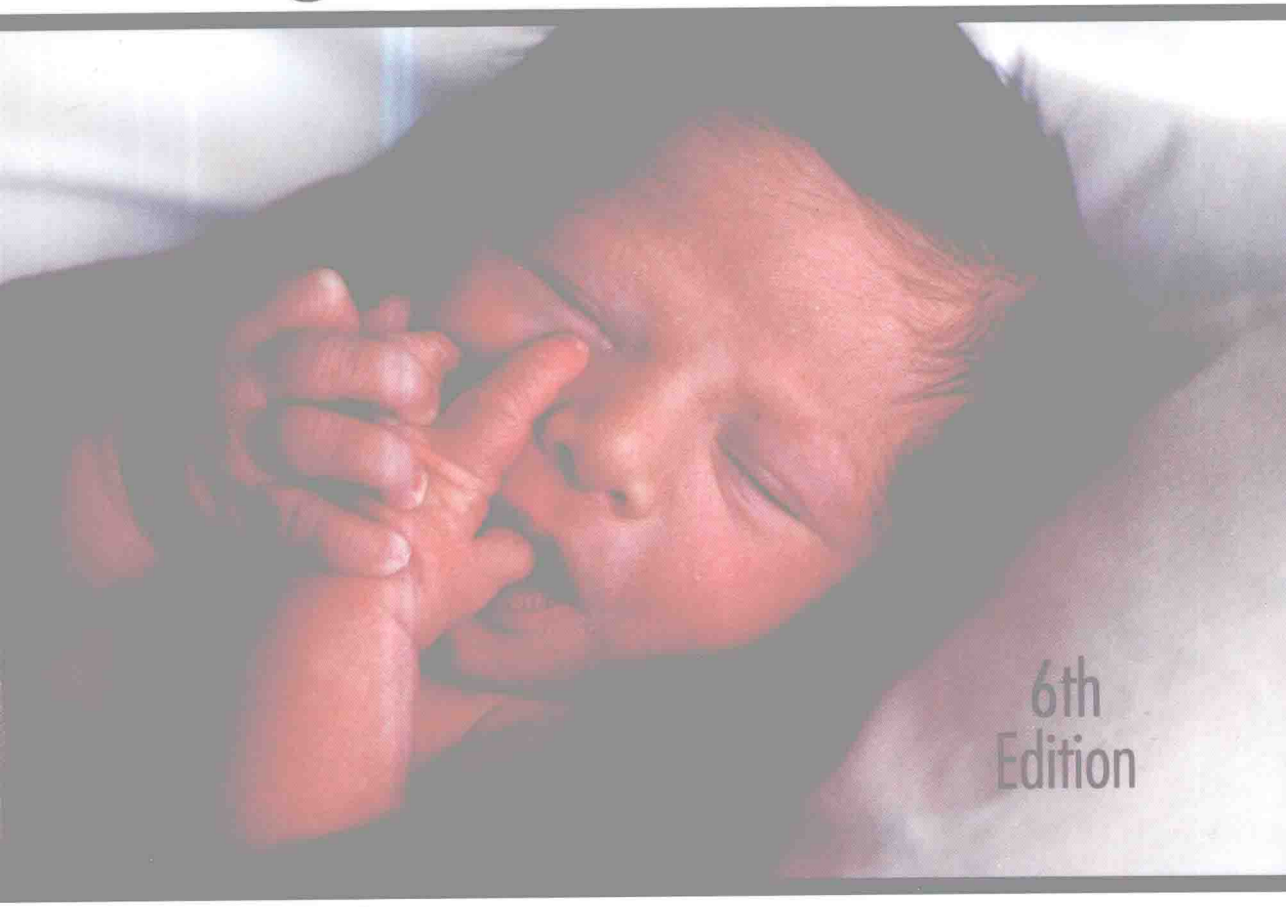
Klaus & Fanaroff's Care of the High-Risk Neonate



Avroy A. Fanaroff & Jonathan M. Fanaroff

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Klaus & Fanaroff's

Care of the High-Risk Neonate

6th Edition

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To all students of perinatology; our patients and their parents;
Roslyn and Kristy Fanaroff; Peter, Jodi, Austin, and Morgan Tucker;
and Amanda, Jason, Jackson, and Raya Lily Hirsh

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Preface

It is with a great deal of humility, as well as satisfaction, that we present the sixth edition of *Klaus & Fanaroff's Care of the High-Risk Neonate*. There have been incredible advances in the field of neonatal-perinatal medicine in the 40 years since the book was first published. These include better understanding of the pathophysiology of neonatal disorders, as well as sophisticated technologic advances that permit monitoring, imaging, and support of even the tiniest, least mature infant. Over the same period, we have witnessed the development of therapeutic agents and strategies to enable maximal survival with the least morbidity for many complicated neonatal structural and metabolic disorders. Although these advances are gratifying, many challenges remain. Prematurity, birth defects, neonatal infections, birth asphyxia, and brain injury remain major causes of neonatal mortality and morbidity.

The dawning of the subspecialty in the late 1950s and the introduction of neonatal intensive care in the 1960s are often referred to as the era of anecdotal medicine, accompanied by many disasters. The first edition of *Klaus & Fanaroff's Care of the High-Risk Neonate*, published toward the end of this era in 1973, addressed the uncertainties in knowledge by offering multiple choices and approaches to management. Many of the gaps in knowledge have been filled, and there is now sufficient data to practice a more unified evidence-based neonatology. However, evidence-based medicine predicts what happens to the masses but not the individual. The next era, individualized medicine, will require the knowledge of the unique genetic makeup of the individual and the application of therapeutics based on predictable responses to pharmacologic agents.

The 10-year interval between the fifth and sixth editions of this book has been characterized by many changes in care practices and the accumulation of extensive data in randomized trials. To update this volume, each chapter has undergone comprehensive revision. To present fresh perspectives and ideas, once again one third of the chapters have been assigned to new authors. However, we have adhered to the basic format, utilizing text, case problems, and critical comments. To emphasize the importance of quality improvement and evidence-based medicine, we have inserted a new lead chapter on this topic, which includes the role and impact of the neonatal networks on modern neonatal intensive care.

Marshall H. Klaus, MD, has become an emeritus author of this book. However, his wisdom, philosophy, and yearning to provide quality, compassionate, and minimally invasive care with emphasis on human milk feeding, alleviation of pain, and psychosocial support for the family, strongly pervades the book. We thank him for his continuing support and inspiration. It has been a uniquely gratifying experience to have Jonathan M. Fanaroff, my son, assume the role of co-editor. We are all grateful that this book continues to serve as a companion and source of information for healthcare providers in many parts of the world. Bonnie Siner, RN, has once again served as in-house editor extraordinaire. Without her we could never have completed this edition, and we are most grateful to have had her skillful assistance. We thank, too, Rachel Miller and Judy Fletcher at Elsevier for their support and assistance. We thank the authors and commenters who gave of their time and knowledge. We also thank Bella Baby Photographers for use of the cover image.

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Contents

Evidence-Based Medicine and the Role of Networks in Generating Evidence

1

Michele C. Walsh and Rosemary D. Higgins

The explosion of clinical research has led to a conundrum in practice: Never before has so much evidence been generated to guide practice, but the sheer volume generated makes it difficult for practitioners to keep pace with the knowledge, and new knowledge rapidly eclipses existing practice. In 2009, it is estimated that more than 120 randomized clinical trials in neonatology were published.[1] This dilemma has made it imperative that every physician become skilled at evidence-based medicine (EBM), which, at its core as defined by Sackett in 1997 is "...a process of life-long, self-directed learning in which caring for our patients creates the need for clinically important information about diagnosis, prognosis, therapy, and other clinical and health issues...".[2] This chapter will review the components of EBM and the contribution of neonatal research networks to the generation of high-quality evidence.

THE EVOLUTION OF EVIDENCE-BASED MEDICINE

When first conceptualized in 1992 by Guyatt, the fundamental principle of EBM was real time application of the best available clinical evidence at the bedside. The chief barriers to such application in neonatology were the absence of high quality evidence and the tedious search for, and synthesis of, available evidence. The development of large research collaboratives has led to the generation of high-quality evidence. Advances in computer technology and information management have made evidence available on the desktop of every clinician. The Cochrane Collaboration in 1990 developed standard approaches to literature review and analyses that have placed the practice of EBM within the reach of most practitioners.[3] Neonatologists are indeed fortunate that the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) has funded online publication of the Neonatal Cochrane reviews for more than a decade. This has contributed to the rapid uptake of EBM among neonatal practitioners. The next innovation in EBM will incorporate rigorous assessments of quality improvement methods to aid us in determining which methods most rapidly lead to the incorporation of evidence-based treatments into practice. Many authors have documented that on average it takes more than 7 years for a new practice that has strong evidence of efficacy to achieve high penetration at the bedside.[4-6] Methods are needed to enhance the dissemination and uptake of these innovations. Physicians who are skilled in EBM are more likely to recognize and incorporate these advances.

A PRESCRIPTION FOR EVIDENCE-BASED MEDICINE FOCUSED PRACTICE

Sackett and colleagues synthesized the steps needed to ask and answer a relevant question using EBM (Box 1-1). To these steps we have added a first step using the phrase by Horbar, "developing the habit for using evidence and implementing change," which has been disseminated among neonatologists by the Vermont Oxford Collaborative.[7]

DEVELOPING THE HABIT FOR EVIDENCE USE

Medical students and residents who are educated in a culture that values, teaches, and models the use of EBM are more likely to apply the method themselves in later

Box 1-1. Steps in the Practice of Evidence-Based Medicine

1. Develop the habit for the use of evidence.
2. Frame the question in a manner that can be answered.
3. Search for evidence with maximum efficiency from the most reliable sources.
4. Critically appraise the evidence for its validity (closeness to the truth) and usefulness (clinical application).
5. Apply the results of this appraisal in practice.
6. Evaluate the performance of the treatment.

Adapted from Strauss SE, Richardson WS, Glasziou P, et al: Evidence-based medicine: how to practice and teach EBM, ed 4, Churchill Livingstone, 2011.

practice.[8] Nevertheless, all physicians can learn and practice the steps needed. Research has shown that physicians who use EBM are more likely to be current in practice 15 years out of training than those who are not practicing EBM.[9] Today, the American Board of Medical Specialties has mandated continuous maintenance of certification, rather than permanent or intermittent recertification, as the best practice for documenting physician competency.[10] EBM will facilitate self-directed lifelong learning and support maintenance of certification.

FRAMING THE QUESTION

To be easily answered, the exact question must be carefully framed. Strauss and colleagues have summarized the four elements of a good question as "PICO": Patient population, Intervention, Comparison, Outcome.[2]

Patient Population

Describe precisely the patient population under consideration; for example, "infants born at <28 weeks' gestation," OR "inborn infants <28 weeks' gestation," OR "very low-birth-weight (VLBW) neonates who remain intubated and mechanically ventilated at 14 days of age." The more precisely the population is defined, the more targeted the search for evidence will be.

Intervention

Describe the main intervention in which you are interested. For example: "Is clindamycin superior to ampicillin in the treatment of necrotizing enterocolitis?" Other questions that may be explored may relate to prognostic factors or to risk factors.

Comparison

What is the main alternative to compare with the intervention (e.g., when compared with supportive therapy alone).

Outcome

State the outcome of interest in as specific terms as possible including a time horizon. For example: "Will adding clindamycin to ampicillin in a VLBW infant with stage 2 necrotizing enterocolitis reduce mortality prior to hospital discharge?"

A busy clinician will generate more questions than they have time to address. To avoid frustration, the questions may be prioritized by how critical the patient is, or which question is of most interest to the clinician. Other questions can be added to a list, which can be used when off-service time can be directed to self-education. Through this process the clinician will be actively practicing lifelong learning.

SEARCHING FOR EVIDENCE

Searching for evidence to answer clinically relevant questions is the most time consuming aspect of practicing evidence-based medicine. Strauss and others have suggested that this is the major barrier to effective implementation.[11,12] Nordenstrom has recommended that clinicians search for evidence using online sources that contain critically reviewed data directed at clinical questions.[13] By prioritizing sources, the clinicians' time is used most efficiently. Nordenstrom recommends that the first source should be the Cochrane Collaboration, followed by meta search engines including Google Scholar. The next step is to search secondary sources focused on clinical questions such as the United Kingdom's National Institute for Health and Clinical Excellence (www.nice.org.uk), the United States Agency for Healthcare Research and Quality Effective Health Care Program (http://effectivehealthcare.ahrq.gov) or Up To Date (www.uptodate.com), a commercial online source generated by content experts. Perhaps surprisingly, Nordenstrom recommends that PubMed be searched last, because 75% of the PubMed content deals with basic science research topics versus clinically relevant questions. Thus, for a

Table 1-1. The GRADE System

Study Design	Quality of Evidence	Lower/Higher Level of Quality if:
Randomized trial	• High (further research is very unlikely to change our confidence in the estimate of effect) • Moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate)	• Risk of bias (serious [–1]; very serious [–2]) • Inconsistency (serious [–1]; very serious [–2]) • Indirectness (serious [–1]; very serious [–2]) • Imprecision (serious [–1]; very serious [–2]) • Publication bias (likely [–1]; very likely [–2]) • Large effect (large [+1]; very large [+2]) • Evidence of a dose-response gradient (+1) • All plausible confounding: would reduce a demonstrated effect (+1); would suggest a spurious effect when results show no effect (+1)
Observational trial	• Low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) • Very low (any estimate of effect is very uncertain)	

Adapted from Scott IA, Guyatt GH: Clinical practice guidelines: the need for greater transparency in formulating recommendations, *Med J Aust* 195(1):29, 2011.

busy clinician other sources are likely to yield a better answer faster.

CRITICALLY APPRAISE THE EVIDENCE FOR VALIDITY, APPLICABILITY AND IMPORTANCE

In this discussion, we will focus on the appraisal of evidence regarding treatments. The highest hierarchy of evidence for these are results from a randomized controlled trial. The following critical questions to ask when assessing the validity of a trial are:

1. Were patients randomly assigned to the treatment?
2. Were all patients who were randomized accounted for in the analysis? Were they analyzed in the group to which they were assigned (intent-to-treat analysis)?
3. Were patients, the clinicians caring for them, and those assessing the outcome kept masked to the treatment assignment?
4. Were the groups similar at the beginning of the trial?

Randomized trials provide the most nonbiased assessment of the effect of a treatment. If the trial is not randomized, it may be best to stop reading and search for other sources. If the only evidence available is from a nonrandomized study, one must view the stated effects with some skepticism because the odds ratios from randomized trials are generally smaller than those from nonrandomized studies.

There are a number of different systems proposed for grading the quality of evidence. The proliferation of systems has made it difficult to adopt and understand any one method. Recently, a group of clinical epidemiologists have proposed a system that combines many of the elements of other systems and termed this the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system.[14] The *British Journal of Medicine* has required a GRADE assessment of recommendations since 2006, and now more than 25 groups who generate systematic reviews, including the World Health Organization, the American College of Physicians, the American Thoracic Society, UpToDate (www.uptodate.com), and the Cochrane Collaboration have adopted the GRADE standard (Table 1-1). The Grade system synthesizes the evidence into a recommendation based first on the quality of the evidence and second on the magnitude of effects, thereby yielding a recommendation which is either "strong" or "weak." The GRADE system classifies quality of evidence into four levels: high, moderate, low, or very low. Evidence from randomized controlled trials (RCTs) begins as high quality, but may be rated down if trials demonstrate one of five categories of limitations. Observational studies begin as low-quality evidence, but may be rated up if associated with one of three categories of special strengths.

The GRADE system suggests that when the desirable effects of a treatment clearly outweigh the undesirable effects, or the contrary, that guideline offers strong recommendations. When the data are less clear, such as when the quality of existing evidence is low or when undesirable effects outweigh desireable effects, the recommendations should be rated as weak, or equivocal. Such a standardized approach

to rating the evidence would clearly benefit clinicians.

Applying the Evidence in Daily Practice

The Institute of Medicine (IOM) focuses on the promise of evidence-based medicine to improve the quality and effectiveness of health care, and has also highlighted barriers in the current system. The IOM cites "an irony of the information-rich environment is that information important to clinical decision making is often not available, or is provided in forms that are not relevant to the broad spectrum of patients—with differing levels of health, socioeconomic circumstances, and preferences—and the issues encountered in clinical practice."[15] In the IOM view, these limitations are driven by a paucity of clinical effectiveness research, poor dissemination of the evidence that is available, and too few incentives and decision supports for evidence-based care. Glenton and colleagues described several factors hindering the effective use of systematic reviews for clinical decision making.[15] They found that reviews often lacked details about interventions and did not provide adequate information on the risks of adverse events, the availability of interventions, and the context in which the interventions may or may not work.

Evaluate the Performance of the Treatment

The final step in EBM is to assess the outcome of the treatment. Did the patient (or their parents) judge their condition to be improved? Was the treatment cost-effective? Did the treatment fit within the context of the unique circumstances and biology of the family? If a similar scenario was encountered again, what would the clinician do differently? This habit for critical self-appraisal and unremitting learning is at the heart of EBM. Only by widespread implementation of the principals of EBM is healthcare quality and value likely to improve.[16,17]

CRITICAL PROGRESS IN GENERATING THE EVIDENCE: THE ROLE OF NEONATAL RESEARCH NETWORKS

Neonatal-perinatal medicine was recognized as a subspecialty by the American Board of Pediatrics in 1975.[18] In the past 2 to 3 decades, it has become increasingly apparent that neonatal research requires observational studies and interventional trials to provide the basis for evidence-based care for newborns. Several groups, including the NICHD the Neonatal Research Network, the Canadian Neonatal Network, the Vermont Oxford Network, as well as international networks, have been established and maintained to investigate evidence-based strategies, including observational studies, interventional clinical trials, and quality improvement initiatives. These networks have made significant contributions to patient care and quality improvement. This chapter will discuss advantages, opportunities, and challenges for research networks as well as selected highlights from the various networks.

Clinical networks can offer large numbers of patients for study. For uncommon or rare conditions, networks can provide the numbers of patients needed to study diseases in an observational or interventional study. Generally, networks are set up to look at specific disease categories. The neonatal networks and collaborations concentrate on diseases of the newborn, particularly those affecting preterm infants and critically ill, late preterm and term infants. Many of the neonatal networks have access to high-risk obstetrics or maternal-fetal medicine consultants at their institutions. In addition, most have level III newborn intensive care units (NICUs) for care of patients and recruitment of patients for clinical studies. Well-developed and established networks have provisions for follow-up of the infants and children after hospital discharge.

The NICHD Neonatal Research Network (NRN) was established in 1986 to form a set of academic centers to conduct common protocols for observational and interventional studies of newborns.[19,20] The goal of the NRN is to provide the research evidence to facilitate advancement of neonatal care by providing infrastructure for a network of academic centers to study required numbers of patients to provide data more rapidly than individual center studies. The perceived advantages of a network of centers included large patient numbers to provide evidence more rapidly than individual study sites, availability of patients with rare or rarer diseases (such as hypoxic-ischemic encephalopathy), and available infrastructure for clinical studies (Table 1-2). Further, specialized needs including high-risk pregnancy study subjects, preterm infants, capability of short-term outcome ascertainment, and longer term follow-up can be mandated in a request for application (RFA).

Table 1-2. Impact of Interventional Randomized Trials of the Eunice Kennedy Shriver NICHD Neonatal Research Network*

Study	Patient Enrollment	Outcome	Impact
A Controlled Trial of Intravenous Immune Globulin to Reduce Nosocomial Infections in Very Low Birth Weight Infants *N Engl J Med* 330:1107, 1994	2416 infants 501-1500 grams randomized by 72 hours of life to IVIG or placebo (phase I)/no infusion (phase II).	IVIG failed to significantly reduce nosocomial infections (17% IVIG vs 19% control). Increased NEC in infused groups.	Routine use of IVIG not recommended for prevention of infection in VLBW infants.
The Effect of Antenatal Phenobarbital Therapy on Neonatal Intracranial Hemorrhage in Preterm Infants *N Engl J Med* 337:466, 1997	610 women with gestation ≥24 and <33 weeks anticipated to deliver within 24 hours randomized to receive phenobarbital or placebo daily until delivery or 34 weeks.	Antenatal administration of phenobarbital did not reduce the incidence of intracranial hemorrhage or early death (24% vs 23%) in infants born <34 weeks.	Prophylactic use of antenatal phenobarbital to prevent intracranial hemorrhage in preterm infants not recommended.
Vitamin A Supplementation for Extremely Low Birth Weight Infants *N Engl J Med* 340:1962, 1999	807 infants ≤1000 grams randomized to receive IM injection of vitamin A or control (sham injection) 3 times per week for 4 weeks.	Vitamin A supplementation significantly reduced risk of CLD or death (55% vs 62%).	Routine use of vitamin A supplementation recommended for infants ≤1000 grams in the first month of life.
Effects of Early Erythropoietin Therapy on the Transfusion Requirements of Preterm Infants Below 1250 Grams Birth Weight: A Multicenter, Randomized Controlled Trial *Pediatrics* 108(4):934, 2001	290 infants 401-1250 grams birth weight randomized to erythropoietin or placebo until 35 weeks' post menstrual age.	Combination of erythropoietin and iron-stimulated erythropoiesis but did not affect transfusion requirements (4.3 vs 5.2 transfusions) in treated vs. control preterm infants ≤1250 grams.	Early use of erythropoietin and iron to reduce transfusion number and exposure of infants to the risks of multiple transfusions not warranted.
Parenteral Glutamine Supplementation Does Not Reduce the Risk of Mortality or Late-Onset Sepsis in Extremely Low Birth Weight Infants *Pediatrics* 113(5):1209, 2004	1433 infants 401-1000 grams randomized to parenteral nutrition with glutamine supplementation or control (standard parenteral nutrition).	Parenteral glutamine supplementation did not decrease rate of mortality or late-onset sepsis (51% vs. 48%) in infants ≤1000 grams.	Routine use of parenteral glutamine supplementation to reduce the risk of death or late-onset sepsis in ELBW infants not recommended. Importance of early protein administration recognized, changing practice.
Randomized Clinical Trial of Dexamethasone Therapy in Very Low Birth Weight (VLBW) Infants at Risk for Chronic Lung Disease (CLD) *N Engl J Med* 338:1112, 1998	371 infants 501-1500 grams treated DOL 14-42 with dexamethasone/ placebo or placebo/dexamethasone.	No clear pulmonary benefit starting dexamethasone at 2 weeks vs. 4 weeks of age (39% vs. 42%). Dexamethasone increased GI perforation, hypertension, and hyperglycemia.	Awareness of harmful effects of dexamethasone therapy for ventilator-dependent premature infants. Decreased use of postnatal steroids.
Inhaled Nitric Oxide for Premature Infants with Severe Respiratory Failure *N Engl J Med* 353:13, 2005	420 infants <34 weeks' gestation with BW 401-1500 grams with severe respiratory failure randomized to receive inhaled nitric oxide or placebo.	No difference in incidence of BPD or death in the inhaled nitric oxide and placebo groups (80% vs. 82%).	No benefit to the early use of inhaled nitric oxide in premature infants with severe respiratory failure.
Whole-Body Hypothermia for Neonates with Hypoxic-Ischemic Encephalopathy *N Engl J Med* 353:1571, 2005	208 term infants with moderate or severe HIE randomized by 6 hours of age to whole-body cooling for 72 hours or usual care (normothermia).	Whole-body cooling safe and effective in reducing the risk of death or moderate or severe disability (44% vs. 62%) among infants with HIE.	Whole-body cooling instituted as standard of care for term infants with moderate or severe hypoxic-ischemic encephalopathy.

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