

NEONATOLOGY TODAY

News and Information for BC/BE Neonatologists and Perinatologists

Volume 1 / Issue 7
November 2006

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www.NeonatologyToday.net

Neonatology Today (NT) is a monthly newsletter for BC/BE neonatologists and perinatologists that provides timely news and information regarding the care of newborns and the diagnosis and treatment of premature and/or sick infants.

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REGIONALIZATION OF NEONATAL INTENSIVE CARE: PAST, PRESENT, AND FUTURE

By *Munish Gupta, MD, MMSc; Camilia R. Martin, MD, MS; and Marie C. McCormick MD, ScD*

Introduction

Since its birth in the 1950s and 1960s, the history of neonatal intensive care has been remarkable. It has grown from a new field with limited resources and limited capabilities into a comprehensive, technologically advanced discipline able to address a wide range of newborn illnesses, and this growth has contributed to a rapid decline in neonatal mortality. Throughout this period, medical providers and public health officials have worked to understand how best to organize increasingly specialized obstetric and neonatal services. Regionalized perinatal care systems were developed to increase access for high-risk mothers and sick newborns to these services. The challenges of today are very different than those of several decades ago, however, and the planning of perinatal care has required continuous reevaluation and change. In this article, we will review the history of regionalization in perinatal and neonatal intensive care, and examine the issues currently facing the medical and public health communities with regards to the optimal organization of perinatal care systems.

Early Efforts at Regionalization

The concept of regionalization of perinatal care and neonatology arose in the early 1970s,

mostly by default. At the time, neonatal intensive care was a new field built upon new technologies, and it was only available in selected centers. It became apparent that care in these specialized units resulted in improved survival of high-risk infants, and regional systems for transferring sick newborns to these centers quickly developed.[1,2] Although initial efforts focused on transfer of the ill newborn, experience showed that outcomes were further improved by the antenatal transport of high-risk mothers to specialized centers with the coordination of high-risk obstetric and neonatal intensive care services. Consequently, efforts began to shift towards systems built around regional perinatal centers.[3-5]

The success of these systems prompted widespread advocacy for formalized planning of regionalized care,[6,7] eventually culminating in a landmark report from the multidisciplinary Committee on Perinatal Health sponsored by the March of Dimes.[8] The report called for regional networks of hospitals stratified by level of maternal and neonatal services, with systems to ensure appropriate transfer of high-risk patients to high-risk centers. Three levels of care were defined: Level I for routine deliveries with minimal risk; Level II for deliveries with moderate risk; and Level III for deliveries with high risk. Level II centers would have intermediate level nurseries, and Level III centers would have neonatal intensive care units (NICUs). This categorization became the basis for

Table 1: Neonatal Intensive Care Units and Neonatal Intensive Care Beds in the U.S.: 1998, 2001, and 2004

Year	1998	2001	2004
Hospitals reporting NICU beds	760	787	839
Total number of NICU beds	13,825	14,997	17,109
<i>Source of data: American Hospital Association Annual Survey, Health Forum, LLC</i>			

much of the organization of perinatal care in the decades to follow.

Numerous studies documented the greater coordination and regionalization of perinatal services throughout the 1970s and early 1980s, with high-risk deliveries being increasingly performed in higher level centers.[9-11] Studies also continued to confirm improvements in neonatal mortality with concentration of high-risk deliveries in Level III centers, particularly for low birth weight (LBW) infants and very low birth weight (VLBW) infants.[11-14] In 1975, the Robert Wood Johnson Foundation sponsored a five year multi-site demonstration program to evaluate the impact of planned perinatal regionalization; trends in regionalization were closely associated with declines in neonatal morbidity, but regionalization was so widespread that it occurred at similar rates in both demonstration sites and control sites.[15]

By the end of the 1970s, most states had organized systems of perinatal care delivery, centered on the coordinated care of high-risk patients at regional Level III centers. Although there was substantial variability among the states in terms of system structure and degree of government involvement, the basic elements were similar: a broad complement of organized maternal and neonatal services integrated with defined programs for consultation, referral, and patient transport.[1]

Trends Against Regionalization

In the 1980s and 1990s, challenges to the development of these regionalized systems began to appear. Evidence accumulated of a growing decentralization of perinatal care, and the distinction between Level II centers, which had been primarily community hospitals, and Level III centers, which had been almost exclusively large academic referral hospitals, began to blur. In Missouri, more VLBW and extremely low birth weight (ELBW) infants were born at Level III centers in 1990-94 as compared with 1982-86, but this was mostly due to redesignation of Level II centers as Level III rather than altered referral or birthing patterns.[16] In Washington and South Carolina, the percentage of LBW and VLBW infants delivered at Level III centers increased until the late 1980s, but then declined.[17,18] A study by the National Perinatal Information Center in 1988 examined six regions and found providers reporting a general deterioration of regionalized care, amidst a widespread trend among community hospitals to provide higher levels of obstetric and neonatal care.[19] A large study from California reported similar patterns. Unlike most other states which classify perinatal services into three levels as outlined in the initial March of Dimes report from 1976, California has categorized hospitals

into four levels: Level I, or basic; Level II, or community intermediate nursery; Level II+, or community NICU with the ability to ventilate infants; and Level III, or regional NICU with the full range of neonatal specialty services. A study of all births in California from 1990 to 1997 found that over that time period, the number of Level III and intermediate Level II NICUs either remained the same or declined, but that the number of Level II+ community NICUs dramatically increased. The percentage of VLBW and ultra-low birth weight (ULBW, under 750 grams) increased in the hospitals with community Level II+ NICUs while decreasing in the hospitals with regional Level III NICUs.[20] Finally, a national survey of neonatal intensive care growth between 1980 and 1995 based on American Hospital Association data found a disproportionate increase in the number of hospitals with small NICUs despite a lack of evidence of increased demand, and concluded there was evidence of significant deregionalization of neonatal intensive care over this time period.[21]

Several factors were postulated to contribute to these trends towards 'deregionalization.' These included:

- *Expansion of neonatal intensive care services and the neonatology workforce:* Rapid expansions of training programs and rapid diffusion of technologies served to increase dramatically the numbers of available NICUs and neonatologists, which had been scarce resources in the early 1970s. One study of neonatal services in metropolitan service areas in the U.S. reported that between 1980 and 1995, the number of hospitals with NICU beds increased 98.9%, the number of NICU beds increased 137.9%, and the number of neonatologists increased 268%, despite only a 17.6% increase in the number of births.[21] American Hospital Association data shows that NICUs and NICU beds have continued to grow, even in recent years. From 2001 to 2004, the number of hospitals in the U.S. reporting NICU beds increased 6.6%, and the total number of NICU beds increased 14.1% (see Table 1).
- *Competition and managed care:* With rising health care costs, competition increased among health care facilities to provide services to large insurance plans. Hospitals sought to increase their market share through expansion of obstetric services, and competition for obstetric care contributed to the proliferation of NICUs in community and suburban hospitals.[1,22] Increased penetrance of managed care was also seen as contributing to deregionalization, by directing referrals of high-risk patients towards lower cost community hospitals and away from large academic regional centers.[23,24] In addition, as hospitals competed

on price, funds to support the educational and consultation functions of regional centers became increasingly scarce. A case study of perinatal services in the Hartford, Connecticut area in the early 1990s found that the existing effective, regionalized system was being directly challenged by forces mostly attributable to market competition and managed care.[25] A study of VLBW infants under 1250 grams born in Illinois from 1989 to 1996 found that high HMO revenues were associated with a lower likelihood of transfer from a non-tertiary hospital to a tertiary hospital,[26] although another study did not find an association between managed care enrollment and patterns of regionalization in four states.[27]

- *Medical malpractice:* Increasing malpractice litigation led obstetricians to exert pressure upon their hospitals to provide support for more high-risk maternity and neonatal intensive care services, again encouraging the development of NICUs in smaller community hospitals.[28]
- *Increased demand for neonatal intensive care:* Finally, the advances in neonatal intensive care also resulted in dramatic increases in the number of infants requiring NICU care. Increasing survival at progressively lower gestational ages produced more infants eligible for neonatal intensive care services, and it is possible that this demand overwhelmed the capabilities of the large regional centers.[29] Indeed, the occupancy rate of NICUs increased 2.7% from 1980 to 1990, despite a dramatic increase in the number of NICU beds.[21]

Regardless of the relative import of these and other factors, the overall effect was seen as “a cessation or even reversal of the general trend toward regionalization.”[1]

‘Deregionalization’ and Neonatal Outcomes

For the most part, the movement towards deregionalized perinatal care was met with concern and trepidation by the medical community, and renewed appeals for continued emphasis on regionalized systems were made by the March of Dimes,[30] the American College of Obstetricians and the American Academy of Pediatrics.[22] However, the actual impact of these altered patterns of organization of perinatal care on neonatal outcomes has not been clear.

Numerous studies in the 1980s and 1990s examined the relationship between level of care and neonatal outcomes, and for the most part, continued to find that high-risk infants had lower neonatal mortality when born and managed at a Level III facility as compared to infants born at Level II facilities. This pattern was seen for infants under 2 kg born in Washington between 1980 and 1991,[17] VLBW infants born in Missouri in 1982 to 1986 and

1990 to 1994,[16] VLBW infants born in South Carolina from 1993 to 1995,[18] infants under 2 kg born in North Carolina from 1974 to 1994,[31] and VLBW infants born in the Cincinnati area between 1995 and 1997.[32] Several reports from a Canadian series examining all infants under 32 weeks admitted to their 17 regional NICUs from 1996 to 1997 found that those infants born at the regional centers had lower mortality and lower morbidities than those infants born at outside centers and subsequently transferred.[33,34]

In addition to level of care, studies began to examine the relationship between NICU size and outcomes. Two studies evaluated outcomes of infants born in California, and found that larger units tended to have better outcomes than smaller units of the same level. One study of all NICU admissions to non-federal California hospitals in 1990 found the risk-adjusted birth weight specific mortality to be lower for births that occurred in hospitals with Level III NICUs with an average daily census (ADC) of at least 15 as compared to births in hospitals with Level III NICUs with an ADC of less than 15.[35] Another study of infants under 2 kg born in California in non-federal hospitals from 1992 to 1993 found that infants born in hospitals with Level III NICUs had lower risk-adjusted mortality than infants born in hospitals with Level II nurseries or Level II+ community NICUs with an ADC of less than 15, but similar mortality to infants born in hospitals with Level II+ community NICUs with an ADC of greater than 15.[36] Of note, a recent study from a region in Germany reported similar results; VLBW infants born under 30 weeks from 1991-1999 were found to have lower neonatal mortality in larger NICUs, defined as greater than 36 VLBW admissions per year, as compared with smaller NICUs.[37]

While these studies provide further support for regionalization and concentration of high-risk deliveries in large Level III centers, other studies lead to a different conclusion about differences in outcomes between large referral centers and certain types of community NICUs. A study in the Chicago area found that short-term outcomes were not different for ventilated infants admitted to the tertiary NICU as compared with community NICUs, after adjusting for birth weight.[38] In Missouri, Level III NICUs formed during the 1980s and early 1990s did not have different neonatal mortality for VLBW infants than older established Level III centers.[16] In Pennsylvania, between 1985 and 1994, small NICUs, defined as having less than 20 beds, had similar neonatal mortality rates as larger NICUs for infants with BW greater than 1000 grams, although larger NICUs had lower mortality rates for infants with BW less than 1000 grams.[39] As mentioned above, the California study examining infants under



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Table 2: Outline of Proposed Definitions for Levels of Neonatal Care, American Academy of Pediatrics⁴³

Level I	Basic care, well-newborn nursery, 35+ weeks
Level II	Specialty care, infants > 32 weeks, > 1500 gm BW:
- Level IIA	- Moderately ill preterm infants, interim assisted ventilation if needed pending transfer
- Level IIB	- Short term mechanical ventilation or continuous positive airway pressure
Level III	Subspecialty care:
- Level IIIA	- Infants > 28 weeks, > 1000 gm, sustained conventional mechanical ventilation, minor surgical procedures
- Level IIIB	- Comprehensive care for ELBW, full range of subspecialists, major pediatric surgeries
- Level IIIC	- Located within institution capable of providing ECMO and cardiac surgery

2 kg born from 1992 to 1993 did not find different mortality rates for infants born at Level III centers than infants born at community hospitals with Level II+ NICUs and an ADC of at least 15. [36] The California study examining all births between 1990 and 1997 found that community Level II+ NICUs and regional Level III NICUs had very similar mortality rates for VLBW and ULBW infants, with parallel declines in mortality rates over that time period.[20] The Vermont-Oxford Network examined over 7000 VLBWs born in 62 of its units between 1991 and 1992, and found that the variability of neonatal mortality among units was not due to differences in patient volume.[40] Finally, two studies in the United Kingdom from the 1990s also did not find NICU volume to be associated with risk-adjusted neonatal mortality.[41,42]

Despite differences in the designs of these various studies, the contrasting results are notable. The range of possible interpretations can be illustrated by the conclusions reached in two of the studies. The authors of the Washington study, in the context of apparent erosion of regionalization of perinatal care in a competitive market, stated, "it would therefore be useful, we believe, to treat tertiary-level perinatal care as a public utility, exempt from the arrangements governing the structure and behaviors of any new health care system." [17] In contrast, the authors of one of the California studies concluded "although this expansion [of community NICUs] has attracted births away from regional NICU hospitals, we do not consider this to represent deregionalization, as we found no evidence that it has created a mismatch between level of need and level of care." [20]

Regionalization in the Current Era

At the least, it appears that the traditional concepts of regionalization of perinatal and neonatal care require reevaluation in the current era. As a field that has experienced continued dramatic

growth and dynamic change over the past several decades, it is not surprising that the optimal organization of neonatal intensive care services cannot be based upon principles developed in the 1970s and 80s. The historical review of the literature above can help identify several important lessons and issues to assist in current and future discussions on regionalization of neonatal care.

First, the traditional classification system of three levels of neonatal care, initially outlined in the 1970s and still widely employed, no longer appears adequate. Originally, the Level III designation was meant to be reserved for large, regional referral centers, typically located within academic medical institutions. At that time, mechanical ventilation was the newest and most invasive technology available for the support of sick newborns, and thus came to be the defining feature of Level III care. Currently, the highest level NICUs are defined by newer and more specialized techniques and technologies, such as high frequency ventilation, nitric oxide, pediatric surgery and extracorporeal membrane oxygenation (ECMO), while conventional mechanical ventilation has diffused into a much more widespread and familiar technology, now used in many different types of neonatal care units. Classification of neonatal units into three levels is thus problematic, and responses to this difficulty have varied; some states have created a Level II+ category while others have broadened the definition of Level III to include very different types and sizes of units.

This need for a more accurate classification system has been recognized by the AAP. As recently as in its 2002 Guidelines for Perinatal Care, the AAP still listed three basic levels of neonatal care.[22] A fourth level, the regional subspecialty center, was acknowledged in that edition, but its roles were limited to education and regional organization. In 2004, the AAP issued a policy statement expanding this classification, further refining



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the standard three levels of care by defining additional categories within Levels II and III. (see Table 2).[43]

Second, the benefits of planned organization of perinatal care services and the conflict between regional cooperation and market competition suggest that regulation of perinatal services by states will continue to be important. However, the involvement of public health departments in the organization of perinatal care is varied, and in some cases limited. As recently as 2003, 15 states did not have formal definitions of levels of perinatal care centers, and only 15 states used gestational age or birth weight as criteria for specifying level of risk.[43] Variability in definitions and extent of regulations between states is likely to undermine the development of optimal systems of perinatal care. In one study, among the Northeastern states, Pennsylvania was thought to have the least specific state regulations, and was found to have had the most dramatic increase in the number of small NICUs over the 1980s and 90s.[21]

Massachusetts, on the other hand, has traditionally had relatively strict state regulations on perinatal care delivery. Number and location of neonatal intensive care beds are carefully controlled, and in the past NICU beds were purposely restricted to tertiary academic centers. In 2002, numerous factors prompted the state to re-examine this policy, including a growing demand for neonatal intensive care beds, changing patterns of obstetric services and deliveries, limited capacity within the tertiary care centers, and growing pressures for cost-containment. In response to these factors, and in recognition of the changing nature of neonatal intensive care, Massachusetts revised its guidelines to allow for the development of its first neonatal intensive care unit within a community hospital.[44] This change in policy was made after extensive consultation



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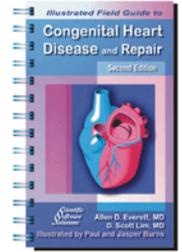
with the public and medical communities, and its consequences will be carefully monitored. The process leading to this change may serve to be a useful example of the ability of a state regulatory agency to manage effectively its perinatal care systems and to respond to changing social, economic, and scientific environments.

Third, studies examining systems of perinatal and neonatal care will need to utilize more refined measures of infant risk and outcomes. The majority of the studies to date have categorized neonates broadly, most typically as LBW or VLBW; these categorizations may not be sufficient, and it appears that different subgroups of these infants may behave differently in different settings. It may be that some VLBW infants, perhaps of extremely low birth weight or extremely low gestational age, may in fact benefit from care at highly regionalized level III centers, while other VLBWs may have similar outcomes at community NICUs. Recent studies have begun to utilize more specific definitions of infant subgroups, in addition to inclusion of risk adjustment based on physiologic variables, and this process should continue. Furthermore, the majority of the previous studies have relied on neonatal mortality as the primary outcome. With improvements in neonatal intensive care, mortality for most NICU patients is thankfully a rare event. Almost certainly, measures of morbidity, short and long-term, will be more accurate descriptors of differences in quality and effectiveness of care. Addressing the issues of morbidity may also require more intensive and continuous efforts to accurately describe differences in types of NICUs beyond simply designating levels of care. Efforts such as those supported by the Vermont-Oxford Network aim at improving care for all units regardless of size.[40,45]

Finally, optimal structuring of perinatal care systems by the states will require careful incorporation of societal and economic considerations in addition to an understanding of the best medical outcomes. Returning to the recent Massachusetts experience, it was the limited availability of intensive care beds in the tertiary centers and changing demographics that prompted a reevaluation of the regulations on NICU beds. The medical consideration of whether certain types of neonatal intensive care might be equally effective in a community hospital as a tertiary hospital was secondary. In certain regions, economic, demographic, or simple supply and demand forces may play as large a role as medical factors in determining the structure of the perinatal care system.

The efforts outlined above will be difficult, and will require cooperation among large segments of the medical community, public health organizations, and local and state governments. The improving quality and scope of recent studies as well as numer-

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ous examples of effective organization and management by states suggest, however, that these efforts are achievable. The goal of the medical and public health communities should continue to be careful planning of regionalized perinatal care systems; however, these efforts should be based on new definitions and measures of regionalization reflecting the current delivery of obstetric and neonatal care.

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MEDICAL NEWS, PRODUCTS AND INFORMATION

Researchers Identify Agents That May Make Vaccines Effective at Birth

Newborn babies have immature immune systems, making them highly vulnerable to severe infections and unable to mount an effective immune response to most vaccines, thereby frustrating efforts to protect them. Researchers at Children's Hospital Boston now believe they have found a way to enhance the immune system at birth and boost newborns' vaccine responses.

In a study published in the online edition of the journal *Blood* on April 25, 2006 Ofer Levy, MD, PhD and colleagues in Children's Division of Infectious Diseases show that the newborn immune system functions differently than that of adults, but that one portion of the immune response is fully functional and can be harnessed to boost immunity in these tiny infants, possibly making infections like respiratory syncytial virus, pneumococcus, pertussis, HIV and rotavirus much less of a threat.

For about a decade it's been known that people's first line of defense against infection is a group of receptors known as Toll-like receptors (TLRs) on the surface of certain white blood cells. Functioning like an early radar system, TLRs detect the presence of invading bacteria and viruses and trigger production of "danger signals" -- proteins known as cytokines that trigger other immune cells to mount a defense against the infection. People have 10 different kinds of TLRs, and Levy's team decided to examine how well they function in newborns by studying white blood cells from their cord blood.

"We found that when most Toll-like receptors are stimulated, newborns' immune responses are very impaired," Levy says. "But there was one important exception."

Levy's team, including Harvard graduate Eugenie Suter and senior author Michael Wessels, MD, showed that one TLR, known as TLR8, triggered a robust immune response in a group of white blood cells (called antigen-presenting cells) that is crucial for vaccine responses. When TLR8 was stimulated by various agents that mimic viral antigens, the cells produced normal, adult levels of two key cytokines - TNF-alpha and IL-12 - and another immune-system stimulant, CD40.

"These findings suggest that agents that stimulate TLR8 could be used to enhance immune responses in newborns, perhaps as adjuvants given along with vaccines," Levy says. "We plan to test this approach in animals, and eventually in human babies."

Levy notes that the ability to vaccinate newborns -- rather than wait until they reach 2 months of age -- would provide important global health benefits. "Birth is a point of contact with healthcare systems," he says. "Families may not see a health care provider after that. From a global health perspective, if you can give a vaccine at birth, a much higher percentage of the population can be covered."

Conceivably, TLR8 stimulators could also be given alone in special circumstances - - to help a baby fight off an infection in progress, or as a preventive measure in the event of a disease outbreak or bioterrorist threat, Levy adds.

Levy's team is uncovering other differences between the newborn and adult immune systems that could lead to additional targets for drugs or vaccines. A related paper, to be published soon in the journal *Pediatric Research*, finds that when newborns' TLRs are stimulated during the first week of life, their white

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cells' production of the cytokine IL-6, which inhibits parts of the immune response, is greater than that in adults.

A third study, to be published in the Journal of Immunology, finds that newborns' cord blood also has high levels of adenosine, providing an explanation for newborns' altered immune response: adenosine alters the physiology of white cells to suppress production of TNF-alpha (but not of IL-6) when TLRs are stimulated. When Levy's team used antagonists to inhibit adenosine's activity, newborns' white blood cells produced normal, adult levels of TNF-alpha in response to bacterial and viral triggers. "In the future, we could try to block adenosine in newborn animals to see if this helps protect against infection," Levy says.

Levy believes the differences his team has uncovered in newborns' immune response patterns may serve an evolutionary purpose. Nature may suppress babies' production of inflammatory cytokines like TNF-alpha and IL-12 before birth because they can trigger preterm labor, while increasing production of adenosine and IL-6, which may have a protective effect on the pregnancy.

In 1999, Levy discovered that newborns are deficient in a

natural antibiotic called bactericidal/permeability-increasing protein (BPI), produced by white blood cells known as neutrophils. Based on this discovery, clinical trials are now underway at the University of Texas Southwestern Medical Center in Dallas to replace the missing BPI in high-risk newborns with heart conditions who are undergoing cardiac bypass operations.

"As we better understand the molecular pathways that account for newborns' susceptibility to infections, we can leverage them to enhance their immune defenses," Levy says.

The current study was funded by the National Institutes of Health and the Patterson Trust. All three studies were presented at the Pediatric Academic Societies meeting on Saturday, April 29, 2006 in San Francisco.

Boosting Newborns' Immune Responses

Newborns are unable to mount an effective immune response to most vaccines, just when they are at high risk for infections. Researchers at Children's Hospital Boston believe they have found a way to boost newborns' immature immune systems,

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The current study was funded by the National Institutes of Health and the Patterson Trust. For more information visit: www.childrenshospital.org.

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ISSN: 1932-7129 (print); 1932-7137 (online).
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IMK111-00249

2/05