Annual Oration for 1978

Necrotizing Neonatal Enterocolitis

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Recently health professionals have been buffetted by the winds of change. In the past decade changing of health conditions, health delivery, and health education have rapidly occurred. The discipline of pediatrics and its surgical subset has not been immune to this phenomenon. Abortion on demand has significantly altered the incidence of certain congenital anomalies, and birth control, a declining birth rate, the control of childhood communicable diseases, and the decrease of infectious childhood entities, have markedly altered the incidence of traditional problems of children. As the middle-aged child has decreased its demand from the pediatrician, this creative physician has insinuated himself earlier and earlier into the life of the infant, until now the neonatologist and his obstetrical counterpart, the perinatologist, meet arm in arm in the birth canal to escort infants of small size and immature organ structure into a world of aggressive resuscitation and life support modalities committed to the subsequent salvage of the immature and small birth weight infant.

While in virtually every other sphere of pediatric practice, disease reduction, both in incidence and in identity has occurred, in the neonatal nursery the winds of change have ushered in new challenges, one of which is a disease entity which has been called, NNE, NEC, or Neonatal Necrotizing Enterocolitis.

The purpose of this presentation is threefold: first to review the etiology, pathogenesis and clinical course of this disease entity. Secondly, to share with you our recent experience in the clinical recognition and response to NEC, and finally to propose a philosophical surgical approach to this often nebulous and vexing clinical syndrome.

Incidence

At the recent American Academy of Pediatrics Section on Surgery meeting it was estimated that NEC now comprises approximately 4000 cases per year in the United States, a figure exceeding the incidence of solid tumors, gastrointestinal obstructive anomalies, tracheal esophageal anomalies, and many other congenital conditions with which pediatric surgery has become identified. For many of us, it has become the single most common reason for which surgical consultation is sought by the neonatal unit physician. In low birth weight premature hi-risk infants its incidence is estimated to affect 5% or approximately one in twenty.

Identified Risk Factors

Infants at risk for developing NEC can be pictured as a premature newborn weighing less than 1500 grams with an episode of perinatal stress. Prenatal and perinatal complications increase the risk, such as premature rupture of membranes, placenta previa, breech deliveries and cesarean section. However, the greatest risk factor involves specific post-partum respiratory or cardiovascular complications, including apnea, respiratory distress syndrome, episodes of hypothermia, and sepsis. A significant correlation with umbilical and venous cannulation has been noted, although it is difficult to incriminate a cause and effect relationship, since these activities are normally carried out in the sicker neonates.

Diagnosis

In 90% of the cases symptomatology begins between the first 24 hours of life and the fourteenth day. A constellation of at least seven signs or symptoms can be pieced together to develop the diagnosis.

Gastrointestinal Dysfunction

Abdominal distention with associated gastric retention or simple failure to take feeds is the single most consistently associated sign. Increased nasogastric draining progressing to bile stained material further attest to gastrointestinal dysfunction. Eventual vomiting may occur in larger infants, but is usually absent in the small premature.

Abdominal Tenderness

Abdominal tenderness may present with an advancing process. Such tenderness may be difficult to elicit in the depressed infant on life support equipment, but in the non-obtunded infant evidences of discomfort occur at a point when bowel integrity is beginning to be compromised.

Abdominal Wall Cellulitis

The presence of a reddened indurated anterior wall signifying an active inflammatory process in juxtaposition to the parietal peritoneum is a physical finding unique to the thin abdominal wall of the neonate, and is usually associated with an advanced process, in many instances signifying imminent perforation.

Hematologic Alterations

Although many variations in the standard blood count and differential are noted, the most significant change relative to NEC involves a visible decrease in platelets. Early in the course, prolongation of the bleeding time may be noted, while a later manifestation involves not only alterations in the bleeding time, but a progressive dissolution of all clotting factors consistent with the syndrome identified as disseminated intravascular coagulation or consumptive coagulopathy.

Hematochezia

Some manifestation of blood in the stool commonly occurs. This may range from a guaiac-positive specimen to mucoid, frankly bloody discharge material. Most commonly, stools show a trace to moderate amount of free unaltered blood. Symptomatic volume loss of red cell mass per-rectum is unusual.

Metabolic Acidosis

Metabolic acidosis unassociated with an obvious etiologic cause such as sepsis, and which fails to respond to corrective measures, is a reasonable indication of clinical deterioration, probably representing persistent lactic acidosis, the result of early cellular death within the bowel wall.

Pneumatosis Intestinalis

Intramural air, or pneumatosis, is a pathognomonic sign of NEC being associated with 70 to 80% of reported cases. The subtle nature of early pneumatosis, often resembling normal fecal matter, may make its early delineation on x-ray difficult. Advancing pneumatosis may be observed as a linear stripe outlining a gas filled intestinal loop, or as bubbles of gas in the wall of the gut. Portal vein gas provides a dramatic demonstration of advanced pneumatosis, although this occurs in less than 10% of cases.

Few babies have all the above signs and symptoms, and each must be evaluated to develop the final equation, which warrants the diagnosis of NEC. Although the constellation of signs and symptoms, including the low birth weight infant with a stressful history associated with gastrointestinal dysfunction, abdominal tenderness, hematest positive stools, and pneumatosis consolidate to make the diagnosis possible in a significant number of cases, the more perplexing problems remain: Why does it happen, and what should be done about it?

Etiology and Pathogenesis

Infection

Because of the commonly reported clustering of cases by time and location, and the frequent association of documented sepsis, the possibility that NEC could be secondary to infectious agents has long been suggested. Evidence at present suggests no demonstrable viral, fungal, or bacteriologic agent is responsible for NEC. The presence of normal gastrointestinal flora invading the bowel wall appears to be a secondary role subsequent to other etiologic processes causing bowel wall necrosis.

Hyperosmolar Feedings

Hyperosmolar feedings have been sighted as causing injury to sensitized mucosal cells in both animals and human studies. For example, prematurely delivered pigs fed hyperosmolar goat milk developed a disease closely resembling NEC, while seven of eight under 1200 grams-sized babies fed a high

osmolar diet developed the characteristic clinical features. However, NEC has continued to increase in the absence of hyperosmolar formula feedings.

Decreased Secretory IGA

The principle immunoglobulin in intestinal secretions is IGA, with its formation centered in plasma cells present in the lamina propria. Such IGA is deficient in the neonate for several days, until food antigens and endogenous flora of the colonized gut serve to stimulate antibody production. During these first few days the primary source of IGA is the colostrum of mothers milk, specifically the colostral leukocytes which provide passive immunity against enteric pathogens. Enteric overgrowth of potentially pathogenic bacteria in the formula fed rat emphasized the importance of protective antibodies in breast milk. Unfortunately, after a spate of enthusiasm for the utilization of breast milk in all infants at risk, breast milk alone has not shown itself to be fully protective against the development of NEC.

Plasticizers—Polyvinal Tubing

Increased tissue concentration of diphthalate, associated with polyvinal catheters and umbilical catheterization, has been incriminated as an etiologic factor. Arterial and venous umbilical catheters are known to disrupt the hemodynamics of splanchnic circulation with portal vein pressure increased by umbilical vein catheterization. However, it is doubtful that this is a causative agent and it is more likely due to the fact that small birth weight infants with difficulties routinely receive vascular access procedures.

Selective Circulatory Ischemia

The most widely held and easiest understood etiologic concept involves selective circulatory ischemia as an asphyxial defense mechanism in the primitive organism. Conceptually, this relates to original experimental activities carried out at the Edward Martin Biological Laboratory at Swarthmore College in the early 1940's, when a paper entitled "The Regulation of Arterial Blood Pressure in the Seal During Diving" was published in the American Journal of Physiology. This work showed a pronounced bradycardia, as well as alteration of blood pressure, occurring during rapid submersion of this mammal. Some 20 years later other investigators utilizing a diving duck model quantitated regional blood flow by following the distribution of rubidium chloride tagged red cells. This experiment compared regional blood flow in the normal breathing state to that occurring in the stressed state of the diving duck in the prolonged submerged situation. Consistent and significant shunting of oxygenated blood occurred away from certain portions of the gastrointestinal tract toward an increased concentration within the heart and brain. Interestingly enough, in the gastrointestinal tract the esophagus was shown to have a minimal alteration of blood flow while the remaining portions of the gastrointestinal tract, particularly the distal small bowel received sharp reduction—a pattern consistent with the gastrointestinal areas of involvement of NEC. This hypothesis is supported

by more recent work involving regional blood flow determination of asphyxiated and resuscitated neonatal piglets. Furthermore, the gut of such asphyxiated and resuscitated piglets showed a rebound phenomenon which resulted in vascular congestion and mucosal hemorrhages strikingly similar to the findings described in infants with NEC. In the opinion of these investigators, local hemorrhages are the primary lesion of necrotizing enterocolitis, resulting from a combination of increased capillary fragility produced by gut ischemia and intramural vascular congestion resulting from the resuscitative effort and rebound phenomenon. Subsequently, local cellular necrosis occurs, invasive bacterial proliferation and transmural inflammation result in gastrointestinal dysfunction and the clinical symptomatology associated with enterocolitis. Primitive reflex mechanisms are most pronounced in the immature and incompletely differentiated organism. The dramatic implementation of these reflexes is postulated to be particularly active in the immature and premature infant. The most logical common pathway would then appear to be hypoxia, which stimulates primitive reflex mechanisms to shunt oxygenated blood away from the gastrointestinal tract—producing ischemic mucosal lesions wherein bacteriologic invasion and subsequent gut necrosis occurs, resulting in cell death and the syndrome of necrotizing enterocolitis.

Clinical Course

The clinical picture can usually be divided into those involving an early versus late onset of symptoms, those involving short isolated segments of gut versus a generalized involvement of the gastrointestinal tract, and those involving fulminate development of symptoms, versus a protracted period of symptomatology. Fulminate development of symptoms is generally associated with poor outcome, whether occurring early or late in the neonatal period, and whether involving short or long segments of the gastrointestinal tract. Localized disease commonly associated with ileocecal involvement provides, in general, a better prognosis than diffuse involvement of the gastrointestinal tract. Delayed onset versus early onset has the least direct influence on outcome. Consequently, a prognostic nomogram might show early onset, fulminate course, and generalized involvement of the gut as having the poorest outcome. Late onset, localized disease, and protracted development of symptoms provide the best prognostic possibilities.

Treatment

In many instances the progressive features of NEC can in fact be aborted if appropriate use of gastrointestinal rest, intravenous alimentation, and systemic antibiotics are utilized. At the earliest sign of gastrointestinal distention with retention of gastric contents, culturing of body orifices and secretions is carried out and the infant begun on a regimen of antibiotics. Our current choice for this is ampicillin (150mg/kg/day) and gentamicin (5mg/kg/day). Regional flora as identified in each nursery may give rise to variation in the choice of antibiotics. The use of enteral antibiotics, although popularized by some, has not received universal acceptance and is not a part of our regimen.

Gastrointestinal Rest

Gastrointestinal rest by a nasogastric tube and/or gastrostomy is desirable. In our hands nasogastric decompression has been used exclusively, while others have preferred a gastrostomy.

One of the most important considerations is continued nutritional support with parenteral alimentation either through a peripheral or a central access port. By utilizing free fat solutions which provide nine calories per gram, peripheral alimentation is possible and maintenance of nearly total nutritional support facilitated. Such therapy obviates the potential septic components of a central venous long term catheter. Removal of umbilical venous and arterial lines is to be encouraged, and if continuing blood gas monitoring is necessary, this can be carried out from a temporal or radial artery site. Gastrointestinal rest with intravenous alimentation is carried out for a minimum of five to seven days, and in most instances of non-progressive NEC is discontinued between the seventh and fourteenth day, when resumption of oral intake occurs.

When surgical intervention is decided upon, the surgical procedure involves resection and reconstruction. Obvious necrotic material is removed but questionable material, particularly in extensive segment involvement, should remain in situ. A second look at 24 or 48 hours is preferable to resecting long segments of questionable viability. To exteriorize the remaining bowel or carry out primary anastomosis is the major intraoperative decision. Many suggest routine exteriorization of all cases. More recently, some evidence indicates that in selective cases, primary anastomosis is a satisfactory procedure. Because of infection and severe catabolism, the risk of disruption is high. In our hands the use of monifilament wires for the fascia has proved useful, while the use of prophylactic retention sutures has not been employed. Fresh whole blood, rather than component therapy, provides clotting factors often depleted in the baby with NEC. As previously indicated, parenteral nutrition in the post-operative period is essential.

The Medical College of Pennsylvania Experience

During the past three years thirty cases of NEC were diagnosed and managed by the neonatal and pediatric surgical service at The Medical College. The seven previously identified signs and symptoms were utilized to establish the diagnosis. Gastrointestinal dysfunction to some degree was uniformly present with the exception of a single case in which the course was so fulminant that dysfunction and diagnosis occurred simultaneously. Hematochezia, metabolic acidosis, and pneumatosis were present in a consistently high percentage of cases. The diagnosis was considered established in this series under the following circumstances: 1. operative or postmortem delineation of disease; 2. pneumatosis associated with a clinical picture compatible with NEC; 3. in the absence of demonstrable pneumatosis any constellation of four of the identified signs or symptoms. In 80% the onset was within the first ten days of life. Twenty-six or 86.6% weighed less than five pounds. It should be noted this leaves 20% to have occurred later than the first ten days of life and some 13%

to be term size infants. All term sized infants presented with symptoms between the third and fifth day of life.

Management

In 16 cases, non-surgical treatment was elected. Of these, 12 survived and four died. Of those dying without surgical intervention, the clinical course was so fulminant as to preclude a surgical consideration. Fourteen received an abdominal surgical procedure. Of these, nine survived and five died.

Surgical Intervention

The decision to surgically intervene was carried out when free perforation was identified in ten of our cases, or when clinical deterioration appeared to be present in the absence of free perforation as occurred in four cases. For effective surgical management to ensue, one must intervene ideally at that point just prior to perforation, and/or immediately thereupon such an occurrence. The generous use of x-rays, or more importantly the close monitoring by trained nursing personnel, produces the middle of night and weekend diagnosis so necessary if surgical intervention is to be helpful.

Exteriorization was carried out in five situations, two of whom survived to have subsequent reconstitution of the gastrointestinal tract, three of whom died after stoma formation, all in the immediate post-operative period. In nine patients primary anastomosis was carried out, seven of whom survived and two of whom died. Both of these deaths were in the immediate post-operative period, and in neither was anastomotic disruption identified at postmortem examination. In all cases 10cm or more of the gastrointestinal tract was involved, and in at least 1/3 of the cases, more than 1/3 of the small bowel was involved. However, at no time was it necessary to remove more than 50% of the gastrointestinal tract. Two patients received a second look procedure to determine ultimate bowel survival. Only two of 21 survivors followed for three months or more have developed strictures. In both instances these were amenable to corrective local resective procedures. This 9.5% incidence of strictures is somewhat lower than that reported in other series. One of our two strictures involved a site of primary anastomosis. All infants have required careful long term monitoring of formula and feeds. One is a persistent gastrointestinal cripple.

NEC—Results of Therapy

The MCP overall survival of 70% is a figure which compares favorably to other reported series. It is of interest to note that based on these reported series there would appear to be progressive improvement in the recognition and response to this entity, probably the result of increased number of physicians having undergone the learning curve necessary to recognize and appropriately respond to a process with so many variables.

Summary and Conclusion

The winds of change then have indeed ushered in a disease of mounting

concern to health professionals caring for children. Its origin is still somewhat obscure, its clinical manifestations are variable and unpredictable, its decision points and outcomes are not easily identified by laboratory studies or programmable computer printouts. Perhaps the message the neonate sends forth to the physician in reality is saying, "Stand by my bedside rather than in the laboratory or x-ray department and look, listen, feel and cerebrate. Operate when your fantasy says perforation is imminent or an immediate reality, whether this is day, night, weekends or holidays; do what you must to remove dead or dying tissue but no more; provide a stoma only if lack of blood supply or increased tension jeopardize my anastomosis; encourage my healing phase with vigorous nutritional support and in many instances I'll survive." Survive as a combination of the marvels of resuscitative mechanized medicine but only when these modalities are sustained by traditional clinical judgment, learned and applied best by day and night and weekend appearances at the bedside or in the operating room where to look, listen, feel, cerebrate, and then only sometimes to operate, are the surgeon's contribution to this challenging disease process ushered upon us by the winds of change.