Necrotizing enterocolitis

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Definitions

Necrotizing Enterocolitis: an acquired neonatal acute intestinal necrosis of unknown etiology NEC is neither a uniform nor a well-defined disease entity

Definitions

Isolated spontaneous intestinal perforation

(SIP): ill-defined clinical syndrome of undetermined cause resembling NEC with less systemic involvement and a less severe clinical course. It may present a variant of classical NEC

The National Institute of Child Health and Human Development Neonatal Network (NICHD): intestinal perforation without evidence of pneumatosis since

Definitions

Acquired neonatal intestinal diseases (ANIDs)

Wider umbrella includes different pathologies affecting

gastrointestinal tract in preterm and term infants. Some

which do lead to the common final pathology of NEC and

some which do not.

Includes:

- **NEC**
- **SIP**
- **Viral enteritis of infancy**
- **Cow’s milk protein allergy**

Epidemiology

Incidence: 0.3-2.4 / 1000 live births

- 2-5 % of all NICU admissions
- 5-10 % of VLBW infants

Over 90 % of cases occur in preterm babies

About 10 % occur in term newborns:

essentially limited to those that have some underlying illness or condition requiring NICU admission

Epidemiology

Sporadic or epidemic clusters

Sex, race, geography, climate, season: No role

- Male VLBW infants are at greater risk of death
- Black infants: increased risk of NEC, and its associated mortality

Risk Factors: Prematurity

Prematurity is the single greatest risk factor

The risk is inversely related to birth weight and gestational age

Risk Factors: Genetics

Familial:

There are report a consanguineous Jewish Ashkenazi family in which three of four children died within a few weeks after birth from severe enterocolitis

Also a Lebanese consanguineous family where three term sibs presented with severe early and lethal enterocolitis, all with delayed meconium passage

a multicenter retrospective study of 450 twin pairs born at < or =32 weeks of gestation, showed that intraventricular hemorrhage,

necrotizing enterocolitis, and bronchopulmonary dysplasia are familial in origin

Risk Factors: G-6-PD deficiency

G6PD deficiency was significantly higher (27.8%) in infants with NEC compared with the 5.3% prevalence

among NICU admissions (odds ratio = 6.9; 95% confidence interval = 2 to 23.5)

G6PD deficiency also was found to be a marker for more severe NEC

G6PD deficiency should be considered a risk factor for NEC

Risk Factors: Cocaine

Maternal cocaine abuse increases the risk by 2.5 folds (95% CI = 1.17 to 5.32, P = 0.02)

Risk Factors: Indomethacin

Indomethacin for Tocolysis: Metaanalysis 2007

Recent exposure (within 48 hours of delivery) to antenatal indomethacin was associated with

necrotizing enterocolitis (OR, 2.2; 95% CI; 1.1-4.2).

Risk Factors: Indomethacin

Indomethacin in Early Life:

Associated with SIP3

Prolonged versus Short Course of Indomethacinfor the treatment of PDA in preterm infants: Systematic Review

- The reduction of transient renal impairment does not outweigh the increased risk of NEC associated with the prolonged course.
- Based on these results, a prolonged course of indomethacin cannot be recommended for the routine treatment of PDA in preterm infants

Risk Factors: Dexamethasone

Combined use of indomethacin and dexamethasone increases the risk of SIP in VLBW neonates

Risk Factors: H2-blockers

Antecedent H2-blocker use was associated with an increased incidence of NEC (OR 1.71, 95% CI 1.34-2.19, P < .0001)

Risk Factors: Co-amoxiclav

Co-amoxiclav should be avoided in women at risk of preterm delivery because of

the increased risk of neonatal necrotizing enterocolitis (RR 4.60, 95% CI 1.98 to 10.72)

Risk Factors: Acyclovir

Term baby, developed NEC after receiving prophylactic acyclovir.

Mother had herpes genitalis and pROM at 32 wks of GA, treated with acyclovir until vaginal delivery

Acyclovir treatment in uteroand after birth is discussed as a possible cause of necrotizing enterocolitis in the infant.

Risk Factors: Kayexalate

Necrotizing enterocolitis in a 850 gram infant receiving sorbitol-free sodium polystyrene sulfonate

Their case report shows that Kayexalateper se, and not necessarily suspended in sorbitol, can lead to

gastrointestinal tract complications and NEC in preterm infants.

Risk Factors: UAC

UAC cause a decrease in mesenteric blood flow

Therefore, their use in hemodynamically unstable neonates or in those with gastrointestinal disease should be very carefully Considered

High vs. low UAC: necrotising enterokolitis are not more frequent with high compared to low catheters

Preprandial SMA BFV and postprandial SMA BFV responses to minimal enteral feedings were not affected by the presence of a UAC

Risk Factors: UVC

Compared long-term (up to 28 days) and short-term (7-10 days) use of umbilical venous catheters in premature infants with birth weights of less than 1251 grams

There were no differences in time to full feedings or to regain birth weight or in the incidence of necrotizing enterocolitis or death

Risk Factors: PDA

No association between significant PDA and NEC

The age at starting feed and full enteral feed was significantly delayed in infants with significant PDA

Risk Factors: in Term babies

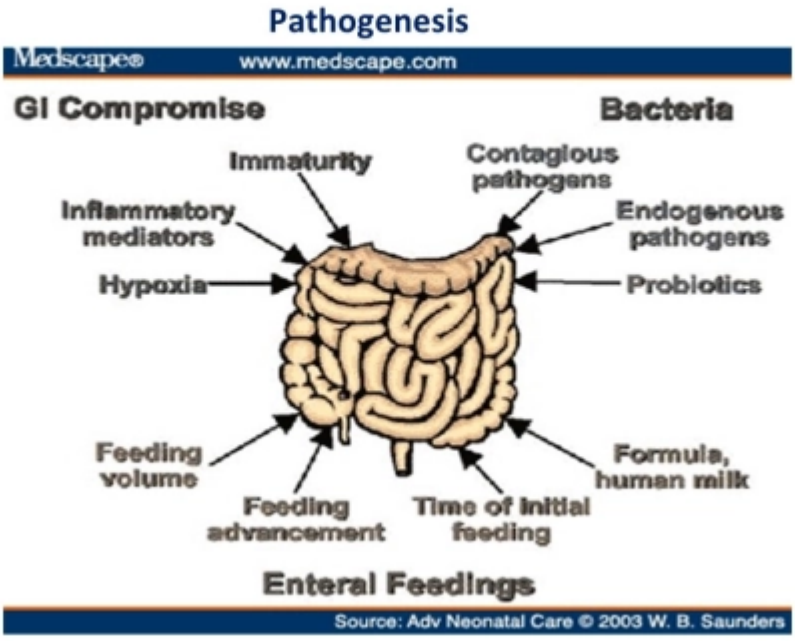
Limited to those that have some underlying illness or condition requiring NICU admission.2

- Congenital Heart Disease
- Intrauterine growth restriction
- Polycythemia
- Hypoxic-ischemic events

Risk Factors: Exchange transfusion

There is no evidence of long-term benefit from partial exchange in polycythaemic infants

The incidence of gastrointestinal injury is increased NEC (RR 8.68; 95% CI 1.06 to 71.1)



Pathophysiology

Hypoxic-Ischemic insult

Enteral Feeding

Microbiologic Flora

Cytokines and Inflammatory Mediators

Hypoxic-ischemic insult

Hypoxia-Reoxygenation.

Ischemia-Reperfusion.

Intramural microcirculation.

Balance between Endothelin-1 and Nitric Oxide.26

Enteral feeding

Formula vs. Donor Breast Milk

Formula is associated with higher risk of NEC

Enteral feeding

Disadvantages of Formula:

Higher osmolality ±

Lack of immunoprotective factors

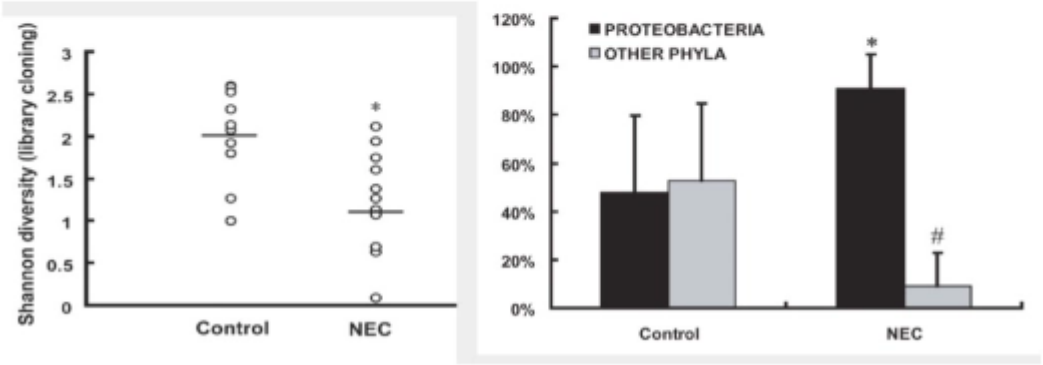
Lack of growth factors

Altering intestinal flora

Microbiome and Infection

- Microbiome and Infection
- Several organisms have been accused, but non has been proven to be causative:

- Enterobacteriaceae
- Enterobacter sakazakii
- Coagulase-negative staphylococci: SIP
- Closrtidium perfringens
- Candida species: SIP
- Cytomegalovirus
- Torovirus
- HIV
- Mucormycosis



Cytokines and Inflammatory Mediators

Platelet Activating Factor (PAF)

Tumor Necrosis Factor (TNF)

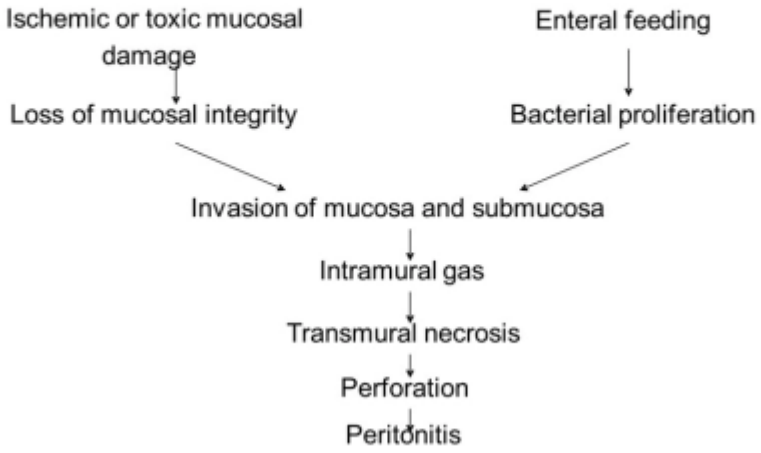
High-mobility group box 1 protein (HMGB 1)

Interferon-gamma (INF-gamma)

Interleukins (ILs)

Matrix metalloproteinases (MMPs)

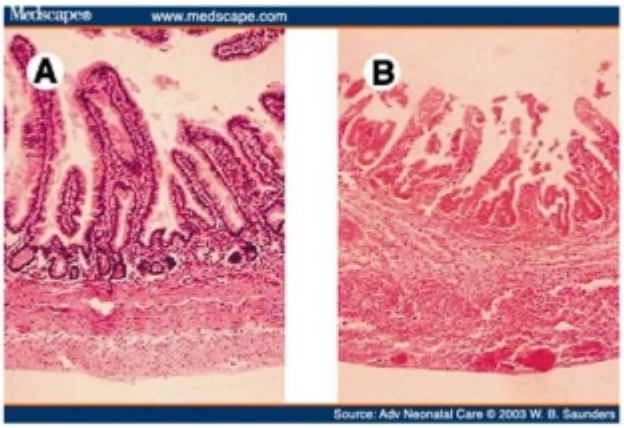
Pathophysiology in summary



Pathology

Closeup of intestine of infant showing necrosis and pneumatosis intestinalis. Autopsy

Pathology



Microscopic images of (A) normal bowel and (B) characteristic findings of NEC, which illustrates hemorrhagic necrosis, beginning in the mucosa and extending to the muscular bowel wall, where the potential for perforation exists. NEC frequently involves the terminal ileum.

Clinical presentation

Onset varies with gestational age

- VLBW 14 – 20 days
- Term first week

Course of the disease

- Fulminant presentation
- Slow, paroxysmal presentation

Clinical presentation

Systemic signs:

- Respiratory distress, apnea, bradycardia
- Lethargy, irritability
- Temp. instability
- Poor feeding
- Hypotension
- Acidosis
- Oligurea

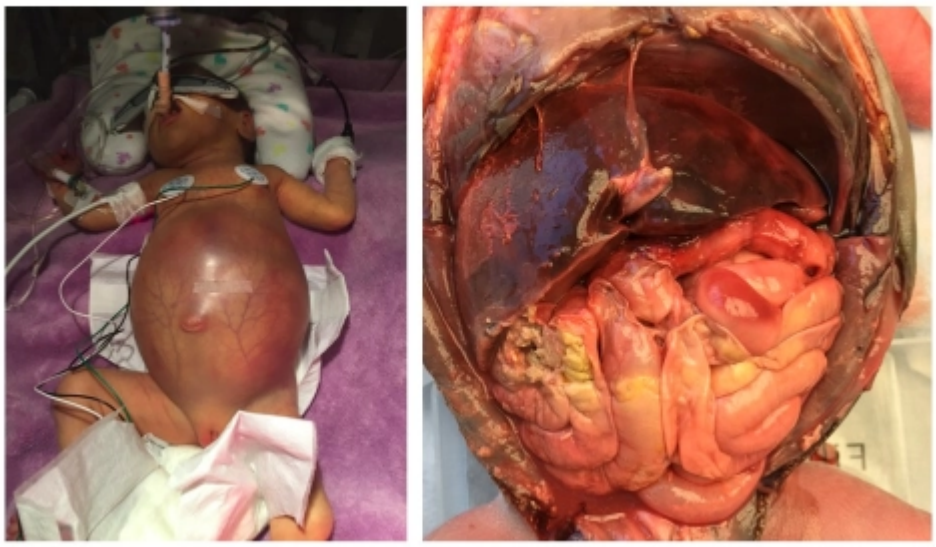
- Bleeding diathesis

Clinical presentation

Abdominal (enteric) signs:

- Distension
- Tenderness
- Gastric aspirate, vomiting
- Ileus
- Abdominal wall erythema, induration
- Ascites
- Abdominal mass
- Bloody stool

Clinical presentation



Diagnosis

A high index of suspicionis required Sometimes cannot be differentiated from sepsis

Diagnosis, laboratory studies

No lab test is specific for NEC

The most common triad(!):

- Thrombocytopenia
- Persistent metabolic acidosis
- Severe refractory hyponatremia

↑ WBC, ↓ WBC, ↓ PMN

Hyperkalemia

Stool: reducing substances, occult blood

Diagnosis, radiologic studies

Abdominal X-ray:

- Abnormal gas pattern, ileus
- Bowel wall edema
- Pneumatosis intestinalis
- Fixed position loop
- Intrahepaticportal venous gas (in the absence of UVC)
- Pneumoperitonium, left lateral decubitus or cross-table lateral views

Diagnosis, radiologic studies

Pneumatosis intestinalis.

Very obvious case.

Tremendous amount of air in bowel walls

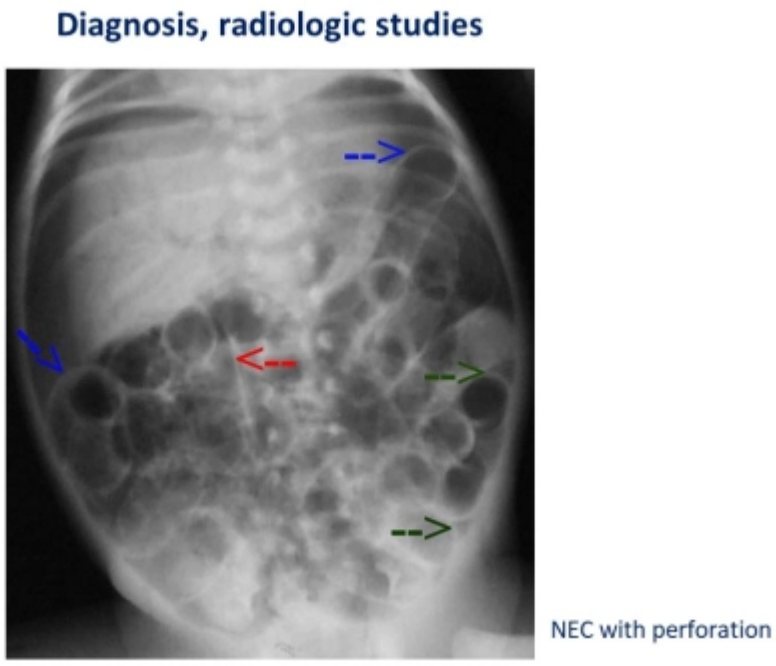
Diagnosis, radiologic studies

Pneumatosis intestinalis. Note the air visible in

the bowel wall. The air dissects the bowel wall

giving it a double lined appearance (ie., ailroad

tracks without the ties)



Diagnosis, radiologic studies

Abdominal ultrasound:

Thick-walled loops of bowel with hypomotility.

Intraperitoneal fluid is often present

Intramural gas can be identified in early-stage NEC

In the presence of pneumatosis intestinalis, gas is identified in the portal venous irculation within the liver

Color Doppler US is more accurate than abdominal radiography in depicting bowel necrosis in NEC

Diagnosis, radiologic studies

Abdominal Doppler ultrasound:

neonates with high resistance patterns of blood flow velocity in the superior mesenteric artery on the first day of life are at increased risk of developing necrotizing enterocolitis

Modified Bell's Staging Criteria

Stage I : Suspected NEC

Clinical signs and symptoms

No diagnostic radiograph

Modified Bell's Staging Criteria

Stage II : Definite (confirmed) NEC

A.Mild NEC

- Sign & symptoms, absent B/S, gross blood in stool
- AXR: ileus, focal areas of pneumatosis intestinalis
-
- A.Moderate NEC
- Systemically ill
- AXR: extensive pneumatosis intestinalis, early ascites, possible intrahepatic portal venous gas

Modified Bell's Staging Criteria

A: Severe NEC without perforation

- Critically ill
- Abdominal wall induration, extensive erythema
- AXR: prominent ascites, paucity of bowel gas, persistent fixed loop

B: Severe NEC with perforation

Differential diagnosis

Systemic infection: sepsis, pneumonia

Surgical abdominal catastrophes

Infectious enterocolitis

Allergic collitis

Feeding intolerance

Management

The main principle of management of confirmed NEC is to treat it as an acute abdomen with impending or septic peritonitis

Isolation: cohort isolation in case of epidemic clusters

Management, medical

Basic NEC protocol: for all stages

NPO

- NGT with low pressure suction
- Close monitoring of vital signs & abdominal girth
- Remove UAC and UVC
- Septic workup: blood, urine, and stool cultures
- LP and CSF culture: controversial
- Antibiotics: ampicillin + gentamicin or cefotaxime
- add Metronidazole or clindamycin if peritonitis or
- perforation is suspected

Management, medical

Basic NEC protocol .....continued

- Monitor for GI bleeding
- Fluid balance: maintain urine output 1-3 ml/kg/hr
- Lab.: CBC, PLT, electrolytes q 8-12 hrs
- PT, PTT, as indicated CR
- Radiology: serial AXR q 6-8 hrs in the first 2-3 days
- Family support

Management, medical
Stage I

Basic NEC protocol

If all cultures are negative, the infant improved clinically, and AXR is normal, antibiotics can be stopped after 2-3 days and feeding can be resumed.

Management, medical

Stage II

Basic NEC protocol

- NPO for 14 days
- TPN, 90-110 kcal/kg/day
- Antibiotics for 14 days
- Respiratory support
- ± Inotropic support
- Surgical consultation

Management, medical

Stage III

- As stage II
- Inotropic support
- Treat anemia, thrombocytopenia, coagulopathy
- Surgical intervention

Management, surgical

Early Surgical Consultation

Indications for surgery:

- Perforation: 20-30 % of cases
- 12-48 hrs after onset
- Full-thickness necrosis
- Deterioration despite aggressive medical treatment

Management, surgical

Surgical Approach:

Exploratory laparotomy

Peritoneal drainage

Management, surgical

Exploratory laparotomy:

The most commonly used approach

Intestinal resection with enterostomy

Primary anastomosis

Management, surgical

Peritoneal drainage:

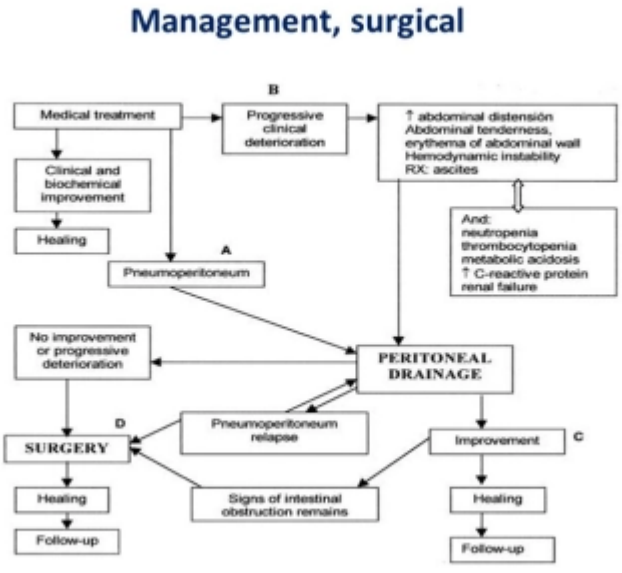
More conservative approach, Started in 1977

Insertion of a peritoneal drainelocal anaesthesia

Initially, used for very sick premature babies, with weight ≤ 1000 g

Now, it is used more commonly with larger and more stable babies

It is used as a definite treatment in some centers



Algorithm for the treatment of necrotizing enterocolitis

Management, surgical

Laparoscopy:

use of laparoscopy on day 30 of life in the treatment of a VLBW infant (900 g)

with perforated NEC

Needlescopic diagnosis is feasible and appears to be safe, even in

critically ill micropremmies less than 1000 g. The technique can provide useful information for surgical decision-making and allows for precise placement of a microlaparotomy incision over the site of perforation, thus minimizing the trauma from open surgery in this special group of patients

Prognosis and Outcome

NEC with perforation: mortality 20-40 %

Recurrent NEC : rare complication, 4%

Subacute or intermittent symptoms of bowel obstruction: strictures, 10-35 %

Short-gut syndrome: FTT, high mortality

The type of operation (peritoneal drain vs. laparotomy) performed for erforated NEC does not influence survival or other clinically important early outcomes in preterm infants

Neurodevelopmental Outcome

Preterm infants who develop NEC are at a significantly higher risk for developing neurodevelopmental disability

Neurodevelopmental Outcome

NEC is associated with significantly worse neurodevelopmental outcome than prematurity alone.

Presence of advanced NEC and need for surgery increase the risk of neurological impairment

Survivors of stage II or higher NEC are at risk for long-term neurodevelopmental impairment, especially if they require surgery for the illness

Prevention

- Breast milk

- Antenatal Steroid therapy
- Oral immunoglobulins
- Oral antibiotics
- Probiotics (Lactobacillus, Bifidobacterium)
- Feeding strategies
- Oral PAF antagonists
- Glutamine
- Arginine
- Polyunsaturated fatty acids (PUFA)
- Lactoferin
- Pentoxifylline

Prevention: breast milk

Formula vs. Donor Breast Milk:

Breast milk is associated with lower risk of NEC slower growth in the early postnatal period ¨

Prevention: Antenatal steroids

Antenatal corticosteroids for women at risk of preterm birth: Systematic Review

Decreased risk of NEC

RR 0.46, 95% CI 0.29 to 0.74, eight studies, 1675 infants

Prevention: Oral imunoglobulin

The evidence does not support the administration of oral immunoglobulin for the prevention of NEC. There are no randomised controlled trials of oral IgA alone for the prevention of NEC

Prevention: Probiotics

Probiotics might reduce the risk of necrotising enterocolitis in preterm neonates with less than 33 weeks' gestation (relative risk 0.36, 95% CI 0.20-0.65) the short-term and long-term safety of probiotics needs to be assessed in large trials Unanswered questions include the dose, duration, and type of probioticagents (species, strain, single or combined, live or killed) used for supplementation

Prevention: Feeding strategie

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Prevention: Glutamine

The available data from good quality randomised controlled trials suggest that glutamine supplementation does not confer clinically significant benefits for preterm infants

The narrow confidence intervals for the effect size estimates suggest that a further trial of this intervention is not a research priority

Prevention: Arginine

The data are insufficient at present to support a practice recommendation. A multicentre randomized controlled study of arginine supplementation in preterm neonates is needed, focusing on the incidence of NEC, particularly the more severe stages (2 or 3)