Umbilical Doppler flow abnormalities occur in 6% of high risk pregnancies. Preterm infants born with abnormalities in the umbilical artery Doppler waveforms such as absent end-diastolic flow (AEDF) or reversed end-diastolic flow (REDF) are at risk of complications related to enteral feeding such as feed intolerance and necrotizing enterocolitis (NEC). The complications result in undue delay in initiation and progression of enteral feeds in such infants thereby prolonging the time to reach full enteral feeds as well the duration of hospital stay.

**Pathophysiology of abnormal doppler flow**

Abnormalities in the placenta and increased placental vascular resistance are the common underlying mechanisms for fetal growth restriction. Fetus with intrauterine growth restriction (IUGR) often shows abnormality in the umbilical doppler flow velocities secondary to adaptive hemodynamic changes in the fetal circulation. Fetal hypoxia and hypercarbia causes cerebral vasodilatation while increased sympathetic activity results in increased peripheral vascular resistance. These changes cause preferential distribution of blood flow to brain, heart and adrenals at the expense of gastrointestinal tract, kidneys, lungs and other organs. Increase in mesenteric vascular resistance leads to reduced intestinal perfusion and hypoxic injury to the gut even before birth. Preferential redistribution of blood to brain and other organs results in reduced diastolic flow in the fetal umbilical arteries eventually leading to absent or reversal of end diastolic flow as detected by Doppler.

**Enteral feeding in infants with AREDF**

Fetal hypoxia along with increased vascular resistance in the mesenteric circulation result in hypoxic ischemic injury of the intestine before birth. This in turn leads to abnormality in the motor, secretory, and mucosal function of the intestine making
it vulnerable to stasis and abnormal colonisation and invasion by bacteria.\(^3\)

Moreover, these circulatory changes tend to persist after birth. Baseline blood flow in superior mesenteric artery (SMA) and celiac axis have been found to be significantly reduced after birth and usually normalize by 1 week of postnatal age.\(^2,3\) Dynamic changes in SMA flow after feeding is also impaired in infants with AREDF. High metabolic demands associated with enteral feeding in the presence of compromised gut perfusion both antenatally and postnatally further affects tissue oxygenation of the intestine. In addition, intestinal stasis and immunological factors in growth restricted fetus also contribute to the development of NEC. The pathophysiology of feed intolerance and NEC in infants with AREDF is summarized in figure 20.1.

Evidence also shows that the risk of developing NEC is two folds higher in infants with AREDF when compared to infants with normal umbilical Doppler flow [OR: 2.13 (1.49 to 3.03)].\(^2\) Because of these concerns, initiation of enteral feeding is often delayed in infants with AREDF resulting in longer time to reach full enteral feeds and prolongation of the duration of hospital stay.

**Feeding strategies in infants with AREDF**

1. **When to start minimal enteral nutrition (MEN) in infants with AREDF?**
   MEN is started in stable ELBW infants from day one of life on the rationale that it would help in early initiation of progressive enteral feeding and attainment of full enteral feeds. However, it is controversial whether infants with AREDF should be given MEN from the day of birth and how long MEN is to be continued before considering progressive enteral feeding.
Figure 20.1: Pathophysiology of feed intolerance and necrotizing enterocolitis in infants with AREDF

IUGR
Prolonged hypoxemia & ischemia

Redistribution of blood flow to vital organs

Increase in mesenteric vascular resistance and altered mesenteric blood flow

Intestinal hypoxic injury before birth

Neutropenia in growth restricted infant

Motor, secretory and mucosal dysfunction

Increased susceptibility to infections

Intestine more susceptible to stasis, abnormal colonisation and bacterial invasion

Persistence of mesenteric blood flow abnormality after birth

Increased risk of feed intolerance, NEC
Panel 1
Time of initiation of enteral feeds: What is the evidence?

Among preterm neonates (27 to 34 weeks’ gestation) with abnormal antenatal Doppler, the incidence of NEC and feed intolerance was not significantly different between neonates who received MEN before 6 days of life and those who received at or after 6 days. However, the time to reach full enteral feeds was delayed and the weight SDS scores at discharge was significantly less in the delayed feeding group.⁴

The Cochrane review on delayed introduction (beyond 4 days after birth) of progressive enteral feeding in VLBW infants or very preterm infants with growth restriction also did not find any reduction in the incidence of feed intolerance or NEC; indeed, there was a trend towards increased incidence of invasive infection in infants in the delayed introduction group.⁵

We routinely initiate MEN on day 1 of life in neonates with birth weight of 1250 g or more and after 24 hours of life in those weighing less than 1250 g and are born before 35 weeks of gestation (Figure 20.2).

1. When to start progressive enteral feeding?

Delayed initiation of progressive enteral feeding should theoretically benefit infants with AREDF because of the limitations already highlighted. While it could potentially reduce the risk of NEC, it is likely to delay the time to reach full enteral feeds and prolong the duration of hospital stay.

In the ADEPT trial, feed volumes were not increased for 2-3 days in neonates with birth weight < 1000 g while it was increased progressively from second day after initiation of enteral feeds in neonates with birth weight ≥ 1000 g.⁴

2. How to advance?

There is wide variation in practice in the rate of advancement of feeds. The quantum of increase in the volume is generally 10-20 mL/kg/day in infants less than 1000g and 20-30 mL/kg/day in infants above 1000g.
One study that evaluated the effect of slow vs. rapid advancement of enteral feeding in two birth weight groups – <1250g (20 vs. 30 mL/kg/day) and ≥1250g (30 vs 40 mL/kg/day) – did not find any increase in the incidence of NEC or feed intolerance. The Cochrane review on slow (15-24 mL/kg/day) vs. rapid (30-40 mL/kg/day) advancement of enteral feeds in VLBW infants reported similar results. However, the number of infants with growth restriction or abnormal antenatal Doppler was small in the included studies.

We increase feed volume by 10 to 20 mL/kg/day in neonates with birth weight <1250 g and by 20 to 30 mL/kg/day in neonates with birth weight of 1250 g or more (Figure 20.2).

3. Which milk to start?
Breast milk is preferred over formula for feeding preterm infants. Mother’s own milk is preferred over donor human milk. NEC has been found to be less if the intake of mother’s own milk exceeds 50% of the total intake. Infants fed with exclusive human milk feeding have been found to have decreased incidence of NEC.

4. How to monitor?
Monitoring for feed intolerance in infants with AREDF is no different from other preterm or LBW neonates. Feed intolerance, if any, has to be managed as per the algorithm in the protocol on ‘Feeding of LBW infants’.

5. How to fortify?
Fortification of breast milk is preferably done once the neonate reaches 100 mL/kg/day of feeds. However, in ADEPT trial, fortification was started after the infants reached 150 mL/kg/day.

Feeding of infants with AREDF can be summarized as in figure 20.2.
**Figure 20.2: Algorithm for feeding infants with AREDF**

- **Gestation < 35 wks**
  - **Birth weight < 1250 g**
    - Start MEN after 24 hrs if no contraindication @ 10 mL/kg/day*
  - **Birth weight ≥ 1250 g**
    - Start MEN on day 1 if no contraindication @ 10-20 mL/kg/day*

- If tolerating well
  - **Gestation ≤ 29 wks**
    - Continue MEN for 48 hrs and then increase feeds @ 10-20 mL/kg/day*
  - **Gestation > 29 wks**
    - Increase feeds @ 10-20 mL/kg/day*

- Increase feeds @ 20-30 mL/kg/day*

- Add fortification once baby tolerates 100 mL/kg/day of feeds and increase feeds till 150-180 mL/kg/day

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*Contraindication to feeding - Abnormal abdominal signs (abdominal distension, visible bowel loops) OR hemodynamic instability OR absent bowel sounds

*Passage of meconium is reassuring sign

# Feed intolerance - Gastric residual > 50%, hemorrhagic aspirates, recurrent non bilious vomiting, bilious vomiting, blood in stools, abdominal tenderness – stop feeds and investigate.

# AG monitoring before each feed, check for gastric residual if AG > 2 cm
References