Newborn Screening for Cystic Fibrosis

IRT is Lower in Infants with Meconium Ileus

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By 2010, newborn screening was the most common diagnostic indication

U.S. CF Foundation Registry

All new diagnoses reported to CFF in each year

Presented at NACFC, November 2011, Anaheim
Age of diagnosis has decreased with newborn screening

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Quick overview of IRT

• Identifies infants before severe malnutrition
• Screening program is part of standard newborn screening panel
• Immunoreactive Trypsinogen (IRT)
  – Pancreatic enzyme precursor
  – Elevated in the blood as pancreas is being damaged
  – Elevated IRT is the first biochemical evidence that an infant has CF
IRT Declines throughout early childhood in CF

Figure 2. Log IRT declines in a predictable manner in children with CF. Longitudinal IRT levels on individual children are represented and overall predicted model for IRT decline. A, Subjects with severe disease (dashed line), with Couper et al’s model overlaid (solid line). B, Infants with meconium ileus (MI). C, Subjects with pancreatic sufficiency. Longitudinal mixed effects modeling with likelihood modified for censored values was used to develop the statistical decline models.

Sontag MK, Corey M et al J Pediatr 2006;149:650-7)
Hypothetical difference in MI and NBS IRT values

IRT (ng/mL) vs Age (months)
IRTs are Lower in Infants with Meconium Ileus, but stable across first four days

Data from 1982 - 2002

Figure 3. IRT levels are lower in infants with meconium ileus (MI) but do not show significant variability day to day. Measurements on different infants with CF on each of the first 4 days of life demonstrate that infants with MI have lower IRT levels than infants without MI (P <.01).

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Questions

• Do infants with CF and meconium ileus have lower IRTs than those with CF without MI?
• How many babies with CF would be ‘missed’ based on newborn screening alone?
Identification of babies

  - Cutoffs 105 ng/mL and 75 ng/mL
- June 1 2008 – June 1, 2011 – IRT/IRT/DNA
  - Cutoffs 60 ng/mL and 60ng/mL
  - ~32 mutation panel
- 132 Babies identified
  - 17 with meconium ileus
  - 118 non-meconium ileus (NBS, Prenatal, FN)
Infants with meconium ileus are at higher risk of being missed by NBS

14/17 screened positive ~82%
116/118 screened positive ~ 98%

RR for being missed by newborn screening if born with MI: 10.15 (95% CI 1.83-56.39).
Does MI matter?

• YES!

• Babies with MI MAY have lower IRT levels than those without MI – but not all will.

• The newborn screen is another way to catch the babies with MI.

• For comparisons of missed cases across states we must have the same definitions.
Pros and Cons of knowing MI Status

**Pros**
- Can accurately calculate statistics for newborn screening program
- Could adjust cut-off for MI babies

**Cons**
- Difficult to collect on newborn screening card
- Can be misdiagnosed or misclassified

Infants with CF and MI may have lower IRT values than infants with CF without MI and are more likely to be missed by IRT based newborn screening.

The clinical presentation of infants with MI needs to be considered in conjunction with IRT values.