UNC SCHOOL OF MEDICINE
DEPARTMENT OF PEDIATRICS

Division of Pulmonology

Terry L. Noah,M.D. *Division Chief*

George Z. Retsch-Bogart, MD
Director, Bronchoscopy Center

Margaret W. Leigh, MD
Director, Cystic Fibrosis Care Center

Marianna M. Henry, MD
Pierre M. Barker, MD
Stephanie Davis, MD
Marianne S. Muhlebach, MD
Sherif E.Gabriel, Ph.D.

Fellows
Thomas E. Mellow, M.D.
Charles R. Esther, M.D., Ph.D.

Nurse Clinicians:
Kathy Abode, R.N.
Bronchoscopy Service
Nancy Lee, R.N.
Cystic Fibrosis
Sheree Berckmans, R.N.
Asthma & Allergy
Patricia Hasbrouck, R.N.
CF Research

Physician's Consultation Center: (800) 862-6264

MEMORANDUM

TO: Medical School IRB

FROM: Terry L. Noah, MD

RE: Proposed protocol 01-PED-632

DATE: March 12, 2002

Per your memo of Feb. 5, 2002, you have disapproved this proposal. I have subsequently met with Drs. Bernard and Nelson to discuss options, and was advised to submit a detailed response letter for review by the full committee at the first April meeting, addressing several key points as an appeal to this decision. This information is attached, in the form of a discussion of the major concerns cited in your memo of Feb. 5.

I would like to thank the Committee in advance for its careful consideration of all of this information, since the study is a potentially important one for children with CF. If my attendance is needed at any meetings related to this, please advise.

Campus Box # 7220
635 Burnett-Womack Building
Chapel Hill, NC, 27599-7220
Telephone: 919-966-1055
Facsimile: 919-966-6179

Responses to concerns raised in disapproval of 01-PED-632
P.I. Terry L. Noah, MD

The objections raised about the proposed study center on the lack of confidence that a research bronchoscopy (as opposed to clinically-indicated bronchoscopy) would directly benefit the subject receiving the procedure. As a reminder, the research procedures are proposed only for children with an established CF diagnosis in early infancy (i.e., those with prenatal diagnosis due to siblings with CF, or those with a newborn history of meconium ileus and subsequent confirmation of CF; estimated < 10 children/year). Control data will be derived from clinically indicated procedures in nonCF patients under a separate, long-established protocol (94-PED-275). Thus, the following discussion only pertains to CF patients.

A. CF lung disease pathogenesis- current concepts

CF is caused by mutation of the *cftr* gene, resulting in dysfunction of a protein controlling the composition of airway secretions, and consequent plugging of airways with viscous mucus. It is presumed that this leads to chronic infection and bacterial biofilm formation. Since no animal model mimicking CF exists (CFTR knockout mice have alternate chloride channels and don't develop lung disease like humans with CF), there is a gap in our specific knowledge about early alterations in mucus composition in CF, which limits us in development of specific preventive strategies in early CF .

B. Current approach to early CF lung disease.

Death from CF, which is virtually universal in the absence of lung transplant, occurs as a result of chronic bacterial lower airways infection, and consequent intense neutrophilic inflammation and destruction of airway supporting tissue. The major current focus of treatment of CF lung disease is therefore identification and treatment of bacterial pathogens with antibiotics. While several bacterial pathogens are commonly isolated from CF lungs, *Pseudomonas aeruginosa* (mucoid phenotype) infection is clearly associated with decline in lung function and more rapid progression of lung disease [1].

Infant BALF studies done since the mid 1990's have documented that:

- Bacterial infection begins in some infants in the first few weeks of life [2-5], and is asymptomatic in 1/3 of cases [4; reprint appended].

- Non-bronchoscopic cultures (deep pharyngeal cultures) do not accurately reflect lower airways cultures [6,7]; thus BALF cultures are the current "gold standard" for diagnosis of lung infection in early CF

- Between 1/3 and 2/3 of infants with CF have significant quantities of bacteria in BALF during research bronchoscopies done in the first few months of life (i.e. procedures scheduled without regard to symptoms) [4,8]

C. Current clinical practice at UNC

Based on the above data, our current practice here at UNC CF Care Center is to routinely perform bronchoscopy for cultures in CF infants at the time of diagnosis if there is any respiratory symptomatology, or in asymptomatic infants with CXR findings (such as hyperinflation). In addition, infants without symptoms or CXR changes but with failure to thrive are often considered for bronchoscopy since lung infection can cause failure to thrive. Since infants and young children with CF do not expectorate sputum, bronchoscopy is also done after diagnosis whenever respiratory symptoms worsen and cultures are needed to direct therapy.

D. Specific responses to concerns raised in IRB memo 2/5/02

1. Concern about 3 bronchoscopies in infants with CF.

While not routine, it is currently also not rare for a child with CF at the UNC CF Care Center to undergo multiple bronchoscopies (3 or more) in the first 12 months based on the above approach.

2. "Bronchoscopy in an asymptomatic infant is not indicated."

Based on the above discussion, this is currently true for *totally* asymptomatic CF children, but not necessarily for those who are asymptomatic from a respiratory standpoint.

3. "Exclusion of children with any signs of acute infection or respiratory symptoms would appear to tip the scales away from those who might benefit from detection of hidden infections."

While this is a seemingly logical conclusion, in fact the published rates of infection for clinically-indicated procedures compared to research procedures are quite similar. In essence, clinical symptoms are poor predictors of chronic bacterial airways infection in CF. Chronic infection, not acute infection, is the main determinant of progression of lung disease and death. ***However, the goals of the study could still be met if we remove the current exclusion of children with clinical exacerbations and simply performed procedures on a schedule without regard to symptoms. In essence, this would include some procedures in children who meet current criteria for clinically-indicated bronchoscopy**.

4. "The committee was also concerned about resistance to antibiotics with early treatment in asymptomatic infants. Is it proven or accepted that antibiotic treatment for bacterial infections in asymptomatic CF patients is beneficial?"

There are not good data to answer this question directly; it is difficult to conceive how such data would be ethically obtained, except by physicians not convinced that infection is important in progression of CF lung disease (I am not acquainted with anyone who takes that view).

Resistance to antibiotics is an ongoing issue in CF as in all conditions in which bacterial infection and antibiotic use play important roles. In the absence of specific data on emergence of resistance in young children, this is a theoretical concern balanced by the certain negative impact in CF of chronic, untreated infection. Available data from the Copenhagen, Denmark CF Center, where identification of *Pseudomonas* infection at any age results in scheduled, quarterly courses of i.v. antibiotics regardless of symptoms, suggest that outcomes are certainly not worse and may be dramatically improved [reviewed in 9,10].

However, the Committee's real concern is probably whether identification of bacteria in a study subject here at UNC would necessarily lead to antibiotic treatment. I have discussed this question with the Pediatric Pulmonology Division faculty, who care for all children with CF in this institution. Based on this discussion, I believe the table below accurately describes our clinicians' responses to BALF cultures in infants with CF, including those derived from a research study. It should be noted that the finding of *Pseudomonas* (which has occurred in 10-30% of infected infants in BALF studies) would result in immediate treatment or alteration of subsequent treatment, depending on quantity. While Pseudomonas represents a special concern, it should be noted that other pathogens more common in early CF (S. aureus, H. influenzae) cause an equivalent degree of inflammation [11; reprint appended] and therefore are likely to present nearly as great a risk to the lung.

Bacteria: (quantity)	***P. aeruginosa* (< 50,000 cfu/ml)**	***P. aeruginosa* (³ 50,000 cfu/ml)**	***Other pathogens* (< 50,000 cfu/ml)**	***Other pathogens* (³ 50,000 cfu/ml)**	***No pathogens***
Asymptomatic infant	Consider abx* Altered choice of initial Rx with subsequent symptoms*	Abx*	No abx	Consider abx* Altered choice of initial Rx with subsequent symptoms	No specific Rx
Symptomatic infant	Consider abx* Altered choice of initial abx with subsequent symptoms* Consider noninfectious causes	Abx*	Consider abx* Consider noninfectious causes	Abx*	Consider noninfectious causes

* Choice of antibiotic varies based on pathogen and in vitro sensitivities

E. References

1. Nixon GM, Armstrong DS, Carzino R et al. 2001. Clinical outcome after early Pseudomonas aeruginosa infection in cystic fibrosis. J Pediatr 138:699-704.
2. Noah, T.L., H.R. Black, P-W. Cheng, R.E. Wood, and M.W. Leigh. 1997. Nasal and bronchoalveolar lavage fluid cytokines in early cystic fibrosis. J Infect Dis 175:638-47.
3. Khan, T.Z., J.S. Wagener, T. Bost, J. Martinez, F.J. Accurso, and D.W.H. Riches. Early pulmonary inflammation in infants with cystic fibrosis. 1995. Am J Resp Crit Care Med 151:1075-82.
4. Armstrong, D.S., K. Grimwood, J.B. Carlin, R. Carzino, J.P. Gutierrez, J. Hull, A. Olinsky, E.M. Phelan, C.F. Robertson, and P.D. Phelan. 1997. Lower airway inflammation in infants and young children with cystic fibrosis. Am J Resp Crit Care Med 156:1197-1204.
5. Armstrong DS, Grimwood K, Carzino R et al. 1995. Lower respiratory infection and inflammation in infants with newly diagnosed cystic fibrosis. BMJ 310:1571-2.
6. Armstrong DS, Grimwood K, Carlin JB, Carzino R, Olinsky A, Phelan PD. 1996. Bronchoalveolar lavage or oropharyngeal cultures to identify lower respiratory pathogens in infants with cystic fibrosis. Pediatr Pulmonol 21:265-6.
7. Rosenfeld M et al. 1999. Diagnostic accuracy of oropharyngeal cultures in infants and young children with cystic fibrosis. Pediatr Pulmonol 28:321-8.
8. Rosenfeld M et al. 2001. Early pulmonary infection, inflammation, and clinical outcomes in infants with cystic fibrosis. Pediatr Pulmonol 32:356-366.
9. Hoiby N. 2000. Prospects for the preventionand control of pseudomonal infection in children with cystic fibrosis. Paediatr Drugs 2:451-63.
10. Hoiby N, Koch C. 2000. Maintenance treatment of chronic *Pseudomonas aeruginosa* infection in cystic fibrosis. Thorax 55:349-350.
11. Muhlebach MS and Noah TL. 1999. Quantitation of inflammatory responses to bacteria in young cystic fibrosis and control patients. Am J Resp Crit Care Med 160:186-191.