SPECIAL ARTICLE

Regular readers will recognize that this article is not "typical" for the JOURNAL. Despite the lack of new material and of documentation for some of the recommendations, it was our consensus that the article reflects a considerable amount of practical experience and contains much useful advice for the generalist caring for patients with this relatively common disease.—*J.M.G.*

The primary care physician and the patient with cystic fibrosis

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Many factors have contributed to the greatly improved survival and decreased morbidity for cystic fibrosis that have occurred over the past two decades.[1] Access to improved treatment techniques, made possible by the network of cystic fibrosis centers under the aegis of the national Cystic Fibrosis Foundation, seems to have played a pivotal role. These centers now provide care for approximately 15,000 CF patients in the United States. However, even though CF care has progressively shifted to the subspecialty centers, the patients usually continue to see primary care physicians (pediatricians, family practitioners, internists) for health maintenance and non-CF illnesses. Thus the majority of these patients have two physicians. In this article, I offer suggestions, some of them admittedly provocative, to help the pediatrician or family physician deal with the more common problems faced in the treatment of patients with CF.

ROUTINE CARE AND NON-CF ILLNESSES

Standard immunizations. With few exceptions, CF patients should receive routine (live and nonlive) immunizations at the ages recommended for normal children. In practice, however, pediatricians often postpone the administration of these vaccines, especially the diphtheria-tetanus-pertussis series. To my knowledge, there is no theoretical basis to support delay. Some parents are told that the baby "has not reached 8 pounds [or some other arbitrary weight]" by the 8-week visit. Others, whose children have overt chronic pulmonary symptoms related to CF, especially wheezing, are told that immunizations must wait until the patient "is better." In my view, these vaccines should be given on time. Apart from a short delay occasioned by a febrile illness, the primary DTP series and the "booster" should not be delayed. There is no evidence that they are ineffective if the patient is symptomatic because of CF. Similarly, there is no theoretic basis for delaying the live polio vaccine solely because of CF-related chronic signs or symptoms. Measles, mumps, and rubella vaccines and the *Hemophilus influenzae* type b vaccine should also be given on time; rubeola can cause a devastating exacerbation of pulmonary infection, often with irreversible anatomic changes. Patients with CF rarely develop pneumococcal disease, and therefore pneumococcal vaccine is not thought to be necessary. However, influenza vaccine should be given yearly. In addition to the medical advantages of preventing these serious illnesses (two of which, pertussis and rubeola, are particularly prone to aggravate CF-related pulmonary disease), I believe there is an important psychologic benefit to giving these vaccines on time. Any "normal well child care" reinforces the subspecialist's contention that the patient should be treated "normally" except for the addition of measures necessary for the care of CF; the opposite message is given when these "normal" immunizations are unnecessarily delayed.

CF	Cystic fibrosis
DTP	Diphtheria-tetanus-pertussis (vaccine)

Minor illnesses. Viral upper respiratory tract illnesses

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may be pivotal events in the natural history of CF pulmonary infection.[2] Prolonged pulmonary exacerbations may follow apparently minor "colds," and the onset of chronic pulmonary symptoms is often precipitated by a particularly severe viral upper respiratory tract infection. The reason, at least in part, may be the suppression of host defenses and other alterations of the host-bacteria interaction induced by viruses.[2,3] Omission or delay of antibiotic therapy and inadequate antibiotic dosage probably play a role in the establishment and progression of some the bacterial pulmonary infections that occur after upper respiratory tract infection. This is a circumstance in which the academic, highly principled pediatrician must "ease up" a bit on demanding proof of a bacterial cause before prescribing antibiotics. On balance, the risk of progressive bacterial bronchitis and bronchiolitis is probably greater than the risk of induction of resistant organisms caused by a short course of antibiotic treatment. An oral cephalosporin to cover *Staphylococcus aureus* and *Streptococcus pneumoniae* should be considered even in the early stages of a minor upper respiratory tract infection. A wider-spectrum agent, to cover *Haemophilus influenzae*, could also be considered. A multicenter study of the effectiveness of continuous oral cephalosporin prophylaxis (even in the absence of any symptoms) in young CF patients is under way now and should clarify the use of antibiotics in infants and young children. The presence of CF should not affect the management of nonrespiratory infectious diseases (e.g., impetigo, monilliasis, tinea). The possibility of adverse drug interactions and of concurrent administration of two similar antibiotics by the patient's two physicians should always be considered.

X-ray examination during minor illness is rarely necessary, particularly if the illness is still consistent with a "cold" (i.e., a respiratory illness of less than 10 days duration that began with rhinorrhea). CF patients are likely to have many x-ray examinations eventually, and avoidance of unnecessary radiation, particularly early in life, is desirable. When chest films are obtained, it is generally not helpful to inform the family that the patient has "pneumonia." In the strict sense, of course, he or she does; CF infection is a "pneumonia" in that it involves the smallest airways, but the layman's understanding of "pneumonia" is different from the physician's, and this term should not be used without a brief explanation. Alternatively, the family can simply be told that the chest film shows "changes typical of CF." Radiologic examination of the sinuses (e.g., to investigate a complaint of "headache" or purulent nasal discharge) is almost never useful; virtually 100% of CF patients have radiologically demonstrable chronic pansinusitis.[4]

Laymen and the media have fallen into the habit of calling every acute illness "the flu." The use of this term to cover every respiratory illness, episode of diarrhea, and headache probably does not do much harm, although it is difficult to imagine that physicians and the general public prefer an inaccurate diagnosis of "the flu" to an accurate diagnosis of "viral infection." However, in CF, the abuse of this term can cause unnecessary problems. When patients, particularly teenagers, receive influenza vaccine every November and then, several times during the subsequent winter, are inappropriately told by primary care physicians that they have "the flu," they are not likely to develop much faith in this important vaccine.

Contagion. Pediatricians are often asked about the risk of acquisition of minor illnesses at preschool. All children are going to be barraged with minor illnesses sooner or later. Parents can delay this by 1 or 2 years by waiting until kindergarten. However, in my view, the potential psychologic advantages of attending preschool, for both child and family, outweigh the risks for the majority of patients.

Participation in exercise. Until relatively recently, avoidance of exercise was commonly recommended for many patients with chronic illnesses, including CF. The recent explosion of interest in the benefits of exercise has led to a change in physicians' views. Most CF physicians now recommend participation in athletics to the fullest extent possible. Except for the patients with a marginal PaO_2, greatly compromised pulmonary function,[5,6] or overt heart failure caused by cor pulmonale, exercise should be encouraged. Externally imposed limitation of activity is rarely worthwhile. However, the physician who is asked by a patient or family to "get me [him/her] out of gym" should listen sympathetically before saying no. Many of these patients are sensitive to locker-room comments about their thinness, short stature, delayed sexual maturation, and so forth. Occasionally, there may be a rigid coach or supervisor who is convinced that all students should be capable of doing a certain amount of running or other exercise. Thus, although the disease may not preclude exercise, having the patient excused from physical education class or providing other intervention may be warranted. The same patient can often be encouraged to participate in after-school exercise programs or athletics.

School (and other) health forms. School officials, particularly in the early grades, should be informed that a student has cystic fibrosis, may need to take medicine with meals, and should have unlimited access to the bathroom. Generally, however, it is unnecessary and usually counterproductive to involve school personnel in actual medical evaluation of the child. School physical education forms or permits to participate in competitive sports should not pose a major problem. Usually all that is needed is a sentence in the "comments" section of such a form, stating that "this

student has cystic fibrosis" and that "externally imposed restrictions on activity are not necessary or desirable." Similarly, work permits for teenagers should be completed by providing only the information requested on the form; specific advice about job limitations (e.g., avoidance of exposure to fumes) should be made in private to the teenager, but if he or she is determined to "pump gas," it is probably futile to try to stop this activity.

Advice about use of drugs. Advice about the dangers of alcohol, cigarette and marijuana smoking, and other types of drug abuse is now incorporated into child and adolescent care by many physicians. In patients with chronic illness, especially those receiving many prescription drugs, information about possible drug interactions should also be supplied. These patients should be warned about the disulfiram-like effect of some antibiotics[7] (e.g., chloramphenicol, certain cephalosporins), about the possibility that alcohol may suppress the cough reflex and has been associated with hemoptysis,[7] and about the possible pulmonary toxicity of cigarette and marijuana smoke.[8] Patients who are thought to be injecting the contents of capsules intravenously should be warned that even the "inert" ingredients of these capsules (talc; starch) are capable of causing pulmonary injury. Patients who are thought to be using drugs by "sniffing" should be warned of possible direct toxic effects on the nasal and bronchial mucosa.

Diet. Pediatricians spend a considerable amount of time trying to calm parents' unjustified fears about their normal child's apparently inadequate dietary intake. Children with CF pose an even greater challenge in that their parents are even more concerned about failure to gain weight or grow rapidly, and physicians often think it is their mission to prevent failure to thrive through dietary advice. There is Proper dietary advice for these patients is controversial. However, I believe that advice to parents about how they handle behavior at meals should be the same for CF patients as for the rest of the family; total caloric intake can rarely be influenced by parents anyway. Furthermore, CF is a disease for which an unusual amount of parent participation in treatment (e.g., medication administration, aerosols, chest physiotherapy) is recommended, and it seems prudent to avoid adding unnecessarily to this load of emotionally charged interactions. Failure to thrive in CF patients (assuming that the family has the money to buy food and medication and that psychosocial functioning is reasonably intact) is almost always related to pulmonary status,[9] although it may also be a contributing factor to worsening lung status. Whether this is true for a particular patient and, if so, whether the parents can successfully intervene by dietary manipulation and "pushing" food consumption is questionable. Treatment of the failure to thrive by circumvention of appetite (tube feedings, parenteral nutrition) is controversial and beyond the scope of this discussion.

Nurturing of physician-patient relationship. Painful procedures are an important, if not the most important, reason for children's fear (and, possibly, eventual distrust) of physicians. Although unpleasant medical experiences during childhood may lead to alienation from medicine later in life, distrust or fear of physicians is rarely a health-threatening problem for normal children. For patients with chronic illnesses, however, painful experiences may play a pivotal role in interfering with the establishment of rapport between physician and child. Furthermore, experiencing pain at the hands of one physician can sour the patient's relationship with other health care workers as well.

I believe that physicians who care for children with chronic illnesses should try especially hard to reduce the frequency and intensity of painful procedures during childhood or, at least, try to prevent the child's association of necessary pain with physician examinations and consultations. I offer some suggestions; obviously, my list is not complete. Consideration should be given to the administration of infant immunizations at a time separate from the actual well-baby checkup; for example, the physician could see the patient on one day and arrange to have a nurse give the DTP vaccine or the mumps-measles-rubella vaccine a few days later. Intramuscular antibiotics should be avoided except under unusual circumstances (e.g., health-threatening, probably bacterial illness in a child who is vomiting); oral antibiotics are usually sufficient for streptococcal pharyngitis and other minor bacterial illnesses.

Painful procedures of borderline necessity should be evaluated carefully from the viewpoint of risk/benefit ratio. The practicality and wisdom of application of these suggestions to general pediatric practice are certainly debatable; in children with chronic illnesses, however, for whom good physician rapport may be crucial to the solving of future diagnostic problems or to achieving compliance with medical advice, the risk/benefit ratio, in my judgment, often favors prompt therapy without overly compulsive use of painful diagnostic procedures that may not be clearly indicated.

Advice to teenagers about sexual activity and birth control. Concern about the acquired immunodeficiency syndrome and other venereal diseases, and rising rates of teenage pregnancy, have led many pediatricians to lower the age at which they begin counseling about sexual activity. This counseling is, of course, at least as important for young people with CF; in fact, if the pediatrician does not feel comfortable doing this counseling, the CF physician should undertake it. In any case, the initiation of counseling may lead these young CF patients to reflect about reproductive issues unique to their own chronic

illness, and physicians should expect some difficult questions. Men with CF are likely to be sterile because of obstructive azoospermia. The "correct" age to present this information to patients is not clear. Premature presentation may result in confusion between fertility and potency; delayed presentation may precipitate anger when a young person is already seriously planning marriage.

Although women with CF are usually fertile if their pulmonary disease and digestive problems are under adequate control, they can expect problems with pregnancy. Pregnancy can worsen CF lung disease in a variety of ways, such as nonspecific physiologic stress; interference with chest physiotherapy; elevation of the diaphragm, hypervolemia, and increased oxygen requirement (which can aggravate or precipitate heart failure); increased nutritional demands; limited choice of antibiotics because of concern for the safety of the fetus; and anemia.[10-12] Sex counseling may also lead a young woman with CF to reflect on ethical issues, such as the risk that her own child will have CF (1 in 40 if the father has no family history of the disease) or the possibility that she may not survive her child's formative years. Sometimes it may be reasonable to refer the patient to a CF physician for advice; however, she may prefer to receive some preliminary opinions from her primary physician in preparation for confronting the problem at the CF center.

Drug interactions. Patients with CF often take multiple drugs for long periods. When additional drugs are prescribed for the treatment of minor illnesses, the possibility of adverse interactions must be considered. Common problems involve the interaction of antibiotics with bronchodilators (e.g., erythromycin, theophylline) or of alcohol (either alcoholic beverages or elixirs, which contain alcohol) with certain cephalosporins or chloramphenicol. Antibiotic duplication or administration of two closely related antibiotics should be avoided.

CYSTIC FIBROSIS–RELATED SYMPTOMS AND PROBLEMS

Cough. Although cough is an important early symptom of worsening CF lung disease, it also occurs with many minor childhood illnesses. Once the pediatrician has determined that the cough is not suggestive of a major exacerbation of CF, symptomatic treatment (i.e., cough suppression) may be indicated. Although long-term suppression of cough is undesirable in CF, extremely frequent cough during a minor illness often interferes with sleep or may be painful and nonproductive. Suppression of cough with codeine may be indicated, especially at bedtime or during the night. The prescription should not be refillable without review of the situation by the physician. Dextromethorphan can be recommended under the same circumstances as codeine, but in my experience it is rarely as effective. Efficacy of expectorants has not been conclusively demonstrated. Glyceryl guaiacolate is commonly used and, although ineffective,[13] is probably harmless; however, potassium iodide ("SSKI") and other iodine-containing "expectorants," although probably equally ineffective, are not always harmless. Thyroid toxic effects (goiter formation, hypothyroidism) are common in CF patients who take iodine-containing cough medicines.[14,15] The risk/benefit ratio is easy to establish (probably no benefit; low to intermediate risk). Finally, antihistamine "cold preparations," because they dry secretions, are best avoided; even when there is convincing evidence of an allergic component to the patient's nasal symptoms, nasal cromolyn is probably a better choice.

Chest pain. When unilateral pleuritic chest pain occurs suddenly, especially if it is associated with shortness of breath, a pneumothorax must be considered and a chest radiograph will usually be necessary. Often, however, the chest pain is less suggestive of pneumothorax, and the pediatrician may be in doubt as to how to proceed with its evaluation. A chest radiograph is rarely helpful in patients whose history or physical examination is not suggestive of pneumothorax. In general, bilateral symmetric chest pain is not pulmonary in origin. Bilateral pain is common during a flare-up of pulmonary disease, particularly if the patient is more dyspneic than usual; this pain is musculoskeletal, and the patient need only be reassured that the pain will not last, whether or not the flare-up is easily controlled with treatment. Midline anterior pain can indicate pneumomediastinum (which is confirmed if subcutaneous air is present) but is usually due to esophagitis. An antacid or a histamine$_2$ antagonist may be useful. Myocardial infarction (or even exertional angina) has not been demonstrated in CF and, if it occurs at all, is very rare even in older patients with advanced pulmonary disease and severe hypoxemia. When pleuritic chest pain is unilateral, but slower in onset and not associated with much dyspnea, pleurisy is likely; nonnarcotic analgesia is usually sufficient. If pleurisy is associated with a generalized flare-up of pulmonary disease, additional treatment, perhaps including hospitalization, may be necessary.

Hemoptysis. The first episode of expectoration of blood tinged or streaked sputum almost always precipitates a telephone call to the physician. In general, patients and families can be reassured that these episodes rarely progress to massive hemoptysis. Vitamin K should be administered (orally) to any CF patient who has hemoptysis (phytonadione, 5 mg two or three times a week). Aspirin and other nonsteroidal anti-inflammatory drugs can precipitate hemoptysis, and the physician should inquire about them; they are not necessarily contraindi-

cated for all patients, but an occasional patient may show an impressive correlation with their use and the onset of bleeding. Expectoration of large amounts of blood or of blood without sputum is potentially a more serious problem and merits subspecialist attention.

Wheezing. Although many pediatricians have been taught that "recurrent pneumonia" is the hallmark of pulmonary disease in CF, wheezing is actually the most common pulmonary symptom during infancy (and the commonest pulmonary presenting symptom). This is not surprising, because early CF pulmonary infection is a bacterial bronchiolitis, and the cardinal manifestation of bronchiolitis is wheezing. Although systemic bronchodilators are occasionally useful and may be worth trying, an aerosolized bronchodilator is more likely to be effective and is usually less toxic. Many of these patients will not improve unless bacterial pulmonary infection is also treated. Much of this treatment may be supervised by a subspecialist. Important to the patient's pediatrician, however, are the following two considerations: First, in CF patients, recurrent or continuous wheezing is not likely to be related to food intolerance, and formula changes are usually not helpful. These patients, in fact, may not thrive well on soy-based formulas. Allergy skin testing is not ly to be productive. Second, the total elimination of ..eezing may not be possible during infancy. Fortunately, most of these wheezing infants, despite a difficult first year, do well in later childhood; even the most severely ill infants, if they survive, have a reasonably good prognosis at least through mid childhood.[16]

Constipation. Although the most common manifestation of inadequate digestion is steatorrhea and bulky stools, some patients develop partial or complete obstruction at the ileocecal valve (a condition unfortunately labeled "meconium ileus equivalent"). Patient and family complaints of "constipation" (i.e., hard stool, no bowel movement for longer than 24 hours, or right lower quadrant pain or mass) should not be taken lightly. If the history and physical examination reveal no evidence of appendicitis, intussusception, or other surgical problem, the patient should be given stool softeners and a laxative. Digestive enzymes should be continued. If the patient does not improve, treatment with orally administered *N*-acetylcysteine (Mucomyst) or with large quantities of a polyethylene glycol oral lavage solution (e.g., GoLYTELY; Colyte) may be successful,[17] but occasionally the patient will require more aggressive treatment, including diatrizoate meglumine (Gastrografin; Renografin) enemas given with radiologic guidance. Usually, therapy for meconium ileus ..ivalent should be given by or in consultation with a CF ..er physician.

Digestive symptoms despite pancreatic replacement enzymes. Patients occasionally complain that "my 'food pills' don't work any more." If digestive symptoms (e.g., steatorrhea, flatulence, gas pain, voracious appetite) suddenly recur despite continuation of a previously effective regimen, the following possibilities should be considered: (1) the patient has "outgrown" his dose; (2) there has been a subtle change in the diet, usually involving the ingestion of increased fat; (3) the timing of the pancreatic enzymes relative to the meal has changed (e.g., the child's school now requires him or her to receive all drugs at a nurse's office, thus separating the dose from lunch); (4) the patient has just started a new bottle of pancreatic replacement capsules that happen to be ineffective (perhaps they are too old or have been left out in the heat); or (5) the patient has an independent (second) gastrointestinal disease. The important point is that clinical failure of pancreatic enzyme therapy almost always has a reasonably simple explanation.

Risk of contagion from social contact with other CF patients. According to the "party line" of CF center physicians for many years, CF patients acquire their gram-negative pulmonary pathogens" from themselves" and therefore are not at added risk from social contact with other persons with CF. The critical factor was thought to be the patient's own pulmonary-immune status, when the disease "reached a certain point," *Pseudomonas aeruginosa* and other gram-negative organisms could gain a foothold. This view seems to be slowly changing. The CF patients who are colonized with *P. aeruginosa* are being separated (even as outpatients) in Denmark[18]; in the United States the epidemic spread of *Pseudomonas cepacia* has spurred some centers to take added precautions against patient-to-patient transmission.[19] In my (not universally accepted) view, based on recent developments, social contact between young children with CF should not be encouraged. Such contacts should not necessarily be totally forbidden if they are unavoidable (e.g., with siblings, family friends), but they should certainly not be brought about intentionally (e.g., attendance at "CF picnics"). Additional data on this question will probably be forthcoming reasonably soon.

Sweat testing of siblings and other relatives. After diagnosis of the index case, the CF center physicians usually recommend, and often arrange, appropriate sweat testing of relatives. However, decisions about the sweat testing of relatives born after diagnosis of the index case are often the responsibility of the primary physician. If the nuclear family members (both biologic parents and at least one child with CF) are available, DNA (restriction fragment length polymorphism) probe tests[20] can almost always establish the exact genetic status of the family's unborn child. However, many families do not pursue

prenatal testing. There is virtually universal agreement that siblings should be sweat tested. The statistical risk (1 in 4) and the parents' anxiety level are both very high. For more distant relatives, the need for sweat testing is less clear. For first cousins, for example, the statistical risk (1 in approximately 160) is fairly low, and the yield of sweat testing, especially of asymptomatic cousins, may not justify the test. However, the parents of these infants (the aunts and uncles of the patient with the index case) are usually so anxious about CF that sweat testing is worthwhile to rule out CF. Decisions about other relatives must be made in the same way.

Noncompliance. Physicians approach noncompliance with medical advice in a great variety of ways. Cystic fibrosis is a lifelong disease in which substantial family and patient participation in treatment plays a major role in decreasing morbidity and improving survival. The long-term goal is to have the patient continue to accept the disease and the need for treatment through the teenage years and during adulthood. This goal can rarely be accomplished by "shoving the treatment program down the patient's throat" throughout childhood. Acceptance of the responsibility for self-care in adulthood is probably best accomplished by encouraging parents to gradually surrender responsibility for parts of the treatment program to their children. Many parents have difficulty doing so. When first given responsibility, children may experiment with omission of one or more parts of the treatment program, sometimes for long periods. In the long run, however, this strategy appears to be best. The overall approach is for the child to understand, gradually, that he or she has a major health problem, that there are people (e.g., parents, physicians) who are willing to help with it, but that the ultimate responsibility is the patient's own. In the long run, with regard to a chronic illness, the physician (and parent) can usually achieve more as friend and adviser, rather than as commanding officer!

Advice about participation in research. In the absence of a satisfactory animal model for this disease, virtually all clinical progress depends on patient enthusiasm for and participation in research. The primary physician may be approached "as a friend" by the patient or family for advice about a study the CF center has proposed. I believe the physician should consider the proposal and make an honest recommendation. However, it is generally in the CF patient's best interest to participate in these studies. If he or she doesn't, who will?

Summary. Although CF has increasingly become a "subspecialty disease," the decisions and practice style of the patient's pediatrician or family physician are extremely important. The primary physician's handling of everything from the timing of infant immunizations to teenage advice about sex and drug abuse have far-reaching medical and psychosocial implications and must be carefully considered.

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