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Chronic Ventilation in Infants with Surfactant Protein C Mutations: An Alternative to Lung Transplantation

To the Editor:

We report a series of patients with surfactant protein C (*SFTPC*) dysfunction mutations who presented with severe and persistent respiratory failure in early infancy, resulting in discussions of lung transplantation and withdrawal of support. All three patients were successfully chronically ventilated and weaned off mechanical ventilation (MV). Institutional review board consent was obtained at the University of Colorado.

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SFTPC mutations were first recognized in 2001, when a 6-week-old child presented with respiratory distress and a family history of lung disease, and genetic studies revealed the *SFTPC* mutation (1). Symptom onset in *SFTPC* dysfunction mutations varies from during the neonatal period to in senior citizens (2–4). In addition, outcomes vary tremendously, from asymptomatic family members to respiratory failure leading to transplant or death (5–9). Hydroxychloroquine has been associated with weaning patients off oxygen, significant weight gain, and improvements in chest radiography (10). However, once a child requires persistent MV, typically discussions arise around withdrawal of support versus transplantation. A case report was recently published of an infant who required persistent MV and was able to wean completely off all support (11).

Patient 1

Patient 1 was born full-term, with no perinatal complications. She was noted to be cyanotic at birth but was stable for discharge at 3 days of life. She had multiple admissions for respiratory distress, and at 2.5 months of age, a chest computed tomography (CT) scan (Figure 1) showed diffuse ground-glass opacities and septal thickening; a biopsy was consistent with a mutation in *SFTPC*: diffuse alveolar proteinosis with type II cell hyperplasia, lipid and iron-laden macrophages, septal widening and fibrosis, and scattered necrotic debris. With this diagnosis, she was started on medical therapies (Table 1). The patient was unable to be weaned from MV. After discussions about tracheostomy with chronic MV versus withdrawal of support versus transplantation, the family elected to proceed with chronic MV at 3.5 months of age. She was ultimately discharged on a home ventilator at 19 months of age and was decannulated by age 6 years (Table 1). She has had subsequent illness but never required reintubation. She has autism and has been unable to cooperate with pulmonary function tests. Her most recent CT scan showed nonspecific interstitial pneumonia findings, diffuse ground-glass opacities, and bronchiectasis (Figure 1). The diagnosis of a surfactant protein C mutation (c.545 G>C, .pGly182Arg) was confirmed by genetic testing once available. Patient 1 had a family history of a maternal uncle dying of pneumonia at 6 months of age and a maternal grandfather dying of lung disease at 49 years of age, but neither one had genetic studies performed.

Patient 2

Patient 2 was born at 36 weeks and 6 days with an antenatal course complicated by preterm labor at 27 weeks and preeclampsia. At 4 hours of life, she developed respiratory failure necessitating intubation and high-frequency oscillation for 3 months. After discussions about tracheostomy with ventilation versus withdrawal of support versus transplantation, the family elected to proceed with chronic ventilation. Her initial hospitalization (at an outside facility) lasted 10 months, and she was ultimately discharged on a home ventilator. Because her lung disease remained undiagnosed, she had a repeat CT scan at 22 months (Figure 1), which showed marked interstitial prominence with alveolar disease and a subsequent lung biopsy. The biopsy showed focal mild fibrosis in areas of endogenous lipoid pneumonia, consistent with a mutation in *SFTPC*. She was started on therapies and successfully decannulated by 5 years (Table 1). She was subsequently lost to follow up. She initially had delayed milestones, but she was catching up rapidly. Genetic testing, once available, confirmed the *SFTPC* mutation (c.563 T>A, p. Leu188Gln). No family history of lung disease was reported.

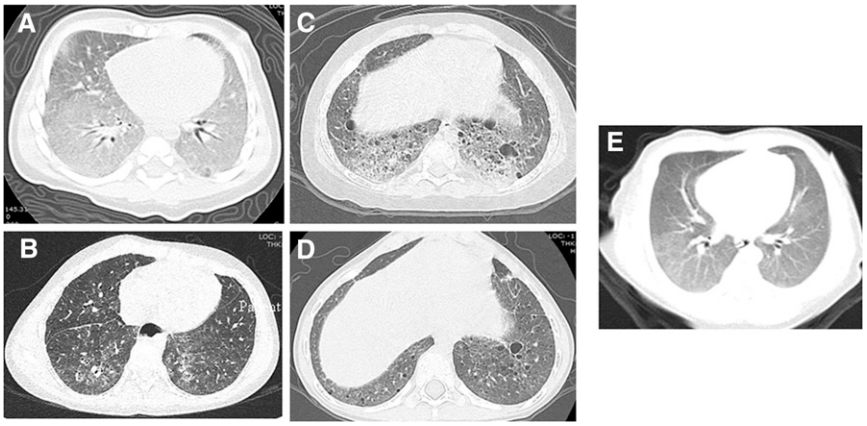

Figure 1. Initial and most recent computed tomography (CT) scan for each patient. (*A*) Patient 1 initial CT scan with diffuse ground-glass opacities and septal thickening. (*B*) Patient 1 recent CT scan with nonspecific interstitial pneumonia findings, diffuse ground-glass opacities, and bronchiectasis. (*C*) Patient 2 initial CT scan with marked interstitial prominence, cystic change, and interstitial/alveolar infiltrate. (*D*) Patient 2 recent CT scan with interstitial prominence and increased number of parenchymal and subpleural cysts. (*E*) Patient 3 only CT scan with diffuse ground-glass opacities.

Patient 3

Patient 3 was born at 39 weeks and 3 days with a perinatal course complicated by chorioamnionitis. He was noted to be tachypneic at 10 minutes of life and required noninvasive ventilation. A CT scan (Figure 1) revealed ground-glass opacities, and subsequent genetic testing revealed a *SFTPC* mutation (c.567 C>G, p.Cys189Trp). He was discharged home on medical therapies with nasal cannula oxygen (Table 1). In the subsequent months, he developed respiratory failure requiring high-frequency oscillation. After discussions about tracheostomy with MV versus withdrawal of support versus transplantation, the family elected to proceed with chronic MV. He was discharged home at 8 months on a home ventilator with medical therapies and was decannulated at age 3 years (Table 1). Since decannulation, he has not had any pulmonary-related hospitalizations, he takes only azithromycin, and he does not require any oxygen therapy. His development is unremarkable. There is no family history of lung disease.

Discussion

We present three patients with *SFTPC* mutations and respiratory failure. Withdrawal of support and lung transplantation were offered to each family, and each family elected to proceed with chronic MV. Different medication regimens were used in these patients, although systemic steroids in some form, dose, and duration were universal to all. Expert opinion and case reports (10, 11) have governed disease treatment, with attention to antiinflammatory agents (steroids, azathioprine, and hydroxychloroquine). The natural history of patients with *SFTPC* mutations is poorly understood and varies considerably, even within families (2–4). Early respiratory failure appears to resolve over time, and it is unknown whether this is secondary to medical therapies or just the natural history of the disease.

Lung transplantation has been a solution for infants with *SFTPC* mutations and persistent respiratory failure. Because lung transplantation has a high risk for complication and mortality, with a median survival of 4.9 years for pediatric lung transplants (12), we propose that chronic MV may be a better option for infants and young children with *SFTPC* mutations because of this potential for recovery over time. With chronic MV, infants with respiratory failure can grow, develop, and ultimately be at home weaning off of ventilatory support without the chronic medications and potential for fatal outcomes with lung transplantation. ■

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Table 1. Summary of Patients' Clinical Courses

Patient	Age at Presentation	*SFTPC* Mutation	Family History	Age at MV Initiation	Maximum Respiratory Support	Age at Tracheostomy (*mo*)	LOS (*mo*)	Age at Decannulation (*yr*)	Respiratory Treatments	Support at Last Contact (Age)
1	7 d	c.545 G>C, .pGly182Arg	Positive	2 mo	CMV	3.5	19	6	Clearance, steroids, hydroxychloroquine	Room air (10 yr)
2	4 h	c.563 T>A, p. Leu188Gln	Negative	1 d	HFOV	3	10	5	Clearance, steroids, azathioprine	0.25 L NC (5 yr)
3	10 min	c.567 C>G, p.Cys189Trp	Negative	4 mo	HFOV	4.5	8	2	Steroids, azithromycin, hydroxychloroquine	Room air (3 yr)

Definition of abbreviations: CMV = conventional mechanical ventilation; HFOV = high-frequency oscillatory ventilation; LOS = hospital length of stay; MV = mechanical ventilation; NC = nasal cannula; SFTPC = surfactant protein C.

Deborah R. Liptzin, M.D.
University of Colorado School of Medicine
Aurora, Colorado

Tarak Patel, M.D.
Baylor College of Medicine–San Antonio
San Antonio, Texas

Robin R. Deterding, M.D.
University of Colorado School of Medicine
Aurora, Colorado

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The Workforce Crisis: A Functioning Solution

To the Editor:

Drs. Kahn and Rubenfeld propose three alternatives to increasing the intensivists workforce: the use of nurse practitioners (NPs) and physician assistants (PAs) for staff coverage in the intensive care unit (ICU), the implementation of telemedicine, and regionalization of existing healthcare facilities (1). Emory Healthcare (EHC) already uses all three strategies.

EHC has extensive experience using NPs and PAs in the ICU. Dr. Donald Finlayson initiated this model in the late 1970s, using two PAs to staff the cardiothoracic surgical ICU from 6 A.M. to 10 P.M. Monday through Friday (2). Beginning in 2009, the use of such advanced practice providers was markedly expanded.

Emory established a system-wide Critical Care Center, embedding more than 80 advanced practice providers, and built a now-accredited residency program training NPs and PAs in critical care medicine (3). Nineteen providers have graduated from this program, and an additional 10 are in training. Thus, critical care–trained advanced practice providers at our academic health science center now constitute the most prevalent providers and are the foundation of around-the-clock coverage.

EHC invested in tele-ICU (eICU; Philips Corporation, Alpharetta, GA) as a telehealth strategy. Recognizing the need for strong cognitive support during unsocial (nights, weekends, holidays) hours, remote support has been operational for more than a year and provides services to 14 ICUs across 5 hospitals, including EHC and external customers over distances as great as 200 miles.

EHC recently incorporated two community-centered hospitals, both of which are equipped with tele-ICU technology at every ICU bed. Transfers from community to academic hospitals to meet specific critical care needs (e.g., neurology critical care, extracorporeal membrane oxygenation services) are now routine. Further regionalization through a partnership with a large community hospital system has recently been proposed and is currently open for public comment (4). If the partnership is completed, it will include 11 hospitals caring for around 1 million lives, with a catchment of more than 10 million lives that may need advanced critical care services.

The EHC implementation of the triad of innovations proposed by Kahn and Rubenfeld has been successful in mitigating the demand for intensivists. Our experience is that effective use of a limited number of intensivist physicians may require rethinking intensivist responsibilities, shifting from primary provider at the bedside toward executive responsibilities that include protocol design and evaluation, population management, and remote provider, in addition to participation in problematic and complex cases. This may well require revisions to training and management of job expectations. ■

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Timothy Buchman, M.D., Ph.D.
Rob Grabenkort, P.A., M.M.Sc.
Craig Coopersmith, M.D.
Heather Meissen, A.C.N.P., C.C.R.N.
Sara Gregg, M.H.A.
Emory Healthcare
Atlanta, Georgia

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