

Aerodigestive Clinics as Emerging Pediatric Care Model: The First 100 Patients in Israel

Yulia Gendler RN PhD^{1*}, Emmanuelle Segulier-Lipszyc MD^{2,13*}, Ari Silbermintz MD³, Moshe Hain MD⁴, Yoram Stern MD^{4,13}, Dragan Kravarusic MD^{2,13}, Keren Politi MD¹², Gabriel Amir MD PhD^{5,13}, Jacob Katz MD^{6,13}, Yelena Zeitlin MD^{6,13}, Sylvia Grozovski MD⁷, Yifat Nitzan SLP⁴, Yuliana Eshel MHA⁸, Adi Shimoni OTR⁸, Yifat Fischer DVM^{1,9}, Dana Serfaty MSc^{1,9}, Tami Shnayderman BPT¹⁰, Kian Assi BSW¹¹, Lior Barbash MBA¹, and Patrick Stafler MD^{1,13}

¹Pulmonary Institute, ²Department of Pediatric Surgery, ³Institute of Gastroenterology, Nutrition, and Liver Diseases, ⁴Department of Pediatric Otolaryngology,

⁵Pediatric Cardiac Surgery Unit, ⁶Department of Anesthesia, ⁷Department of Radiology, ⁸Department of Occupational Therapy, ⁹Nutrition and Dietary Unit,

¹⁰Department of Physical Therapy, and ¹¹Department of Social Services, Schneider Children's Medical Center, Petah Tikva, Israel

¹²ALYN Hospital, Jerusalem, Israel

¹³Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT **Background:** Aerodigestive clinics are run by interdisciplinary medical and surgical teams, and provide complex care coordination and combined endoscopies.

Objectives: To describe the design and patient population of the first pediatric aerodigestive center in Israel.

Methods: A retrospective single-center cohort study was conducted describing patients followed in the aerodigestive clinic of Schneider Children's Medical Center of Israel, a tertiary pediatric hospital, between its inception in January 2017 and June 2020.

Results: During the study period, 100 patients were seen at the combined respiratory and digestive (NoAM) clinic, with a total of 271 visits. Median age at first assessment was 29.5 months (range 3–216). Fifty-six patients (56%) had esophageal atresia and tracheoesophageal fistula. Thirty-nine patients had an identified genetic disorder, 28 had a primary airway abnormality, 28 were oxygen dependent, and 21 were born premature. Fifty-two patients underwent triple endoscopy, consisting of flexible bronchoscopy, rigid bronchoscopy, and gastroscopy. In 33 patients, esophageal dilatation was necessary. Six patients underwent posterior tracheopexy at a median of 6 months of age (range 5 days to 8 years) all with ensuing symptom improvement. The total mean parental satisfaction score on a Likert-type scale of 1–5 (5 = highest satisfaction) was 4.5.

Conclusions: A coordinated approach is required to provide effective care to the growing population of children with aerodigestive disorders. The cross fertilization between multiple disciplines offers a unique opportunity to develop high quality and innovative care. Outcome measures must be defined to objectively measure clinical benefit.

IMAJ 2021; 23: 569–575

KEY WORDS: aerodigestive, care coordination, pediatric, posterior tracheopexy, triple endoscopy

Advances in the care of critically ill children have created a growing population of children with complex chronic conditions. The greatest growth is observed in children with chronic conditions affecting two or more body systems, especially the respiratory and aerodigestive tracts. These children account for the highest proportion of inpatient days and healthcare expenditures [1]. The recognition of the inter-relatedness of these disorders and resulting need to co-ordinate care across a range of specialties, has led to the establishment of multidisciplinary aerodigestive centers. The concept of pediatric aerodigestive care was conceived in the United States, where the first centers were founded in the late 1990s [2].

A recent consensus statement on pediatric aerodigestive care defines a pediatric aerodigestive patient as, “a child with a combination of multiple and interrelated congenital and/or acquired conditions affecting airway, breathing, feeding, swallowing or growth that require a coordinated interdisciplinary diagnostic and therapeutic approach to achieve optimal outcomes”. This definition includes, but is not limited to, structural and functional airway and upper gastrointestinal tract disease, lung disease due to congenital or developmental abnormality or injury, swallowing dysfunction, feeding problems, genetic diseases, and neurodevelopmental disability [3].

Aerodigestive disorders in children pose diagnostic and treatment challenges. Their care is complex, often characterized by the need for multiple invasive procedures, heavy reliance on technology and imaging, anesthesia, and multi-specialist care, as well as frequent hospitalizations. These challenges cause not only frequent healthcare utilization, but also result in significant stress for the family [4]. In addition to the concern about a chronically ill child, parents experience frustration with lack of coordinated care plans, leading to confusion and at times contradiction in treatment pathways [5].

*These authors contributed equally to this study

The aim of aerodigestive centers is to provide consistent, efficacious, cost-effective, outcome-driven, patient-centered, family-focused care for this medically fragile population [2]. As part of this effort, and due to the interwoven nature of respiratory and gastrointestinal disease, many aerodigestive patients undergo combined endoscopic evaluation of their upper and lower respiratory tract as well as the upper gastrointestinal tract under the same anesthesia. The administration of such comprehensive and coordinated care has been shown to decrease the time, cost, and financial burden on families [6].

While this is a noble goal, the introduction of such a care model is fraught with difficulties, including the need to divert staff from traditional clinical work patterns to multi-disciplinary collaboration, changes in coding and billing protocol, and coordination with a variety of stakeholders including operating theater personnel, hospital administration, and community services.

The aim of the present manuscript is to describe the patient population as well as the design of the first pediatric aerodigestive center in Israel, including challenges and opportunities associated with its formation.

PATIENTS AND METHODS

This retrospective, single-center cohort study describes patients who were followed at the aerodigestive clinic at Schneider Children's Medical Center of Israel, a tertiary pediatric hospital, between its inception in January 2017 and June 2020.

Data were extracted from electronic medical records, following approval by the institutional review board (0818-20-RMC). Parental consent was obtained for publication of anonymized case vignettes.

CLINIC SET UP

During the first months of the budding aerodigestive collaboration, the core NoAM (capital letters of *NoAM* in Hebrew designating *respiratory and digestive combined*) team, consisting of eight medical and paramedical professionals, spent a 10-day period at Cincinnati Children's Hospital Medical Center (CCHMC), USA, where the concept of aerodigestive pediatric medicine was first conceived 20 years earlier. The team studied care paradigms, work practices, and patient flow. A further and active collaboration including bi-directional working visits was further established with the Esophageal and Airway Treatment (EAT) Center at Boston Children's Hospital, USA, where novel treatment approaches for children with complex aerodigestive disease are being pioneered. The inception of the NoAM clinic was publicized via presentations at local and national conferences.

PATIENT REFERRALS

Patients between the ages of 0 and 18 years were referred to the aerodigestive clinic from various disciplines within Schneider Children's, as well as from other hospitals and the community setting. Criteria for patient recruitment were adapted with

permission from the Mayo Clinic Children's Center, shown in Table 1 [7]. All new referrals were vetted by the nurse coordinator (YG) and program director (PS) to give preference to those who could benefit the most from the services but were not receiving adequate care within existing care settings.

Table 1. Criteria for patient referrals to the aerodigestive service

Core Services*	Major** conditions	Minor** conditions
Pulmonology Gastroenterology Otolaryngology	Airway stenosis*** Aspiration (known or suspected) Chronic lung disease Global CNS impairment Chiari malformation Esophageal dysmotility Esophageal stricture Genetic conditions* Laryngeal cleft (current or prior) Sleep disordered breathing Tracheo-esophageal fistula (current or prior) Tracheostomy Vocal cord paralysis	Developmental delay Feeding problems GERD Laryngomalacia Noisy breathing Recurrent chest infections Tracheomalacia/bronchomalacia

Adapted, with permission from Boesch RP, Balakrishnan K, Grothe RM, et al. Interdisciplinary aerodigestive care model improves risk, cost, and efficiency. *Int J Pediatr Otorhinolaryngol* 2018; 113: 119-23.

* at least 2 required

** either 2 major, or 1 major and 2 minor required

*** subglottic stenosis, glottic stenosis, laryngeal web, laryngeal stenosis, tracheal stenosis, complete tracheal rings

+ Trisomy 21, CHARGE, 22q11, VACTERL, Pfeiffer, Opitz, craniofacial syndromes, Cornelia deLange, Crit du Chat

CNS = central nervous system, GERD = gastroesophageal reflux disease

PATIENT JOURNEY

The patient journey begins prior to the initial clinic visit with a formal intake procedure, conducted by the nurse coordinator. This process consists of an initial telephone interview and the collection of relevant documents and imaging before the first appointment. According to the patient's individual needs, an individualized itinerary is devised, which enables the families to meet with all relevant professionals during the same day (one stop shop). An exemplary itinerary is shown in Table 2, and the tasks of the various team members are shown in Table 3.

At the end of the clinic day, the team discusses the results. Imaging is reviewed under the direction of a radiologist and a unified treatment strategy devised. A single, customized summary document is produced, which reflects the recommendations of each team member and details future investigations and treatment. After the meeting, the nurse coordinator phones the family to ensure they are fully informed about the course of action. In tandem, the the community healthcare provider is

Table 2. Exemplary clinic itinerary, designed to cater to individual patient needs

Name	Gastrointestinal	Pulmonology	ENT/SLP	Surgeon	Neurologist	OT	Physiotherapist	Dietitian	Social worker	Procedures
Patient 1	10:30	9:30	8:00		12:30	11:00	X	X		CXR, Sputum
Patient 2	9:00	10:00	11:00	8:00		12:00		X	X	PFT + CXR
Patient 3	11:30	8:30	10:00		13:00	9:00	X	X		FEES
Patient 4	8:30	11:00	9:00	8:15		10:00			X	CXR
Patient 5	10:00	10:30	12:00	8:45	13:30	8:00	X	X	X	

CXR = chest X-ray, ENT = ear, nose, and throat, FEES = functional endoscopic evaluation of swallow, OT = occupational therapist, = pulmonary function test, SLP = speech and language pathologist

updated to ensure seamless integration with the primary care sector. The administrator assumes responsibility for scheduling and tracking the patient’s progress along the investigation and treatment pathway.

TRIPLE ENDOSCOPIES AND INNOVATIVE SURGICAL INTERVENTIONS

As part of the aerodigestive evaluation, double or triple endoscopies are conducted under the same anesthesia when indicated. These procedures can include any combination of (a) rigid micro-laryngo-bronchoscopy to assess upper airway anomalies [8] including laryngeal cleft [9], which has a high prevalence in esophageal atresia (EA) with tracheoesophageal fistula (TEF) patients and contributes to aspiration lung disease, (b) flexible bronchoscopy to comprehensively examine airway dynamics, and (c) esophagogastroduodenoscopy. Endoscopies are supplemented as needed, by fluoroscopy, three dimensional angiography/ bronchography, broncho-alveolar lavage, intestinal biopsies, and procedures to restore esophageal patency, including balloon dilatations, botulinum toxin, steroid injections and needle knife incisions.

When conservative treatment was insufficient for the treatment of severe tracheo-bronchomalacia, surgical techniques were employed to achieve tracheo-bronchial patency and optimize secretion clearance. These included traditional approaches, such as anterior aortopexy, but also more recently described treatment modalities, such as posterior tracheopexy, to address posterior tracheal membrane intrusion causing excessive dynamic airway collapse [10,11], a technique developed at Boston Children’s Hospital.

PATIENT CHARACTERISTICS, INTERVENTIONS, AND SATISFACTION SCORES

We extracted demographic and clinical data for patients treated at the NoAM clinic between its inception in January 2017 and June 2020. This search was supplemented by a satisfaction questionnaire that was completed by the parents after the first clinic visit in an effort to continuously improve services.

RESULTS

During the study period, 100 patients were seen at the NoAM clinic, with a total of 271 visits. The mean number of professionals encountered during a clinic day was 7 (range 6–9).

PATIENT POPULATION

Median age at first assessment was 29.5 months (range 3–216 months). The most common reasons for referral to the clinic were EA/TEF (56/100 patients) and primary upper airway abnormality (28/100 patients). Thirty-nine patients had an identified genetic disorder and 36 were diagnosed with developmental delay. Ninety-three patients had multiple symptoms on presentation. Chronic cough and recurrent pneumonia were the most common primary symptoms (75% and 74%, respectively). At the time of presentation, 10 patients had a medical condition that required tracheostomy. Two underwent a weaning process and were successfully decannulated during the study period. Patient characteristics and the primary presenting symptoms are shown in Table 4.

DIAGNOSTIC WORKUP

Clinic evaluation always included a thorough medical history and physical examination completed by each provider. Based on clinical presentation and following team discussions of the patient’s history and prior investigations, a coordinated itinerary of consultations and further diagnostic testing was devised. The ensuing diagnostic and endoscopic evaluations are displayed in Table 4. The most common diagnostic test was functional endoscopic evaluation of swallow (FEES) performed by ear, nose, and throat (ENT) physicians in collaboration with the speech and language pathologist during the clinic visit. Half of all patients underwent FEES. The most common endoscopic procedure, performed in 52 patients, was combined triple endoscopy consisting of flexible bronchoscopy (with or without bronchoalveolar lavage), rigid microlaryngobronchoscopy, and esophagogastroduodenoscopy (EGD).

Table 3. Disciplines and roles of the multi disciplinary aerodigestive team

Discipline	Role
Nurse coordinator	<ul style="list-style-type: none"> • Preliminary review of medical records • Obtain medical and social history • Obtain anthropometric data of the child • Provide educational information to families • Co-ordinate medical procedures involving multiple teams • Ongoing communication with families and referring team • Seamless integration between hospital and community services
Clinical dietitian	<ul style="list-style-type: none"> • Assess nutritional intake and schedule • Conduct nutritional analysis and integrate into feeding plan • Ongoing monitoring of nutritional intake considering different feeding routes and restrictions
Pulmonologist	<ul style="list-style-type: none"> • Clinical assessment to screen for aspiration lung disease, obstructive sleep apnea • Use chest radiographs, CTs to assess parenchymal damage, identify and treat bronchiectasis/ airway disease • Surveillance of bacterial lung milieu • Monitor lung function • Manage tracheomalacia • Endoscopic treatment of strictures, fistulas
Gastroenterologist	<ul style="list-style-type: none"> • Assess esophageal patency, inflammation and motility • Screen for and manage gastro-esophageal reflux disease, eosinophilic esophagitis, • Restore esophageal patency using dilatations, steroid and mitomycin injections, needle knife • Evaluate for malabsorptive conditions and manage nutritional needs • Endoscopic treatment of fistulas
Otolaryngologist	<ul style="list-style-type: none"> • Evaluate laryngeal structure and vocal cord function • Identify and treat airway dysfunction leading to dyspnea, aspiration and dysphonia • Perform FEES in collaboration with speech and language pathologist • Endoscopic treatment of strictures, fistulas • Laryngeal and tracheal surgeries • Tracheostomy insertion and management
General and cardiothoracic surgeons	<ul style="list-style-type: none"> • Evaluate and treat children with esophageal atresia/ strictures • Performance of a variety of aerodigestive tract surgeries, including stricturoplasty, esophagostomy, tracheopexy, aortopexy, Nissen's fundoplication and diaphragm plication • Complex tracheo-esophageal fistula management
Anesthetist	<ul style="list-style-type: none"> • Manage airway in various stages of sedation during comprehensive assessment, e.g., 3-stage dynamic bronchoscopy • Enable simultaneous endoscopy procedures, e.g. flexible bronchoscopy and gastroscopy • Manage difficult airway in complex and challenging patient population
Neurologist	<ul style="list-style-type: none"> • Assess milestones across developmental realms • Provide framework to optimize psycho-social adaptation • Integrate medical and rehabilitation needs
Radiologist	<ul style="list-style-type: none"> • Advice on appropriate imaging tools for specific question at hand • Interpret imaging from a variety of sources, including plain films, CT, MRI, salivagram, milk scan, gastric emptying study, upper GI studies, ventilation/ perfusion scan, video-fluoroscopic swallowing studies
Occupational therapist	<ul style="list-style-type: none"> • Evaluate oral motor skills and positioning aspects of feeding • Explore use of adaptive equipment • Develop feeding plans congruent with patients' condition and parental preference • Perform videofluoroscopic swallowing evaluations in cooperation with radiologist
Speech language pathologist	<ul style="list-style-type: none"> • Assesses the child's communication signals, including verbal and non-verbal • Assess vocal cord function • Document clinical signs of swallowing dysfunction • Perform FEES in collaboration with the otolaryngologist
Physiotherapist	<ul style="list-style-type: none"> • Educate parents to perform airway clearance maneuvers • Collect deep suction and induced sputum to inform lower airway bacterial growth • Assess for musculoskeletal abnormalities (e.g., scoliosis) and provide treatment strategies for postural support • Asses for neurodevelopmental abnormalities and provide treatment strategies and follow-up
Social worker	<ul style="list-style-type: none"> • Inform families about rights and benefits • Assist in maneuvering various support systems • Support families of hospitalized children and assist with functional and emotional difficulties • Identify children at risk of receiving inadequate care and source support agencies accordingly
Administrator	<ul style="list-style-type: none"> • Co-ordinate multi-disciplinary clinics • Plan triple endoscopies in various care settings, including operating rooms and catheter laboratory • Devise and adapt billing and coding procedures • Support publicity work of the clinic, such as website design and management

CT = computed tomography, FEES = fiberoptic endoscopic evaluations of swallowing, GI = gastrointestinal, MRI = magnetic resonance imaging

Table 4. Patient characteristics and diagnostic and endoscopic evaluation

Characteristic	Value, n
Total number of patients	100
Sex (male)	57
Age, in months, at first evaluation, median (range)	29.5 (3–216)
Syndromes/ Chromosomal	
VACTERL association	20
Down's syndrome	4
CHARGE association	2
Other	13
Neurologic disease*	
Developmental delay	36
Cerebral palsy	6
Other CNS impairment	10
TEF + EA**	56
Primary Upper Airway disease***	28
Preterm < 37 weeks	21
Gestational age in months of preterms, median (range)	32 (25–36)
Oxygen dependant	28
NIV	19
Tracheostomy	10
Gastrostomy or jejunostomy feeding	48
Presenting symptoms*	
Cough	75
Recurrent pneumonia	74
Dysphagia	62
Noisy breathing	54
Aspiration (known or suspected)	42
Choking episodes	38
GERD	37
OSA	19
More than one symptom	93
Diagnostic evaluation	
Sleep study	24
Salivagram	13
Upper gastro-intestinal tract follow through study	49
Video fluoroscopic swallow study	27
pH/pH-impedance study	18
Chest CT scan	36
FEES	50
Endoscopic procedures	
Flexible bronchoscopy alone	28
EGD alone	39
Esophageal dilatation	33
Direct laryngoscopy alone	6
Combined bronchoscopy + EGD	28
Combined bronchoscopy flexible + rigid	15
Triple endoscopy (bronchoscopy flexible + rigid + EGD)	52

*not mutually exclusive

**with or without VACTERL association

***congenital malformation of the larynx, laryngomalacia, obstructive sleep apnea, congenital stridor, congenital central hypoventilation syndrome, vocal cord paralysis

CHARGE association = coloboma, heart defect, atresia choanae (also known as choanal atresia), restricted growth and development, genital abnormality, and ear abnormality
 CNS = central nervous system, EDG = esophagogastroduodenoscopy, FEES = functional endoscopic evaluation of swallow, GERD = gastroesophageal reflux disease, NIV = non-invasive ventilation, OSA = obstructive sleep apnea, TEF/EA = tracheoesophageal fistula and esophageal atresia, VACTERL association= vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities

POSTERIOR TRACHEOPEXY

Throughout the study period, six patients underwent posterior tracheopexy at a median of 6 months (range 5 days to 8 years). All had undergone primary surgical repair at birth for EA/TEF type C. Three patients required a second operation, all around the age of 6 months, for resection of a recurrent tracheoesophageal fistula. Two patients, aged 3 and 8 years, underwent isolated posterior tracheopexy, indicated for severe chronic pneumonias secondary to impaired secretion clearance and severe exercise limitation, respectively. These two patients underwent surgery in conjunction with Dr. Jennings from Boston Children's Hospital during his team's visit to Schneider Children's. One patient underwent primary posterior tracheopexy at birth during esophageal atresia and TEF repair, following a pre-operative bronchoscopic diagnosis of significant tracheomalacia. Clinical outcomes were successful in all cases.

PATIENT SATISFACTION

The total parental satisfaction score, based on a Likert-type scale of 1–5 (5 indicating the highest satisfaction) was on average 4.5 based on the following items:

- Care plan was customized to the needs of my child (4.5)
- Following entry into the NoAM clinic I spent less time off work than in the previous care settings (4.5)
- A sufficient amount of time was spent with each care provider (4.7)
- The visit was well coordinated by the nurse (4.6)
- The aerodigestive team works together in a cohesive way (4.4).

CASE VIGNETTE

A three-year-old girl was referred to the NoAM clinic for evaluation of a chronic cough. At birth she had been diagnosed with esophageal atresia and what was presumed to have a type C, distal tracheoesophageal fistula. Following fistula dissection and esophageal anastomosis on day two of life, she underwent one esophageal dilatation at the age of 6 months and struggled to establish oral feeding and gain weight. She was admitted to hospital frequently with severe respiratory tract infections requiring intravenous antibiotic treatment. Recurrent bronchoscopies demonstrated severe tracheomalacia, but the diverticulum at the original fistula site appeared closed and no additional fistula was identified. Upper gastrointestinal follow-up showed impaired esophageal peristalsis and a mild anastomotic stricture but no contrast leaks. To comprehensively investigate the reason for her severe respiratory presentation, a triple endoscopy was conducted with the following findings: moderate anastomotic esophageal stricture with macroscopic inflammatory changes, type 1 laryngeal cleft, demonstrated by hockey stick palpation of her arytenoids via rigid bronchoscope, severe posterior type tracheal intrusion with complete coaptation of the mid-trachea during cough and copious purulent secretions throughout the airway, and a previously unidentified small groove-like fistula in the upper trachea,

visualized by target oxygen jet insufflation of the suspicious posterior tracheal groove and directed methylene blue injection of the esophagus and simultaneous visualization of the trachea via flexible bronchoscopy [12]. The diagnosis was thus revised to type D TEF and she underwent upper fistula closure with cervical tracheoplasty and esophagoplasty, as well as posterior tracheopexy via thoracic approach to enable optimal secretion clearance in view of the bronchiectasis, which had already been established by the age of 3 years. Due to the absence of aspiration clinically and on video-fluoroscopy, the type 1 laryngeal cleft was not repaired concomitantly. Her pulmonary status subsequently improved, although she continues to require intensive airway clearance and frequent antibiotic therapy to manage her bronchiectasis.

DISCUSSION

We describe the process of establishing a new care model catering for pediatric patients with complex aerodigestive conditions. According to the Institute for Healthcare Improvement, care strategies aimed at complex patient populations should address three considerations [13]:

- Improving the experience of care
- Improving the health of populations
- Reducing the per capita costs of healthcare

ADVANTAGES OF COORDINATED CARE

The advantages of coordinated complex care clinics in general and aerodigestive clinics in particular include improved parent satisfaction and decreased caregiver strain [3,14,15], a decrease in non-intensive care unit length of stay [2] and reduction in cost and anesthesia time [6]. We have modeled our clinic in keeping with essential elements recommended in this context: interdisciplinary medical and surgical team, care coordination, team meetings, and combined endoscopy procedures [2]. Most aerodigestive patients followed at the NoAM clinic presented with a combination of multiple symptoms. The evaluation and management included a vast array of invasive and non-invasive modalities, reflecting multi-system involvement. Regular team meetings and the frequent performance of triple endoscopy procedures were essential in understanding the inter-relatedness of the respiratory and digestive system. These procedures were followed to obtain precise diagnoses and formulate targeted treatment plans, as exemplified by the case vignette. To facilitate such collaboration, it was necessary to change work practices and schedules as well as revise preconceived attitudes and develop readiness to learn the terms and considerations of an unfamiliar specialty.

THE ROLE OF THE NURSE COORDINATOR

The role of a clearly identified care coordinator is essential for the success of aerodigestive clinics and traditionally filled by a nurse or nurse practitioner [16]. This individual serves as the primary point of contact for the family, which ordinarily has

primary and sole responsibility to navigate through a labyrinth of consultations, investigations, and treatments. In an eloquent plaidoyer that should be compulsory reading in medical school and beyond, parents of children with complex medical conditions have suggested 10 ways to support them on the management of their journeys [17]. The suggestion was for healthcare providers to consider is that interventions targeted at any one aspect of care affect the physical and mental aspects of the whole child. Aside from synchronizing care, the nurse coordinator provides emotional support to families, develops and delivers educational content, and identifies program development needs. By acting as an effective mediator between families and members of the multi-disciplinary team, feedback on the quality of care can be delivered swiftly so that any deficiencies can be remedied in a timely fashion [6]. This approach relieves physicians of some of the direct communication burden with a large number of caregivers and streamlines the flow of information [16-18]. The nurse coordinator must be conversant with all aspects of the healthcare system to be able to coordinate the services required for comprehensive assessment and treatment.

REDUCTION IN ANESTHESIA TIME AND PARENTAL BURDEN

To the best of our knowledge, the only study published to date, which specifically investigates the impact of an interdisciplinary approach to pediatric aerodigestive care, estimated a reduction in anesthesia episodes and associated cost as well as parental burden of multiple trips to the medical center [19]. Judging from the numerous double and triple scope procedures in our cohort, it can be surmised that our patients also benefited from an overall reduction in anesthesia time and parental burden.

CONCLUSIONS

A coordinated approach is required to provide effective care to the growing population of children with aerodigestive disorders. The cross fertilization between multiple disciplines offers a unique opportunity to develop qualitative and innovative care. Outcome measures must be defined to objectively measure clinical benefit.

ACKNOWLEDGMENTS

The authors thank Orian Lusana, the soul of the NoAM clinic, administrator, and guarantor for smooth running of the service. We thank the directors of the various Schneider institutes for their ongoing support, including Raanan Shamir MD, Hannah Blau MBBS, Dario Prais MD, Eyal Raveh MD, Naftali Freud MD, Ayelet Keller, Irit Poraz PhD, Daphna Busani, Ofra Aran PhD, and Efrat Harel. We are grateful to the aerodigestive team at Cincinnati Children's Hospital Medical Center, in particular Robert E. Wood MD, Claire Miller PhD MHA CCC-SLP, and Michelle Cohen for their hospitality and willingness to share work practices. Finally, we extend our deep appreciation to the Esophageal and Airway Treatment Center (EAT) team at Boston Children's Hospital, in particular Russell W. Jennings MD, Michael Manfre-

di MD, Carlos Munoz MD, Dorothy Gallagher, and Beatriz Lorenzo for their ongoing and generous guidance and support. Last, our thanks go to the Fisher family, for their continuous encouragement and generous financial support for the NoAM endeavor.

Correspondence

Dr. P. Stafler

Pulmonary Institute, Schneider Children's Medical Center, Petah Tikva 49202, Israel
Phone: (972-3) 925-3654
Fax: (972-3) 925-3308
email: pstafler@hotmail.com

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Capsule

SARS-CoV-2 mRNA vaccines induce persistent human germinal center responses

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) mRNA-based vaccines are about 95% effective in preventing coronavirus disease-2019 (COVID-19). The dynamics of antibody-secreting plasmablasts and germinal center B cells induced by these vaccines in humans remain unclear. **Turner** and co-authors examined antigen-specific B cell responses in peripheral blood (n=41) and draining lymph nodes in 14 individuals who had received two doses of BNT162b2, an mRNA-based vaccine that encodes the full-length SARS-CoV-2 spike (S) gene. Circulating IgG- and IgA-secreting plasmablasts that target the S protein peaked one week after the second immunization and then declined, becoming undetectable 3 weeks later. These plasmablast responses preceded maximal levels of serum anti-S binding and neutralizing antibodies to an early circulating SARS-CoV-2 strain as well as emerging variants, especially in individuals who had previously been infected with SARS-CoV-2 (who produced the most robust serological responses). By examining fine needle aspirates of draining axillary

lymph nodes, the authors identified germinal center B cells that bound S protein in all participants who were sampled after primary immunization. High frequencies of S-binding germinal center B cells and plasmablasts were sustained in these draining lymph nodes for at least 12 weeks after the booster immunization. S-binding monoclonal antibodies derived from germinal center B cells predominantly targeted the receptor-binding domain of the S protein, and fewer clones bound to the N-terminal domain or to epitopes shared with the S proteins of the human beta coronaviruses OC43 and HKU1. These latter cross-reactive B cell clones had higher levels of somatic hypermutation as compared to those that recognized only the SARS-CoV-2 S protein, which suggests a memory B cell origin. These studies demonstrate that SARS-CoV-2 mRNA-based vaccination of humans induces a persistent germinal center B cell response, which enables the generation of robust humoral immunity.

Nature 2021; 596: 109
 Eitan Israeli