Brave new world or the unfortunate natural history of “lethal” disease: when to push the envelope?

To the Editor,

We recently witnessed a neonatal intensive care unit infant succumb to tracheal agenesis and noticed, at the same time, in the news headlines of adults being “saved” by “lab-made tracheas” [1]. This stimulated our curiosity to review recent developments in tissue engineering and stem cell research that may challenge prior authors’ claims that tracheal agenesis is “uniformly fatal” [2]. Although prior tracheal reconstructive efforts have not had long-term success [2], what our review found seems to bring science fiction (Aldous Huxley’s Brave New World, 1931) into reality and allows the creation of a new trachea using the child’s umbilical cord stem cells.

Prior attempts at repair have typically used the native esophagus, but this is usually complicated with the need for positive pressure to keep the esophagus from collapsing [3]. Other problems such as esophageal stenosis, ulceration, pneumonia, and aspiration after esophageal reconstruction may plague the child and result in an untimely demise [4].

No long-term data are available on recent attempts to use external esophageal stenting and donor aortas with a vascular stent [5]. Devising a “new” repair that would not require long-term reliance on positive pressure ventilation and would preserve the native esophagus seems warranted. Elements of this trachea repair strategy would include a prenatal diagnosis of tracheal agenesis and screening for coexisting anomalies, use of both an ex utero intrapartum treatment (EXIT procedure) to extracorporeal membrane oxygenation (ECMO), and obtaining a suitable trachea replacement or growing the patient a new trachea using stem cells in a laboratory.

Improvements in high-resolution ultrasonography have now allowed for prenatal detection of tracheal agenesis [6]. According to a 2009 report by Zhou et al [6], hyperechoic lungs, a dilated trachea and bronchi without fluid flow, a flattened or inverted diaphragm, and compression of the heart are sonographic suggestions that a trachea agenesis may exist. Because there is an association with other life-threatening VACTERL abnormalities, a complete evaluation would need to be performed around the perinatal period with possibly fetal magnetic resonance imaging and echocardiography at birth. After diagnosis and screening, planned delivery as close to term as possible with immediate surgical management of the consequences of tracheal agenesis should follow. Some describe intubating the esophagus, tracheoesophageal fistula, or just using a face mask to bag ventilate at birth [4]. All of these methods are unreliable and force air into the gastrointestinal tract, which can cause aspiration and worsening oxygenation [4]. An optimal strategy to minimize the risk of central nervous system ischemia might be the use of an EXIT procedure to ECMO.

The EXIT procedure was first described in the mid to late 1990s to secure the airway in cases where airway compromise at birth is expected, such as cervical teratomas and cystic hygromas [7]. Introduced in the early 21st century, the EXIT to ECMO strategy improved early survival of...
children with anticipated life-threatening respiratory insufficiency or hemodynamic consequences upon the first breath of life or the reversal of fetal circulation [8]. Cases treated with EXIT to ECMO strategy have included giant pulmonary sequestrations, congenital cystic adenoid malformations, congenital diaphragmatic hernia, and other thoracic masses [9]. Tracheal agenesis diagnosed prenatally may soon be added to this list.

After a planned birth with EXIT to ECMO, a suitable “neo-trachea” would need to be obtained to repair the tracheal agenesis. Although it sounds like science fiction, techniques and technologies now exist that allow the harvesting of stem cells from an infant’s umbilical cord at birth, which then can be used to repopulate a decellularized animal or human donor trachea. In 2008, a group from Spain reported an adult (and a United Kingdom child in 2010) with successful transplantation of a bioengineered airway using an acellular tracheal matrix [10-12]. In the 1 adult case, the acellular cadaver matrix was seeded with the patient’s own cells from biopsies of respiratory mucosa and bone marrow aspirates [11]. An acellular tracheal matrix scaffold could be prepared from either donor human cadavers or animals with a similar-sized airway as a newborn [13]. Fortunately, infants are born with an abundance of stem cells in what would otherwise be considered biological waste. Stem cells from the umbilical cord could provide the cells to repopulate a tracheal matrix within 2 weeks, providing a suitable tracheal replacement for a child that is rejection free and mechanically, functionally, and physiologically similar to the patient’s normal native trachea [1,11,12]. When the trachea graft is mature, it could be implanted on ECMO, and then ECMO support can be weaned and decannulated as the infant could then be conventionally ventilated.

We hope to stimulate the readers to contemplate the question of when to “push the envelope” with new technologies for tracheal agenesis and other malformations and diseases typically thought of as lethal. The advancements outlined above could be used for malformations such as tracheal agenesis but has inherent risks and would clearly require substantial financial resources. There is potential morbidity from each component of the intervention strategy, and complications from the EXIT, ECMO, and tracheal replacement may occur. Because value cannot be placed upon a life, we recommend that each institution evaluate their resources and ability to care for unusual entities such as tracheal agenesis. With enhanced
fetal imaging, we expect that prenatal consultation regarding this rare disorder will occur, and it may no longer be acceptable to recommend only palliative measures for a condition that was once considered “universally fatal” (Figs. 1-4).

Sincerely,

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References


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