Basic Science Review

Wound Healing

Wound healing involves three temporally overlapping stages: an inflammatory stage, a proliferative stage, and a phase of contraction and remodeling.

The inflammatory stage begins with the initial injury. It involves active vascular retraction and constriction followed by vasodilation mediated by prostaglandins. Platelets adhere to the exposed collagen forming a hemostatic plug. There are numerous active mediators that are released including adenosine diphosphate, platelet derived growth factor, transforming growth factor, clotting factors and vasoactive substances such as 5-hydroxytryptamine, thromboxane and histamine. The coagulation cascade is activated which lays down the fibrin network. Platelets release proteolytic enzymes that activate the complement system. The complement cascade contributes to bacterial killing and wound debridement and supplies chemoattractant signals to effect cells.

Polymorphonuclear lymphocytes (PMNs) enter the wound at about 6 hrs post-injury. They reach their greatest concentration at 24-48hrs post-injury and disappear within 72hrs. The PMNs phagocytize debris and bacteria from the wound and release proteases that lyse devitalized tissue.

T and B cells enter the wound after the PMNs and are most numerous at 6 days after injury. T cells secrete regulatory lymphokines. Helper T-cells are necessary for wound healing. Suppressor T cells down-regulate healing.

Macrophages enter the wound within 48-96 hrs after injury. Large concentrations of macrophages are found in the wound at 3-5 days and can persist for several weeks. Macrophages are the only cells that can function in area of low oxygen tension at the wound center. These cells release many different enzymes but they primarily direct the proliferative and synthetic activity in the wound. This is achieved by interleukin-1 and tumor necrosis factor –alpha. Studies have shown that macrophages are essential to wound healing but PMNs can be absent without impairing the process.

Growth factors secreted by cells in the wound are major regulators of healing. Growth factors are chemotactic, mitogenic, and sometimes have an inhibitory effect on cells involved with wound repair. All growth factors interact with cellular receptors to modify the cells activities. IL-1 directly stimulates fibroblast activity including proliferation.
and collagen synthesis. IL-2 is produced by helper T cells. It has an indirect effect on wound healing by stimulating lymphocyte and macrophage activity.

Structural components essential to successful wound healing include fibronectin, collagens, glycoproteins and glycosaminoglycans. Fibronectin is secreted by fibroblasts and endothelial cells. It cross-links fibrin and glycosaminoglycans. Several types of collagen are found in the healing wound. The production of collagen by fibroblasts is a complex process. Hydroxylation requires Vitamin B, iron and Vitamin C. Glycoproteins and glycosaminoglycans function in cell-matrix interactions and in controlling wound resilience.

The proliferative phase lasts 10-14 days. It begins with re-epithelization. This process of resurfacing the defect begins at about 12 hrs after injury. The epithelial cells 1-2mm from the wound edge undergo phenotypic changes. The cells replication rate increase 17 fold. Epithelial cell migration is dependent on local humidity and oxygenation. If the wound is dry, epithelization occurs slower. If the wound is occluded, the epithelial cells migrate much quicker and resurface faster.

The next part of the proliferative phase is neovascularization in which blood vessel regeneration begins with the migration of endothelial cells. Macrophages secrete angiogenic factors in response to high lactate levels and low wound oxygen levels. The result of endothelial migration is capillary bud formation. Certain conditions such as diabetes mellitus or radiation therapy impede neovascularization.

Collagen deposition begins when fibroblasts enter the wound at 48-72 hrs post-injury. The collection of fibroblasts, inflammatory cells and capillary buds is referred to as granulation tissue. Granulation tissue persists until epithelial resurfacing is complete.

The final phase of wound healing is the wound contraction and remodeling phase. Wound contraction begins at 6-7 days after injury and is maximal for 10 days. Wound contraction eventually decreases the defect by 40-60%. Skin flaps and grafts can reduce the amount of wound contraction by 50-70%. Myofibroblasts, a modified fibroblast, provides the contractile force required for contraction. They have many characteristics of smooth muscle cells and are distributed throughout the wound. Wound collagen levels reach maximum at 2-3 weeks after injury, however, tissue strength is still only 5-10% of that of unwounded skin. The wound’s neomatrix is gradually replaced over 6-12 months by stronger interwoven cartilage as Type I collagen displaces Type III cartilage. Remodeling results in a scar with as much as 80% of the skin’s original tensile strength.

Introduction

Subglottic stenosis is a congenital or acquired narrowing of the subglottic airway. Although it is relatively rare, it is the third most common congenital airway problem (after laryngomalacia and vocal cord paralysis). Subglottic stenosis can present as a life-threatening airway emergency. It is imperative that the Otolaryngologist be an expert at dealing with the diagnosis and management of this disorder. Subglottic stenosis can affect both children and adults, however we will focus this presentation on the diagnosis and management of subglottic stenosis in children.

Anatomy

The infant larynx differs significantly in size and position when compared to the adult larynx. The infant larynx is proportionately larger than the adult larynx compared with the remainder of the tracheobronchial system. The vocal process of the arytenoid
takes up half the length of the vocal cord in the infant larynx, while it only takes up about \( \frac{1}{4} \) of the length of the vocal cord in the adult. The narrowest portion of the airway in the older child and adult is the glottic aperture, while the narrowest part of the airway in the infant is the subglottis. One millimeter of edema circumferentially in the subglottis reduces the cross-sectional area by 60%.

The infant larynx is positioned higher in the neck than the adult larynx. The superior border of the larynx of the infant is located at about the level of the first cervical vertebrae with the cricoid positioned at about the fourth cervical vertebrae. In comparison, the adult cricoid rests about the level of the sixth cervical vertebrae. The structures of the infant larynx are more pliable and less fibrous making the infant airway more susceptible to narrowing from edema and less easily palpable.

**Embryology**

The respiratory system is an outgrowth of the primitive pharynx. The development of the lower respiratory system begins at 26 days after conception as the laryngotracheal groove at the ventral aspect of the foregut.

The laryngotracheal diverticulum becomes separated from the foregut by the tracheoesophageal folds which fuse to become the tracheoesophageal septum. This septum divides the foregut into a ventral laryngotracheal tube and a dorsal esophagus. Failure of the tracheoesophageal folds to fuse during the fourth and fifth weeks can lead to a tracheoesophageal fistula.

The larynx develops from the fourth and fifth branchial arches. The laryngotracheal opening lies between these two arches. This primitive laryngeal aditus is altered to become a T-shaped opening by the growth of three tissue masses. One is the hypobranchial eminence. This mesodermal structure eventually becomes the epiglottis. The second and third growths are two arytenoid masses. As these masses grow between the fifth and seventh weeks, the laryngeal lumen is obliterated. Recanalization occurs by the tenth week. Failure to recanalize may result in atresia, stenosis or web formation in the larynx. The arytenoid masses are separated by an interarytenoid notch which eventually becomes obliterated. If obliteration does not occur, a posterior laryngeal cleft can result leading to severe aspiration in the newborn.

**Congenital Subglottic Stenosis**

Congenital subglottic stenosis is thought to be secondary to failure of the laryngeal lumen to recanalize properly during embryogenesis.

Subglottic stenosis is defined as a subglottic lumen 4.0mm in diameter or less at the level of the cricoid in a full term infant. The normal newborn subglottic diameter is 4.5 – 5.5mm and in premature neonates around 3.5mm. A subglottic diameter of less than 3.5mm in a premature infant is stenotic . Subglottic stenosis is considered congenital if there is no history of endotracheal intubation or other forms of laryngeal trauma.

Congenital subglottic stenosis is divided histopathologically into membranous and cartilaginous types. Membranous subglottic stenosis is usually circumferential and consists of fibrous soft-tissue thickening caused by increased fibrous connective tissue or hyperplastic submucous glands. It may involve the vocal folds as well. The cartilaginous type usually results from a thickened or deformed cricoid cartilage that forms an anterior subglottic shelf that extends posteriorly allowing only a small posterior opening. Other malformations can occur such as an elliptical cricoid leaving a slit-like
opening or a trapped first tracheal ring. Membranous subglottic stenosis is usually less severe than the cartilaginous type.

The severity of congenital subglottic stenosis depends on the degree of subglottic narrowing. The symptoms can range from mild with a picture of recurrent croup to severe with respiratory distress at delivery.

Congenital subglottic stenosis is often associated with other congenital malformations. A thorough search for associated anomalies is necessary.

**Acquired Subglottic Stenosis**

The causes of acquired subglottic stenosis include endotracheal intubation, external trauma, infection or inflammation or thermal or caustic injuries. By far, the most common cause of acquired subglottic stenosis is endotracheal intubation resulting in 90% of the cases. Because advances in neonatology have resulted in the survival of very premature infants, the number of infants requiring prolonged periods of endotracheal intubation have increased. As a result, the incidence of acquired subglottic stenosis has also increased. Acquired subglottic stenosis is now more common than congenital subglottic stenosis.

The reported incidence of subglottic stenosis in intubated patients ranges from 1-8%. The pathogenesis of acquired subglottic stenosis is not completely understood. Several theories exist. One such theory includes mucosal compression by the endotracheal tube leading to mucosal edema, ischemia and ulceration. This ulceration leads to perichondritis which extends into the cartilage leading to chondritis. The cartilage may necrose and collapse. Healing is by secondary intention with granulation tissue proliferation and deposition of fibrous tissue. This results in a weak cartilage framework and a firm scar narrowing the subglottic airway.

Risk factors for the development of acquired subglottic stenosis in neonates include prolonged endotracheal intubation, size of the endotracheal tube, increased motion of the endotracheal tube, repeated or traumatic intubations, birth weight less than 1,500 gms, infection, compromised immune status, presence of nasogastric tubes and the presence of gastroesophageal or laryngotracheal reflux.

Many feel the most important risk factor for the development of acquired subglottic stenosis is the length of intubation. However, there is no “safe” period of intubation since subglottic stenosis has been reported in as early as 17 hours of intubation. Premature infants tolerate prolonged intubation better than adults most likely due to the more yielding and pliable airway cartilages. It has been suggested that tracheotomy should be considered after 50 days of intubation in neonates.

The ideal endotracheal tube size allows an air leak at an inspiratory pressure of 20cm of H2O. The absence of an audible air leak is indicative of an excessively large tube (3). A study done in France reported a very low incidence of post-extubation stridor. The authors recommend the following tube sizes based on weight: infants <2500g size 2.5mm, children 2500-4000g size 3.0mm, children >4000g size 3.5mm.

Tube motion causes abrasion and trauma to the mucosa. This can be minimized by securing the tube carefully and by adequate sedation of the intubated patient.

Repeated or traumatic intubations can also lead to mucosal injury. Routine tube changes should not be performed.

Fortunately, the overall incidence of acquired subglottic stenosis has decreased in the past 20-30 years, mainly due to better education of physicians and nurses caring for these infants. Another factor in the decreased incidence of acquired subglottic stenosis is the routine use of surfactant for premature neonates with respiratory distress syndrome.
Diagnosis

Children with subglottic stenosis usually present with stridor and/or respiratory distress. Symptoms include irritability, restlessness, dysnea, tachypnea and cyanosis. The stridor is typically biphasic (inspiratory and expiratory components) due to turbulent airflow through the partially obstructed airway.

The diagnosis of either congenital or acquired subglottic stenosis begins with a complete history. The parents should be questioned regarding the following: duration, progression, history of prematurity or birth trauma, history of endotracheal intubation, feeding problems, change in the baby’s voice or cry, recent trauma, suspected foreign body aspiration and any other congenital malformations.

The child should be examined at rest and when agitated. Auscultation over the nose, mouth, neck and chest should be performed. The quality of the child’s voice should be noted (aphonic? , hoarse?)

If the child’s respiratory status permits, a flexible fiberoptic examination should be performed. Special attention should be paid to vocal fold motion. The subglottis can sometimes be visualized below the cords.

Radiographic evaluation includes AP and lateral views of the neck and chest. A narrowed subglottic air column suggest a diagnosis of subglottic stenosis or croup. If inspiratory and expiratory films are difficult to obtain, airway fluoroscopy can be beneficial. A barium swallow can help rule out airway compression by a vascular anomaly. The use of computerized tomography has not been proved to be beneficial in assessing the pediatric airway.

The gold standard for diagnosis of subglottic stenosis remains rigid endoscopic evaluation under general anesthesia. It is imperative to have all of your equipment arranged and checked prior to the patient coming into the operating room. Be sure to have a wide range of bronchoscope sizes in case the airway is much smaller than you anticipated!

Magnification with the Hopkins telescopes helps better define the pathology. Palpation of the cricoarytenoid joints is part of any complete examination. When examining the subglottic region after removing an existing endotracheal tube, make sure you wait a few minutes to evaluate for edema that the endotracheal tube may have been stenting.

Historically, classification of subglottic stenosis has been a problem. Measurements were done either subjectively or by using various instruments including rigid bronchoscopes, laryngeal forceps and angioplasty catheters.

Today, there is still no universally accepted staging system for subglottic stenosis. The most commonly used system was developed by Cotton in 1984 then revised in 1989. The percentage of obstruction and anatomic location of the lesion were determined endoscopically and assigned a grade I-IV based on perceived percentage of obstruction. Although this system was successful at relating the severity of the obstruction with the prognosis for decannulation, it remained imprecise and dependent on skilled judgement. For these reasons, Myer, Conner and Cotton proposed a grading system based on endotracheal tube sizes. This system was intended for firm mature stenosis. The endotracheal tube that would pass through the lumen (if one exists) and has normal leak pressures (10-25mm H2O) was compared to the expected age-appropriate endotracheal tube size. The maximum percentage of airway obstruction was then determined. Grade I - <50% obstruction, Grade II – 51-70% obstruction, Grade III – 71-99% obstruction, Grade IV – no detectable lumen.
Management

Management of subglottic stenosis begins with prevention. Control of risk factors is essential. Although controversial, many feel that gastroesophageal reflux disease should be treated with maximal medical management prior to consideration of any surgical therapy. Halstead recently demonstrated that significant GERD is an important cofactor in many pediatric airway disorders, particularly subglottic stenosis. She showed that anti-reflux therapy allowed successful airway surgery and decannulation in several children in whom previous surgeries had failed.

Acquired subglottic stenosis is typically more severe than congenital subglottic stenosis and is much more likely to require surgical intervention. Many of these patients will require a tracheotomy to provide an adequate airway while planning definitive treatment.

The management of subglottic stenosis is dependent on the severity or grade of stenosis. Mild stenosis (Grades I and II) can usually be treated with endoscopic techniques such as dilation or CO2 laser resection. Factors associated with failure of these endoscopic techniques include: previous attempts at endoscopic repair, circumferential scarring, loss of cartilaginous support, exposure of cartilage during laser excision leading to chondritis, severe bacterial infection, posterior inlet scarring with arytenoid fixation, combined laryngeal or tracheal stenosis or vertical scar length >1cm. Endoscopic dilation has had disappointing results, however, reported success rates with endoscopic laser resection of Grade I and II stenosis range from 66-80%.

Grade III or IV stenoses usually require some form of open surgical procedure. Several techniques have been described. The goal of any open procedure to correct subglottic stenosis is to maintain a functional voice and allow for early decannulation in the tracheostomy dependent. Absolute contraindications include inability to tolerate general anesthesia, persistent need for tracheotomy, significant GERD, and an ICU not equipped to handle the post-operative care.

Some of the more popular procedures include the anterior cricoid split, laryngotracheoplasty, either stented or in one stage, and end-to-end anastomosis.

Anterior Cricoid Split

The anterior cricoid split (ACS) procedure was originally described for a neonate who had failed extubation instead of performing a tracheostomy. This procedure is also used for older infants and those who are status-post tracheotomy. The criteria for ACS include: extubation failure on two occasions due to laryngeal pathology, weight >1500g, no assisted ventilation for 10 days prior to evaluation, O2 requirements <30%, no CHF for one month prior to evaluation, no acute respiratory tract infection, no antihypertensive medications ten days prior to evaluation. The procedure is performed after direct laryngoscopy and bronchoscopy confirmation of the diagnosis. All other airway pathology must be ruled-out. A vertical midline incision is made through the cricoid cartilage and first two tracheal rings as well as the lower thyroid cartilage. Prolene stay sutures are placed on either side of the cricoid cartilage and the skin is re-approximated after placement of a drain. The child is then left intubated, sedated and paralyzed in the ICU for 7-14 days. Cotton has guidelines for endotracheal tube sizes for stenting and for duration of stenting based on the infants weight.

Laryngotracheal Expansion Surgery

Laryngotracheal expansion surgery involves scar division with distraction of the edges by interposition of graft material to widen the airway lumen. There are several techniques depending on the location and severity of the stenosis. Laryngotracheoplasty
can be performed with a tracheostomy and formal stenting or by using the endotracheal tube as a stent, the latter known as a one-stage LTP. There are a variety of materials that can be used for stenting including silicone stents, Teflon stents, and T tubes. The primary consideration when deciding on the type of reconstruction and stent material is to provide a safe airway and adequate support for the graft. One-stage laryngotracheoplasty is gaining popularity.

**Anterior Laryngofissure with Anterior Lumen Augmentation**

This technique is good for subglottic stenosis that does not involve the glottis or have significant loss of cartilage support. Autogenous costal cartilage is the material of choice. Many other materials have been used for grafting including auricular, hyoid and thyroid cartilage and bone.

**Laryngofissure with Division of Posterior Cricoid Lamina**

This is indicated for patients with subglottic stenosis who have glottic involvement or significant cricoid deformity. Long-term stenting is usually necessary (3-6 months).

**Laryngofissure and Division of Posterior Cricoid Lamina with Anterior and Posterior Grafts**

This should be used for patients who have subglottic stenosis similar to those above but with a significant amount of stenosis posteriorly such that grafting is necessary to maintain the adequate separation.

**End-to-End Anastomosis**

This technique is indicated if there is severe deformity of the cricoid making grafting very likely to fail. Most say that there must be at least 10millimeters of normal airway below the glottis, however Cotton states that the resection can be up to the vocal folds but expect prolonged edema. This technique is technically difficult due to the close proximity of the vocal cords and recurrent laryngeal nerves. Stenosis less than 4cm can be resected by laryngeal release and cervical tracheal mobilization. Stenting is not required and the tracheotomy tube can usually be removed at around 4 weeks. Monnier et al performed this technique on 15 children, 13 which had Grades III and IV stenosis. They report a decannulation rate of 93%, 12 of which were decannulated within 6 months.

**Post-operative Care**

Patients undergoing open laryngeal surgery for subglottic stenosis require post-operative care in an ICU that has an intensivist and staff familiar with the specialized care these children require. Since most of the children undergoing open laryngotracheoplasty have more severe subglottic stenosis they have usually have had a tracheotomy for a while. Children who undergo laryngotracheoplasty with stenting typically only require only a few days of care in the hospital to be sure that the parents are educated about tracheotomy care and have all necessary equipment at home. Since they have a stent in place, they should be given perioperative antibiotics. H2 blockers should also be considered. The stent is typically removed in the operating room at around 3 months. A repeat DL and bronchoscopy is done a few weeks after the stent is removed. If the airway looks patent, the patient is decannulated.
Infants and children who undergo either ACS or one-stage LTP require more intense post-operative care in the ICU. They usually stay intubated for 7-14 days with the endotracheal tube acting as a stent. The patient requires heavy sedation with or without paralysis. The patients should be treated with broad-spectrum antibiotics and H2 blockers. Chest physiotherapy and log-rolling the patient Q 4 hrs is important to prevent atelectasis and pneumonia. The patient undergoes extubation when an air leak develops or after a certain time period. An audible air leak at a pressure of 20cm H2O is a good prognostic indicator for successful extubation. Decadron is usually given in the peri-extubation period.

Complications are infrequent but can include (in decreasing order of frequency): atelectasis, pneumonia, malpositioned endotracheal tube, accidental extubation, occluded ET tube, wound infection, granulation tissue and tracheocutaneous fistula. Some complications related specifically to ACS and one-stage LTP that require prolonged intubation with sedation include narcotic withdrawal and transient skeletal muscle paralysis related to the prolonged muscle relaxation.

Outcomes

The goal of management of subglottic stenosis is decannulation. Success rates are dependent on the cause of the stenosis, the number of previous failed attempts, the status of the remainder of the airway, especially the glottis and the severity of the stenosis. Cotton has reported an overall laryngotracheal reconstruction success rate of 92%, 97% for Grade II, 91% for Grade III, and 72% for Grade IV.

Dysphonia following laryngotracheal reconstruction has not been extensively studied. Many authors report that a functional voice is restored in most patients. MacArthur et al published a series of 12 patients (average age 6yrs) who underwent LTR. Most patients underwent both endoscopic evaluation and speech analysis. They found that 78% of the children had altered anatomy, 44% had altered function and 100% had decreased voice quality. They concluded that children with high grade subglottic stenosis and a history of multiple prior surgeries are at risk for a poor voice outcome after laryngotraheal reconstruction.

References

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