EMBRYOLOGY MEETS ENDOSCOPY:
THE ROLE OF ENDOSCOPY IN
CONGENITAL
GASTROINTESTINAL MALFORMATIONS

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Goals

• Understand the embryological development of select gastrointestinal malformations
• To be able to recognize common clinical presentations
• Understand the role of endoscopy in the diagnosis and treatment

Embryology

• Embryology can greatly contribute to understanding the mechanisms underlying malformations of the human foregut
• However: still much controversy on developmental mechanisms
Gut Development

https://www.youtube.com/watch?v=yXUv4MPuENT

Normal Esophageal Development

- Ectoderm of primitive foregut differentiates
  - Ventral (lung field)
  - Dorsal (esophagus)
- Tracheal (Respiratory) bud develops
  - Forms both trachea and lungs
  - Separates itself from the esophagus
Esophageal-Tracheal Embryology

- Three main theories have been proposed to try to explain the development of the esophagus, trachea and lungs
  - Mesenchymal septum theory
  - Outgrowth theory
  - Foregut folds theory

Mesenchymal Septum Formation

- Longitudinal ridges start to proliferate
- Ridges fuse in the midline of the primitive foregut from the epithelial septum
- Apoptosis takes place in the central areas of this septum (Caudal to Cranial direction)
- Mesenchymal tissue expands into the area between trachea and esophagus
  - Causes separation of the respiratory tract from the esophagus
  - Occurs between 6 and 7 weeks gestation

- Respiratory system develops as a result of rapid outgrowth from the original foregut tube
- Later completely detaches from the foregut during the subsequent stages of development
- Esophagus is formed following the rapid downward (caudal) growth of the trachea and bronchopulmonary structures
Foregut Folds

• Movement of three folds
  - Laryngeal fold (anterocranial)
  - Tracheal-esophageal fold (Inferior)
  - Pharyngo-esophageal (Dorsal)

• Caudal movement of anterior foregut folds results in separation of the pharynx and esophagus

• Cranial movement of the tracheoesophageal folds results in reduction of the tracheoesophageal space and separating the two structures

• Dorsal fold approximates the boundary of the pharynx and esophagus

• Longitudinal growth of the trachea and esophagus proceeds after separation

Gross Classification of Esophageal Atresia

• The overall incidence of EA/TEF ranges from one in every 2500 to 4500 live births

Based on abnormal embryogenesis

• Tracheoesophageal separation becomes arrested

  - Following arrest the undivided foregut assumes the histological characteristics of trachea

  - Initially separated esophagus becomes the fistula that connects the trachea to the stomach

  - The upper atretic esophagus results from rearrangement of the anterior foregut
Abnormal Embryogenesis Based on outgrowth theory:

- Tracheoesophageal malformations are fundamentally caused by failure of tracheal growth
- Bronchopulmonary buds originate directly from the foregut
- Foregut rostral to the bronchi assume tracheal characteristics
- Foregut distal to the bronchial connects to the stomach and becomes a fistula
- The upper atretic esophagus results from rearrangement of the anterior foregut

Abnormal Embryogenesis Based on foregut fold Theory:

- Abnormal movement of the folds leads to:
  - Failed division of the tracheoesophageal space
  - Subsequent trachealization of the undivided structure
- Similar to the outgrowth theory

Insult Theory:

- Esophageal atresia occurs secondary to an insult to the embryo
- Tracheoesophageal fistula grows from the trachea at the level of the lung buds to reconnect to the stomach
Clinical Presentation

• Prenatal finding of a small or absent stomach bubble with maternal polyhydramnios
• Most infants are symptomatic in the first few hours after the first feed

Fast Forward to Post Repair

Esophageal Stricture

• Incidence of anastomotic stricture post EA repair has varied in case series from as low as 9% to as high as 80%.
• Factors implicated in the pathogenesis of anastomotic stricture
  - anastomosis under excessive tension
  - ischemia at the ends of the esophageal pouches
  - two suture layers
  - use of silk suture material
  - esophageal gap length greater than 4 cm
  - post surgical anastomotic leak
  - post-operative gastroesophageal reflux
Symptoms

- feeding difficulties
- coughing and choking during feeds
- food impaction
- regurgitation of undigested material
- feeding refusal
- apnea

General Approach to Stricture Management

- Dilation Strategy: Routine vs. Symptomatic
- Studies in Type C esophageal atresia should
  - No difference in outcomes between routine dilation schedule vs. symptomatic dilations
- Symptomatic approach to dilation does not apply for patients with risk factors for stricture development

Types of Dilation

Balloon Dilation
Mechanical (bougie) Dilators
  - Savary-Gilliard
  - Maloney

Image copied from http://www.hopkins-pi.org
**Mechanical Dilation**

- Delivers both radial and longitudinal force from proximal to distal portion of the stricture
- Can be passed over a guidewire or freely into the esophagus

**Balloon Dilation**

- Delivers equal radial force *simultaneously* across the entire length of the stricture
- Can be done through the scope or over a wire

**EA Stricture Outcomes**

- Systematic review analyzed 5 studies that looked at outcomes of balloon dilation in children with esophageal atresia
  - 139 children with a total of 401 balloon dilation sessions
  - Reported success rate ranged from 70% to 100%
  - Approximately 3 dilations sessions per child
  - Reported perforation rate for the combined studies was 1.8%

**Treatments of Refractory Strictures**
- Intralesional Corticosteroid Therapy
- Stent Placement
- Mitomycin C
- Endoscopic Incisional therapy

**Congenital Esophageal Stenosis**
- Rare condition (1:25,000 to 50,000 births)
- Has been associated with other anomalies like EA (5% to 14%)
- Intrinsic stenosis of the esophagus caused by congenital malformation of esophageal wall
  - faulty tracheobronchial separation and/or differentiation
**Congenital Esophageal Stenosis**

- Three Types
  - Fibromuscular thickening (FMT) (54%)
  - Tracheo-bronchial remnants (TBR) (30%)
  - Membranous web (MW) (16%)

- Location of stenosis by type
  - FMT: middle or lower third of esophagus
  - TBR: lower third of esophagus
  - MW: upper or middle third of esophagus

**Presentation**

- Clinical Presentation
  - Progressive dysphagia and vomiting, generally after the introduction of semisolid or solid foods around the age of 6 months

- Diagnosis
  - Contrast study
  - Endoscopy: esophageal narrowing with normal appearing mucosa at the level of the stenosis
  - Endoscopic Ultrasound

**Endoscopic Ultrasound**

- Use of high frequency mini-probes (20MHz or 30MHz)
- Higher frequency increases resolution of mucosa and submucosa
- Used to identify cartilage of a TBR stenosis

**TBR** ideally managed by surgery rather than dilation due to high rate of perforation

Treatment

- Dilatation:
  - Balloon
  - Bougie
- Surgical resection (more challenging in EA)
- Endoscopic Incisional Therapy
- EUS can help stratify patients (systematic review)

- EUS group pooled studies
  - Success rate: 89.7% (n=68)
  - Perforation rate: 7.4% (n=68)
- Non-EUS pooled studies
  - Success rate: 28.9% (n=97)
  - Perforation rate: 23.9% (n=67)

Terui K et al. Endoscopic management for congenital... World J Gastro Endos 2015 March 16; 7(3):183-191

Incisional Therapy

Before and After
Endoscopic Incisional Therapy

- Successfully performed in 7 of 8 patients with congenital stenosis.
  - 6 FMT
  - 2 TBR
- All had diagnosis of Esophageal Atresia as well
- Unsuccessful case had TBR
- All had contained leaks
  - All had concomitant stenting to facilitate healing

Duodenal Atresia and Stenosis/Webs

Duodenal Atresia

- Developmental disorder of the proximal intestine that leads to a complete absence of the duodenal lumen
- Reported frequency ranges from 1:6,000 to 1:40,000
- Atresia is a complete obstruction
  - 3 types
- Stenosis: partial obstruction secondary to a fenestrated web or membrane
Types of Duodenal Atresia

- Type I (92%): complete membrane or web
  - Membrane: mucosal and submucosal tissue
- Type II (1%): proximal and distal ends blind joined by fibrous cord
- Type III (7%): proximal and distal blind ends have no connection with each other

Embryology

- Duodenal epithelial mucosa begins proliferating around the 4th week of gestation.
- 5th and 6th week
  - Proliferation obliterates the lumen
- Duodenal lumen start to recanalize
  - With appearance of vacuoles that open up the solid epithelial
  - The vacuolization coalesces and by end of the embryonic period and the duodenum is completely recanalized

Errors of the process

- Lead to occlusion
- Partial stenosis or web formation
- Third and fourth portion
- Webs under the pressure of peristalsis and food may form a pulsion-type diverticulum
Clinical Presentation and diagnosis

• Atresia – Most common type of atresia diagnosed in utero
  • Fetal double bubble sign
  • Bilious emesis
  • Double Bubble x-ray

Web Clinical Presentation

• Webs can present later in childhood and also into adulthood
• Symptoms include:
  • Nausea
  • Vomiting
  • Early satiety
  • Weight loss
  • Peptic ulcers
  • Pancreatitis

Diagnosis

• Upper GI shows:
  • Dilated duodenum with a radiolucent crescent shaped filling defect representing the wall of the web
• Endoscopy can be diagnostic and therapeutic
Treatment

• Surgical
  - Duodenoplasty
  - Duodeno-duodenostomy or duodeno-jejunostomy
• Endoscopic
  - Kay et al. in 1992 describe four cases of endoscopic laser ablation of duodenal webs in infants.
  - 25% success
  - 50% perforation

Treatment

• Endoscopic Therapy Techniques:
  - Described in case reports and series of 1 to 10 patients
    - Laser ablation
    - Hot Biopsy forcep
    - Snare
    - Balloon dilation
    - Spnicterotome
    - Needle knife
  - All series report minimal complications with good success

Endoscopic Web Therapy
Pancreas development

Pancreas Formation

- Originates from two endodermal buds that
  - arise from the caudal part of the foregut (duodenum)
  - Ventral bud
  - Dorsal bud
**Merging of two buds**
- ventral pancreatic bud
- Mouth of the common bile duct
- migrate posteriorly around the duodenum toward the dorsal mesentery
- Occurs during 6th week

[Video](https://www.youtube.com/watch?v=cBSyOgjTGVU)

**Pancreas**
- Ventral and dorsal pancreatic buds fuse to form the pancreas
  - Late in the sixth week
- Main pancreatic duct (of Wirsung)
  - Contains distal part of the dorsal pancreatic duct
- Entire ventral pancreatic duct

**Normal Pancreas**
- Proximal portion of the duct connecting the dorsal bud to the duodenum usually degenerates
  - The proximal dorsal duct may also persist as an accessory pancreatic duct (of Santorini)
  - Drains into the duodenum at a minor duodenal papilla
Pancreas divisum

• Pancreas divisum (PD) – most common congenital variant of the pancreas
  • Failure of embryological dorsal and ventral pancreatic duct fusion at 6-8 weeks gestation
  • Present in up to 7% of the population
    • Caucasian populations (4% to 10%)
    • Asian populations (1%-2%)

Pancreas divisum and Pancreatitis

• Pancreatic drainage occurs mainly through the minor papilla which is small and possibly stenotic
• Pancreatitis and/or chronic abdominal pain
  • May result from high intrapancreatic dorsal duct pressure
  • Poor drainage of dorsal duct

Pancreas Divisum Normal Variant?

• Clinical relevance of PD has been a matter of great debate
• More than 95% of patients with PD are asymptomatic
• Increased frequency of PD (12 – 26 %) in subjects with idiopathic pancreatitis
• Pancreas divisum has been reported in 7.4% of all children with pancreatitis
• 19.2% of children with acute relapsing or chronic pancreatitis
• However critics dispute this association
  • Don’t take into account genetics factors

Diagnosis

- Magnetic resonance cholangiopancreatography (MRCP)
  - Secretin improves ductal visualization during MRCP.
  - Prominent duct of Santorini passes anterior and cranial to the common bile duct.


ERCP

- Diagnosis of pancreas divisum is still usually made by endoscopic retrograde cholangiopancreatography (ERCP).
  - Involves cannulation of the minor papilla.
  - Best achieved with the endoscope pushed into the long position.
  - Tapered catheter of 5Fr or smaller.
  - Smaller guidewire (0.018- or 0.021-inch).

http://www.gastrohep.com

Treatment

- Endoscopic minor papilla sphincterotomy (papillotomy)
  - Initial dilation of the orifice to 5 to 7 Fr followed by cannulation with mini-papillotome or standard papillotome.
    - Generally wire-guided
    - 4 to 6 mm incision in approximately the 10 to 12 o’clock position.
  - Placement of a 3 to 4 Fr plastic stent
    - Followed by a needle-knife cut, generally in the 10 to 12 o’clock position to a depth of 3 to 4 mm and a height of 4 to 6 mm, using the stent as a guide.
Treatment

Systematic review of all case series and case control studies
- Twenty-two studies total of 838 patients
  - Acute Recurrent Pancreatitis: 76% mean response rate
  - Chronic Pancreatitis: 42% mean response rate
  - Chronic Abdominal Pain: 33% mean response rate


Treatment Response

Conclusion

- The endoscopist and not just the surgeon has a role in treatment of several congenital malformations
- These procedures are higher risk and should be performed by experienced endoscopists
  - Surgical back up should always be available
- With emerging endoscopic suturing technology we may see even more roles for endoscopy in these disorders in the future
Thank you
Pancreaticobiliary Maljunction

- Pancreaticobiliary maljunction (PBM) is a congenital anomaly defined as a junction of the pancreatic and bile ducts
  - located outside the duodenal wall
  - forming a markedly long common channel
- Pancreatic and bile ducts are joined outside the duodenal wall
  - Reduces the effect of the sphincter of Oddi
  - continuous reciprocal reflux between pancreatic juice and bile occurs
  - resulting in various pathologic conditions in the biliary tract and pancreas
  - Hydrostatic pressure within the pancreatic duct is usually greater than that in the bile duct, pancreatic juice frequently refluxes into the biliary duct in PBM
Main pancreatic duct and the common bile duct meet and empty their secretions into the duodenum at the major duodenal papilla or ampulla of Vater.

Anomalous pancreaticobiliary junction (pancreaticobiliary maljunction) occurs when the union of the main pancreatic duct and common bile duct occurs before the ducts enter the duodenal wall.

Appearance of anomalous pancreaticobiliary junction is confirmed at ERCP through identifying a long common channel (>15 mm) between the duct of Wirsung and common bile duct.
Refractory Strictures

- No uniform definition
- Definition is important to truly evaluate new treatment techniques
- Proposed definition:
  - Inability to successfully remediate the lumen to a diameter of 14mm over 5 session at two week intervals.
  - Inability to maintain a lumen patency for 4 weeks once the target diameter of 14 mm has been achieved

Treatments of Refractory Strictures

- Intralesional Corticosteroid Therapy
- Stent Placement
- Mitomycin C
- Endoscopic Incisional therapy
**Intralesional Corticosteroid Therapy**

- **Proposed mechanism:**
  - Local inhibition of inflammatory response resulting in reduced collagen formation
- **Multiple studies have shown effect in reducing recurrent stricture formation**
  - Most small uncontrolled studies
  - Strictures of diverse etiology
  - Prospective study in peptic strictures
- **Hirdes et al.:** double-blind placebo control trial (n= 60) adults with benign esophagogastric anastomotic strictures
  - No statistically significant decrease in frequency of repeat dilations: corticosteroid group: median dilations 2 (range, 1-7) vs. control group 3 dilations (range, 1-9) (p = 0.36)

**Questions:**

- **Type of Steroid**
  - triamcinolone acetate
- **Dose of Steroid**
  - 10mg/ml administered in four quadrants in 0.1 to 0.2ml aliquots
  - No standard pediatric dosing (1-2mg/kg)
- **Number of injection sessions**
  - Limit to three
- **Injection technique**
  - Pre or Post dilation

**Potential Complications**

- Adrenal suppression
- Candida esophagitis
- Delayed esophageal perforation
- Spontaneous rupture of the right aortic arch
Esophageal Stenting

Dilating the esophagus for prolonged periods of time
- may reduce the risk of recurrent stricture formation
- may be an alternative treatment option to serial esophageal stricture dilations

Two types of stents for temporary placement

Types of Stents

- Self Expanding Plastic Stents (SEPS)
- Fully Covered Self Expanding Metal Stents (FCSEMS)

Adult Stent Literature for Benign Strictures

<table>
<thead>
<tr>
<th>Author</th>
<th>Stent Type</th>
<th>n</th>
<th>Reported Success*</th>
<th>Population</th>
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<td>SEPS</td>
<td>15</td>
<td>80%</td>
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<td>Dua (2008)</td>
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<td>38</td>
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<td>Barthel (2008)</td>
<td>SEPS</td>
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<td>12%</td>
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<td>Fiorini (2001)</td>
<td>FCSEMS</td>
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<td>Kim (2008)</td>
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<td>Bakken (2010)</td>
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* Reported success defined as no recurrent stricture
Pediatric Stent Literature

<table>
<thead>
<tr>
<th>Author</th>
<th>Stent Type</th>
<th>n</th>
<th>Reported Success*</th>
<th>Population</th>
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<tr>
<td>Broto (2003)</td>
<td>SEPS</td>
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<td>Zhang (2005)</td>
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<td>75%</td>
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<td>Best (2009)</td>
<td>FCSEMS</td>
<td>7</td>
<td>86%</td>
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* Reported success defined as no recurrent stricture

Esophageal Stenting

• 23 patients with EA underwent a total of 40 stenting sessions.
  • SEPS (n =14) and FCSEMS (n=26)
  • Procedural success was defined as requiring no additional therapy after stent removal at ≥30 days and at ≥90 days.
  • Stricture resolution for ≥30 days after final stent removal was 39% (9/23)
  • 90 day success rate of 26% (6/23)

Esophageal Stenting

• Mean duration of stent placement was 9.7 days (2 to 30 days)
  • Complications of stent placement included migration (21% of SEPS and 7% of FCSEMS)
  • Granulation tissue (37% of FCSEMS and 0% of SEPS)
  • Deep tissue ulcerations (22% of FCSEMS and 0% if SEPS)
  • Pain and retching (26% of FCSEMS and 23% of SEPS)
Mitomycin C

- Antineoplastic agent
  - disrupts base pairing of DNA molecules
  - inhibits fibroblast proliferation and induces apoptosis in higher doses
- Has been used as an antiproliferative agent since the 1980’s in ophthalmology
- Long term effect on the esophagus is unknown

Topical Mitomycin C

- **Questions:**
  - Dose: range from .004mg/ml to 1mg/ml
    - .4mg/ml at our institution
  - Frequency of applications and limit
    - Unknown however it appears safe to have multiple applications
  - Technique
    - Topical with soaked pledget: care must be given to contact scar tissue only therefore placed with use of overtube, friction fit cap, rigid scope

Topical Mitomycin C

Technique

- Alternatively dripped on mucosa with sclerotherapy needle or placed with ERCP double lumen cytology brush

Length of time

- The drug is applied for 2 to 5 minutes

Irrigate or not Irrigate with saline

- No consensuses at our institution we irrigate the area after application to minimize any potential toxicity
Mitomycin C

<table>
<thead>
<tr>
<th>Author</th>
<th>No of patients</th>
<th>Conc of MMC used</th>
<th>Exposure time of MMC (min)</th>
<th>Success rate**</th>
<th>Complications</th>
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<td>None: 18.7%</td>
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<tr>
<td>Afzal et al., 2002</td>
<td>1</td>
<td></td>
<td></td>
<td>100%</td>
<td>None</td>
</tr>
</tbody>
</table>

**Defined as no recurrent stricture or decrease dilation frequency

Chapuy L et al. Mitomycin-C application… Journal of pediatric gastroenterology and nutrition 2014;59:608-11

Mitomycin C

- Majority of success has been in caustic strictures
- Anastomotic strictures have shown less promising results

Potential Complications
- Hypothetical risk of secondary malignancy with Mitomycin C
- Reports of de novo gastric metaplasia around the areas of the anastomosis in 2 of the 6 cases that received topical mitomycin C

Endoscopic electrocautery incisional therapy (EIT)

- Involves the use of a needle knife to make incisions into a stricture at its most dense points.
- Electrosurgical generator (ERBE) applies a cut current to make the incision
- After the incision, a dilation balloon is inflated to allow preferential tearing where the incision was made.
Incisional Therapy

- Use needle knife cautery in order to make radial cuts into the stricture
- Use ERBE cut settings of 100 to 200W
- Considered in refractory anastomotic strictures
### EIT Procedural Success Rate

<table>
<thead>
<tr>
<th>Stricture Category</th>
<th>6 month EIT success rate n/n (%)</th>
<th>12 month EIT success rate n/n (%)</th>
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<tr>
<td>Non-Refractory</td>
<td>14/15 (93%)</td>
<td>14/15 (93%)</td>
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<tr>
<td>Refractory</td>
<td>15/18 (83%)</td>
<td>16/18 (89%)</td>
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<tr>
<td>Severe Refractory</td>
<td>7/12 (58%)</td>
<td>6/12 (50%)</td>
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</table>

Overall procedural success at 6 months n/n (%): 36/45 (80%)

Overall procedural success at 12 months n/n (%): 36/45 (80%)