




# EMBRYOLOGY MEETS ENDOSCOPY:

## THE ROLE OF ENDOSCOPY IN CONGENITAL GASTROINTESTINAL MALFORMATIONS

Michael A Manfredi, MD  
 Co-Director Esophageal Atresia Treatment Center  
 Boston Children's Hospital  
 Harvard Medical School

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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

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### Embryology

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

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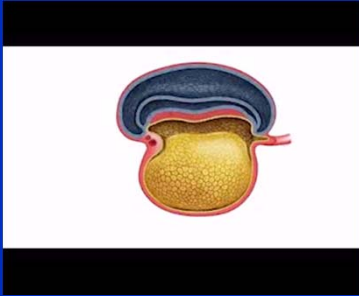
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## Gut Development



<https://www.youtube.com/watch?v=yXUv4MPuNTA>

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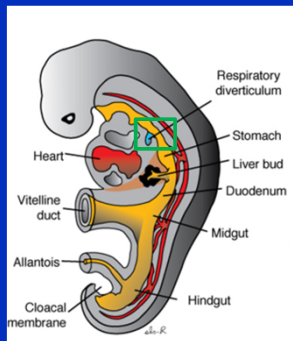
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## Gut Development




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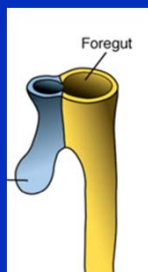
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## Normal Esophageal Development

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




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## 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

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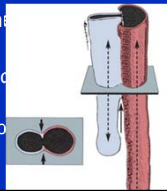
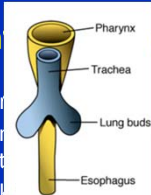
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## Mesenchymal Septum Formation

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




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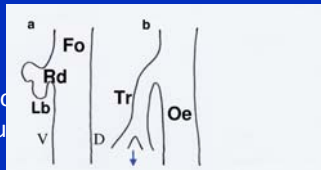
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- respiratory diverticulum (RD) forms as a rapid outpocketing of the foregut tube
- later completely detaches from the foregut during the subsequent stages of development
- esophagus is formed following the rapid downward (caudal) growth of the trachea and bronchopulmonary structures




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- Movement of the foregut
  - Laryngeal folds
  - Tracheal folds
  - Pharyngeal folds
- Caudal movement of the laryngeal folds
- cranial movement of the tracheal folds
  - results in separation of the trachea and esophagus
  - Dorsal esophagus
- longitudinal movement of the pharynx and esophagus

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### Gross Classification of Esophageal Atresia

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

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Based on the following:

- tracheal arrest

- 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

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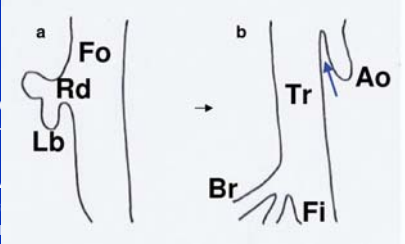
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Based on Foregut fold Theory:

- tracheal fundus grows out from the foregut
  - Branches form the bronchi
  - 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




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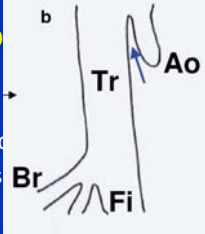
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### Abnormal Embryology

Based on foregut fold Theory:

- Abnormal movement of the foregut
  - Failed division of the tracheoesophagus
- subsequent trachealization of the undivided structure
  - Similar to the outgrowth theory




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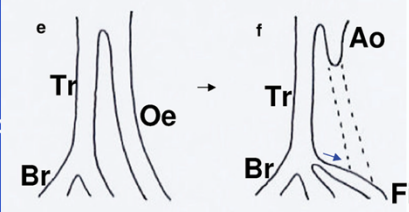
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Insult

- Esophageal atresia
  - a tracheoesophageal fistula
- Tracheoesophageal fistula grows from the trachea at the level of the lung buds to reconnect to the stomach




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# Clon

- Preoperative
- Postoperative
- First
- Second
- Third
- Fourth
- Fifth
- Sixth
- Seventh
- Eighth
- Ninth
- Tenth
- Eleventh
- Twelfth
- Thirteenth
- Fourteenth
- Fifteenth
- Sixteenth
- Seventeenth
- Eighteenth
- Nineteenth
- Twentieth
- Twenty-first
- Twenty-second
- Twenty-third
- Twenty-fourth
- Twenty-fifth
- Twenty-sixth
- Twenty-seventh
- Twenty-eighth
- Twenty-ninth
- Thirtieth
- Thirty-first
- Thirty-second
- Thirty-third
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- Thirty-fifth
- Thirty-sixth
- Thirty-seventh
- Thirty-eighth
- Thirty-ninth
- Fortieth
- Forty-first
- Forty-second
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- Forty-fourth
- Forty-fifth
- Forty-sixth
- Forty-seventh
- Forty-eighth
- Forty-ninth
- Fiftieth
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- Fifty-fourth
- Fifty-fifth
- Fifty-sixth
- Fifty-seventh
- Fifty-eighth
- Fifty-ninth
- Sixtieth
- Sixty-first
- Sixty-second
- Sixty-third
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- Sixty-fifth
- Sixty-sixth
- Sixty-seventh
- Sixty-eighth
- Sixty-ninth
- Seventieth
- Seventy-first
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- Eightieth
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- Eighty-sixth
- Eighty-seventh
- Eighty-eighth
- Eighty-ninth
- Ninetieth
- Ninety-first
- Ninety-second
- Ninety-third
- Ninety-fourth
- Ninety-fifth
- Ninety-sixth
- Ninety-seventh
- Ninety-eighth
- Ninety-ninth
- One hundred

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# Fast Forward to Post Repair

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# 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

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## Symptoms

- feeding difficulties
- coughing and choking during feeds
- esophageal stricture is defined as an intrinsic food impaction
- luminal narrowing that leads to the patient regurgitation of undigested material
- feeding refusal
- apnea

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## 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

Koivusalo A et al., Is Routine Dilatation After Repair of Esophageal Atresia With Distal...*Journal of Pediatric Surgery*, Vol 39, No 11, 2004; pp 1643-1647

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## Types of Dilation

Balloon Dilation

Mechanical (*bougie*) Dilators

- Savary-Gilliard
- Maloney



Image copied from <http://www.hopkins-gi.org>

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## 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



Image copied from <http://www.hopkins-gi.org>

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## Balloon Dilation

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



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## 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%

Thivoka M. *et al.* Balloon dilation of anastomotic strictures. *Pediatric radiology* 2013;43:808-901

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### Treatments of Refractory Strictures

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

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### Congenital Esophageal Stenosis

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### 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

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## 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

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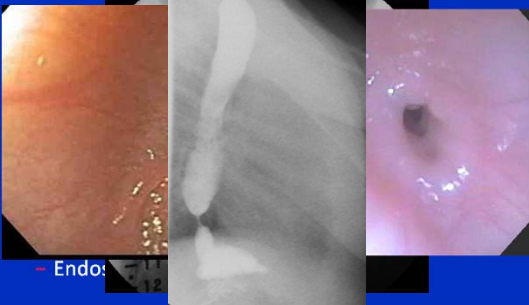
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## Presentation



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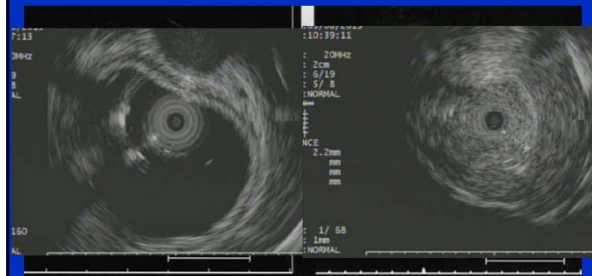
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## Endoscopic Ultrasound



Usui N, et al. Usefulness of Endoscopic Ultrasonography. JPed Surgery, Vol 37, No 12, 2002: 1744-1746

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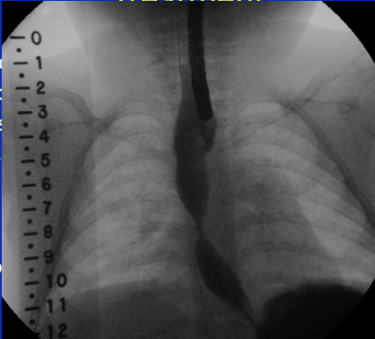
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### Treatment

- Dilatation
- Surgery
- Endoscopy
- EUS guided
- EUS guided
- No
- No



ew)

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

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### Incisional Therapy




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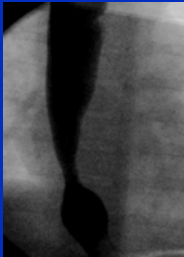

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### Before and After

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## 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

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## Duodenal Atresia and Stenosis/Webs

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## 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

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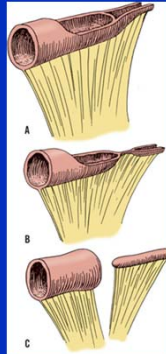
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## Types of Duodenal Atresia

- 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




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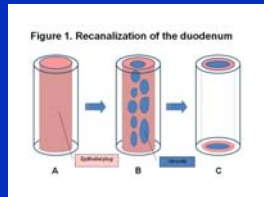
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## Embryology

- Duodenal epithelial mucosa begins proliferating around the 4<sup>th</sup> week of gestation.
- 5<sup>th</sup> and 6<sup>th</sup> 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

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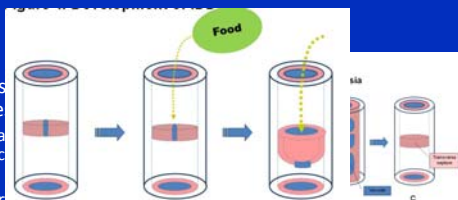
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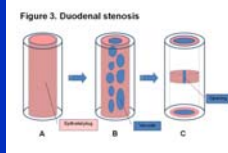
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- Errors in the recanalization process
  - Leads to duodenal atresia
  - Partial duodenal stenosis or web formation
    - Third and Fourth portion



- Webs under the pressure of peristalsis and food may form a pulsion-type diverticulum




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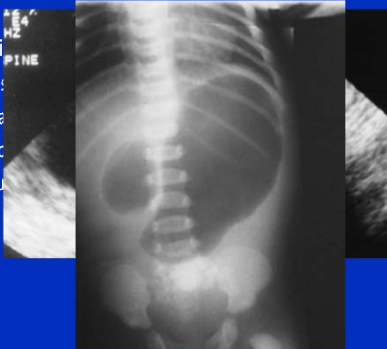
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## Clinical Presentation and diagnosis

- Atresia
  - Most common
  - Fetal
  - Bilirubin
  - Double



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## Web Clinical Presentation

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

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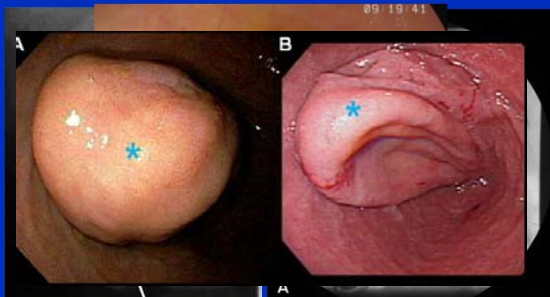
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## Diagnosis



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## 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

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## Treatment

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

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## Endoscopic Web Therapy



DiMaio C, et al. Pediatric therapeutic endoscopy: endoscopic management...GASTROINTESTINAL ENDOSCOPY Volume 80, No. 1 - 2014

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## Pancreas

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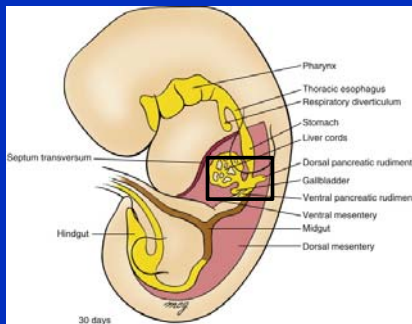
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## Pancreas development




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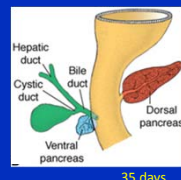
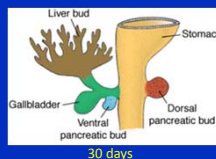
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## Pancreas Formation

- Originates from two endodermal buds that
  - arise from the caudal part of the foregut (duodenum)
  - Ventral bud
  - Dorsal bud




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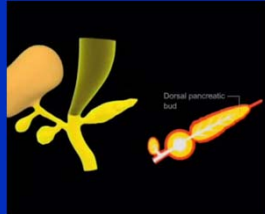
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## Merging of two buds

- ventral pancreatic bud
- Mouth of the common bile duct
- migrate posteriorly around the duodenum toward the dorsal mesentery
- Occurs during 6<sup>th</sup> week



<https://www.youtube.com/watch?v=c8SyOgiTGVU>

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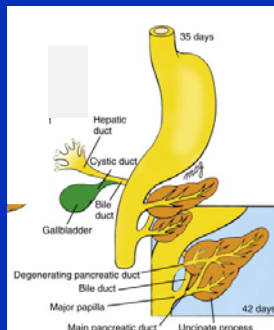
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## Pancreas

- 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




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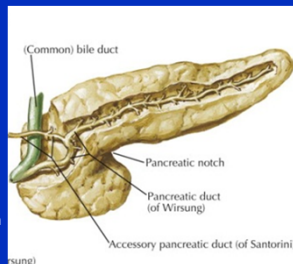
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## Normal Pancreas

- 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




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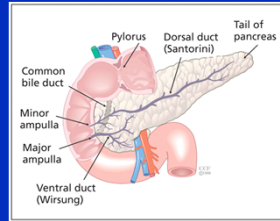
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## Pancreas divisum

- 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

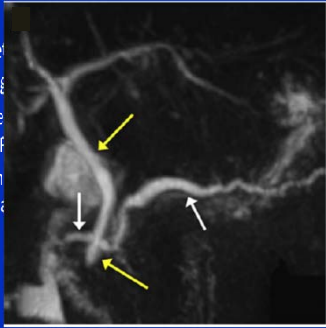
## Pancreas Divisum Normal Variant?

- 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

Nebblett W et al. Surgical management of recurrent pancreatitis...Ann Surg. 2000 Jun;231(6):899-908

## Diagnosis

- Magnetic resonance cholangiopancreatography (MRCP)
  - Secretin-enhanced MRCP
  - prominent cranial loop



Alexander LF. Congenital Pancreatic anomalies...Radiol Clin N Am 50 (2012) 487–498

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## ERCP

- Diagnosis of pancreas divisum is still usually



- Tapered catheter 5fr or smaller
- Smaller guidewire (0.018- or 0.021-inch)

<http://www.gastrohep.com>

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## 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

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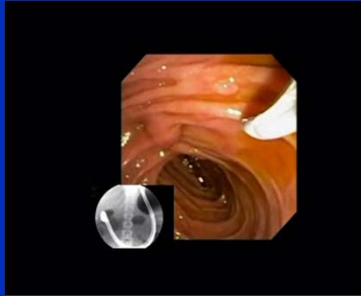
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## Treatment



Sepe: <http://youtube.com/watch?v=hwQglFO8gOY>

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## Treatment Response

- 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

Kanth R, et al. Endotherapy in symptomatic pancreas divisum...Pancreatolgy 14 (2014) 244e250

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## 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

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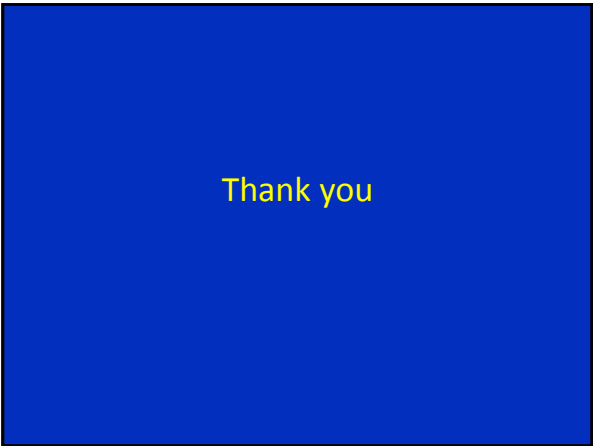
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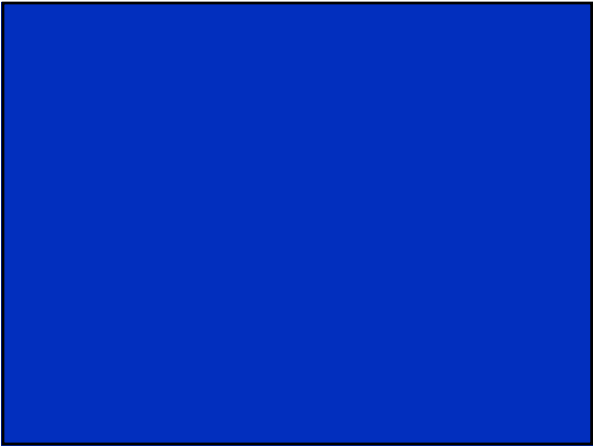
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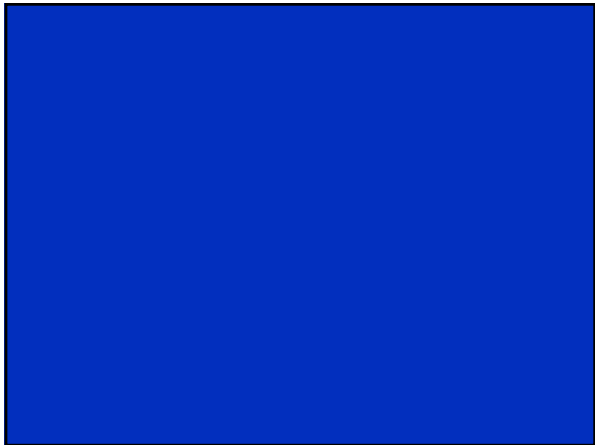
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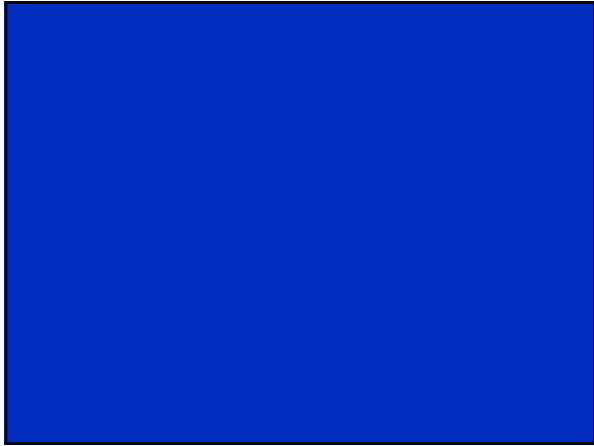
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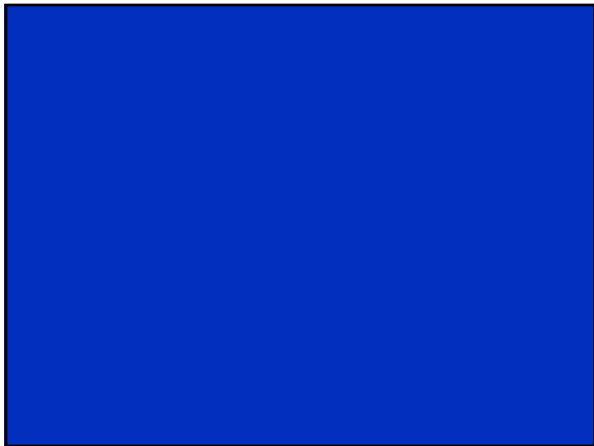
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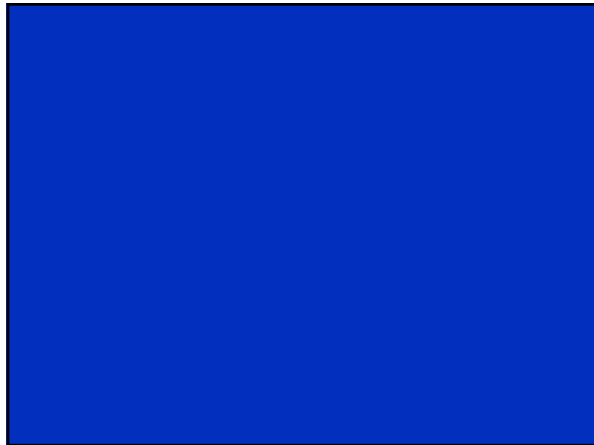
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## Pancreaticobiliary Maljunction

- 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
  - Hydropressure within the pancreatic duct is usually greater than that in the bile duct, pancreatic juice frequently refluxes into the biliary duct in PBM

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- 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

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- 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

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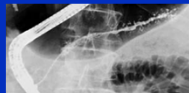
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### Refractory Strictures

- 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

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### Treatments of Refractory Strictures

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

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## 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).

Hirdes et al. Endoscopic corticosteroid injections...journal of the American Gastroenterological Association 2013;11:795-801

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## Intralesional Corticosteroid Therapy

### 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

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## Intralesional Corticosteroid Therapy

- Potential Complications
  - Adrenal suppression
  - Candida esophagitis
  - Delayed esophageal perforation
  - Spontaneous rupture of the right aortic arch

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## 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

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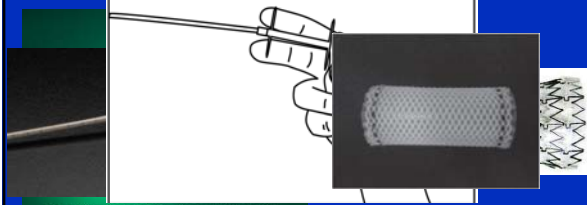
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## Types of Stents

- Self-expanding stents
- Fully covered self-expanding stents (FCSEMS)



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## Adult Stent Literature for Benign Strictures

Author	Stent Type	n	Reported Success*	Population
Repici (2004)	SEPS	15	80%	mixed
Dua (2008)	SEPS	38	32%	mixed
Barthel (2008)	SEPS	8	12%	anastomotic
Pennathur (2008)	SEPS	9	22%	mixed
Fiorini (2001)	FCSEMS	10	50%	mixed
Kim (2008)	FCSEMS	55	33%	mixed
Bakken (2010)	FCSEMS	10	20%	mixed

\* Reported success defined as no recurrent stricture

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## Pediatric Stent Literature

Author	Stent Type	n	Reported Success*	Population
Broto (2003)	SEPS	10	50%	caustic
Zhang (2005)	FCSEMS	8	75%	caustic
Best (2009)	FCSEMS	7	86%	mixed

\* 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)

Manfredi MA et al. The use of a retrievable self-expanding stent...Gastrointestinal endoscopy 2014;80:246-52

## 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

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## 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

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## 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 consensus at our institution we irrigate the area after application to minimize any potential toxicity

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## Mitomycin C

Author	# of patients	Conc of MMC used	Exposure time of MMC (min)	Success Rate**	Complications
Rosseneu et al, 2007	16	0.1 mg/ml - 0.3mg/ml	Range: 2-5	Major: 62.5 %; Partial: 37.7%; None: 18.7%	None
Uhlen et al, 2006	4	1mg/ml	2	100 %	None
Heran et al, 2008	2	0.1mg/ml	1	100%	None
Chung et al, 2010	2	0.1 mg/ml	3	100%	None
Olutoye et al, 2006	1	4 micrograms/ml	1	100%	None
Afzal et al, 2012	1	0.1 mg/ml	2	100%	None

\*\*Defined as no recurrent stricture or decrease dilation frequency

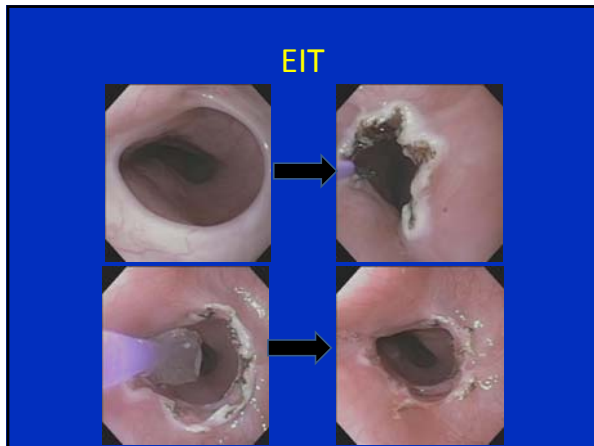
Chapuy L et al. mitomycin-C application...Journal of pediatric gastroenterology and nutrition 2014;59:608-11

## Mitomycin C

- 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.




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### 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

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### Incisional Therapy




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## EIT Procedural Success Rate

Overall procedural success at 6 months n/n (%)	36/45 (80%)	
Overall procedural success at 12 months n/n (%)	36/45 (80%)	
Stricture Category	6 month EIT success rate n/n (%)	12 month EIT success rate n/n (%)
Non-Refractory	14/15 (93%)	14/15 (93%)
Refractory	15/18 (83%)	16/18 (89%)
Severe Refractory	7/12 (58%)	6/12 (50%)

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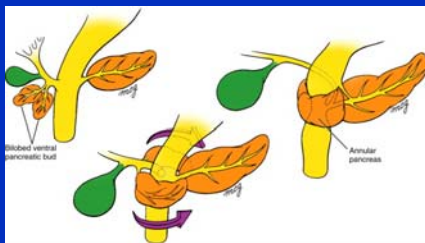
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