Disorder	Etiology *and* Epidemiology	Pathophysiology *and* Presentation	DIAGNOSIS *and* DIFFERENTIAL	Treatment
GUT DEVELOPMENTAL DISORDERS				
ABDOMINAL WALL DEFECTS	**Omphalocele** Midline defect (at umbilicus) Major chromosomal anomalies Trisomy 13, 18, 21 Associated with *cardiac structural anomalies* **Gastroschisis** Lateralized defect (away from umbilicus) Associated with *intestinal atresia* Non-GI anomalies are RARE	**Omphalocele** The bowel and peritoneum are covered by a midline membranous sac **Gastroschisis** The bowel is not covered by a sac Foreshortened bowel Intestinal atresia **BOTH**: associated with gut malrotation and midgut volvulus		
ESOPHAGEAL ATRESIA and TRACHEOESOPHAGEAL FISTLAE	Polyhadamnios in 50% of mothers Associated with gestational estrogen and progesterone May been seen in VACTERL syndrome (50 – 70%) Associated with hypospadias, undescended testes, duodenal atresia, hydrocephalus	There are 5 anatomic variants 80 – 90%: blind upper esophageal pouch + lower TEF 10%: two terminal pouches (upper, lower) without TEF These anomalies present earlier due to non-communication between the oral pharynx and the stomach		
DUPLICATIONS	Typically occur as isolated anomalies **Meckel Diverticulum** Incidence is 2% < 2' from iliocecal valve Ectopic gastric or pancreatic mucosa Mostly symptomatic if < 2 yrs	**COMPLICATIONS** Obstruction, ulceration, pain, GI bleeds, perforation, fistulae **Intestinal** Mostly in the ileum (50%) Located on mesenteric side of bowel; common blood supply The histologic layering is similar to that of normal alimentary tract		Surgical excision

		Gastric (5 – 7%) Cystic entities on the greater curvature Non-communicating **Duodenal** (<6%) Typically cystic Non-communicating 10 – 15% with ectopic gastric mucosa → ulceration and bleeding May present with bowel obstruction **Colorectal** Higher incidence of constipation, obstruction, volvulus Associated with GU malformation DDx: prolapsed rectum, hemorrhoids, perirectal abscess, fistulae Prone to malignant transformation **Meckel Diverticulum** Derived from the omphalomesenteric duct May result in massive lower GI bleeding due to autodigestion by ectopic pancreatic mucosal secretions		
MALROTATION OF THE SMALL BOWEL	Universally associated with gastroschisis ad omphalocele	*Bilious vomiting*, abdominal pain **Nonrotation** The most common defect Cecum to left of SMA Small bowel of right of SMA Results in narrowed mesentery → strangulation of the SMA ostium → midgut ischemia Midgut volvulus due to non-fixation		Laprotomy
ESOPHAGEAL FOREIGN BODY		**Presentation** Dysphagia, wheezing, hoarseness, anorexia, drooling	Neck X-ray	

		Common sites of occlusion Cricopharyngeal complex (UES) Impression of aortic arch LES		
CAUSTIC ESOPHAGEAL INJURY	Occur in peds < 5 yrs	Alkaline agents produce deeper and more severe necrosis Acids cause damage in the stomach and duodenum Necrosis and perforation are acute sequelae	Endoscopy 24 – 28 hrs after ingestion	Prevent structures Feeding, steroids, ABx, stenting, dilatation, esophagectomy
PYLORIC STENOSIS	6 – 8 : 1000 live briths 4:1 male predominance Most common obstruction in infancy	Regurgitation and forceful emesis at 3 – 6 wks Dehydration, FTT *Hypochloremic hypokalemic metabolic alkalosis* Malnourishment Visible gastric peristalsis	U/S Upper GI X-ray	Pyloromyotomy
INTUSSESCEPTION	Occurs between 2 mos – 5 yrs Peak incidence at 4 – 10 mos. Second leading cause of obstruction in infants	Abdominal colic with periods of apathy Pallor Vomiting Currant-jelly stool If ilio-cecal: sausage-like mass in RUQ The bowel is insinuated into itself Typically **ileo-colic** without obvious lead point May be due to hypertrophic Peyer's patches, Meckel diverticulum, intestinal polyp, duplication, hemangioma (HSP, hemophilia), CF with inspissated stool,	U/S Contrast enema	Rehydration Decompression Surgical excision Contrast enema Pneumatic reduction
DUODENAL ATRESIA	1:5000 live births Associated with: Trisomy 21, esophageal atresia, malrotation,	Vomiting immediately after birth Obstructed Ampulla of Vater		Gastric decompression Duodeno-duodenostomy

	cardiac anomalies			
JEJUNO-ILEAL ATRESIA	Due to ischemic infarct of distal small bowel	Bilious vomiting after birth Abdominal distension There are four variants of J-I ATRESIA I: continuous II: continuous with mesenteric defect IIIA: solitary atresia with mesenteric defect IIIB: solitary atresia and spiraled blind ilium IV: multiple atresias		Resection
HIRSCHPRUNG DISEASE	Most common cause of lower GI obstruction in neonates Due to absence of enteric neurons, extending proximally from the anus 75% of cases limited to rectum and sigmoid colon Associated with congenital heart disease, Down Syndrome	Results in megacolon		
OROPHARYNGEAL DYSPHAGIA				
OROPHARYNGEAL DYSPHAGIA	**Neurologic**: stroke, PD, neoplasm, TBI **Systemic**: arthritis, DM, polymyositis, scleroderma, Sjogren's, AIDS **Iatrogenic**: meds, XRT, chemoTx, surgery **Obstruction/Anatomic:** cervical	**Presenting Symptoms** *Oropharyngeal Dysphagia without aspiration* Drooling, oral residue, difficultly with mastication, bolus sensation, anorexia, aversion to food, changes in eating habits, expectoration, weight loss, coughing *Aspiration* Coughing with meds or postprandial Increased secretions	**Videofluoroscopic Swallow Study (VSS)** Analysis of bolus transport Real-time analysis or treatment response **Esophogram** Endoscopy Can only visualize structure in static state due to obliteration of view while swallowing Manometry U/S Scientography	Technique Modification e.g. chin tuck, supraglottic swallow, vocal cord adduction head turn Postural modification Dietary modification Textural alternation (solid and liquid) Lingual exercises

	osteophytes, H/N tumor, esophageal structures, diverticulae **Psychiatric**: dementia **General deconditioning** due to underlying medical condition **Risk Groups** Infants: prematurity, congenital syndromes Peds: cerebral palsy, TBI Adults: age	Gurgling voice Pneumonia *Silent Aspiration* Due to pathology of the sup. laryngeal nerve OR profoundly diminished cognition OR Stroke in R parietal cortex: results in anosognosia and neglect of aspiration + depressed cough reflex **Complications** Dehydration, pneumonia, mortality, decreased rehabilitation potential, decreased QoL, malnutrition	CT, MRI	**Medical Therapy** If secondary to GERD: H2 inhibitors, PPIs, Antacids Also, TX underlying Dz e.g. L-DOPA in PD **Surgery** Correction of glottis insufficiency NG tube Prostheses for velar insufficiency

ESOPHAGEAL DYSPHAGIA

General Features

The FOREMOST priority in assessment of esophageal dysphagia is R/O mechanical obstruction
- Strictures, external neck mass, intrinsic tumor, rings, foreign body, esophagitis

The NEAR-OCCLUSION SIGNS of esophageal blockage
- Weight loss, nutritional deficiencies, dehydration, difficulty handling medication, pain

In SPASTIC DISORDERS: the EDG and esophagram may be NML, since pathology is functional

In terms of prevalence: Nutcracker esophagus > Non-specific Inefficient Motility > DES > Hypertensive LES > Achalasia

ACHALASIA	Lowest prevalence amongst the esophageal dysphagias	**Pathogenesis** Unknown etiology Results in loss of enteric neurons from the LES and proximally Degeneration of the Vagus nerve Degeneration of the DMN Decreased intramuscular efferent nerve	**Barium Esophagram** Loss of the peristaltic wavefront Bird's beak LES Dilated esophageal body **Manometry** Hypertensive LES	CCB, Nitrates, Anticholinergics Botulinum toxin injection into LES Myotomy with fundoplication

		density **Main findings**: incomplete relaxation of LES, hypertonic LES, aperistalsis, low-amplitude simultaneous contractions Dilation of esophageal body **Presenting Symptoms** Regurgitation of undigested food Chest pain Weight loss Nocturnal regurgitation with aspiration Pyrosis due to fermentation and production of lactate	Incomplete relaxation of the LES Aperistalsis Hypertensive esophageal body Low-amplitude simultaneous contractions **DDx** Tumor of the gastric cardia Chagas' disease Amyloidosis Post-XRT Severe esophageal stricture	Endoscopic pneumatic dilation **Dietary**: small and frequent meals, semi-liquid foods, latency before reclining, PEG tube
DIFFUSE ESOPHAGEAL SPASM	May degenerate into achalasia : 10% conversion rate	Simultaneous series of contractions occurring > 30% of swallows Requires intermittent episodes of dysphagia with periods of normal deglutition LES incoordination	**Manometry** Sequences of simultaneous contractions alogn length of esophagus **Esophagram** Undulating esophagus with pockets of barium	**Tx acid reflux**: empiric therapy for all patients presenting with dysphagia dueto dysmotility
NUTCRACKER ESOPHAGUS		Main symptoms: chest pain upon swallowing Normally sequenced peristalsis with high-amplitude (> 180 mmHg) contractions Increased contractile duration (> 6 s) LES retains NML function but may be hypertensive Dysphagia is rare due to normal peristaltic program	**Manometry** Possibly hypertensive LES High amplitude contractions (> 180 mmHg) Increased duration (> 6s) Normal peristaltic propagation	CCBs, Nitrates, Tricyclics, Boltulinum toxin, PDE inhibitors, L-arginine Long tract myotomy

HYPERTENSIVE LES		Presents as intermittent dysphagia High LES resting pressure (> 40 mmHg) Spastic (hypercontractile) LES after relaxation NML relaxation and peristalsis	LES pressure > 40 mmHg Spastic LES	
NON-SPECIFIC INEFFICIENT ESOPHAGEAL PERISTALSIS				
SECONDARY ESOPHAGEAL DYSMOTILITY	Secondary to Scleroderma, neuromuscular disorders (MG, MS), Chagas, age			
REFLUX				
GASTROESOPHAGEAL REFLUX DISEASE (GERD)	**Complications** *Peptic structures* Located at the GEJ May lead to solid dysphagia Occur in 25% of GERD Precursor lesion is the Shatzke ring *Bleeding* Hematemesis, melena, iron deficiency anemia *Barrett's Esophagus* Intestinal metaplasia with conversion of squamous epithelium to columnar form Incidence is 10% amongst GERD patients *Erosive esophagitis* *Esophageal ulceration*	**Classic Diad of Symptoms** Heartburn (pyrosis) + Reflux PPV > 90% *Other presentations* Regurgitation: the acid brash Increased salivation Chest pain: mimics cardiac angina Asymtomatic **Atpyical GERD** Asthma Chronic cough and hoarseness Non-anginal chest pain Hiccoughs Night sweats Deteriorating dentition	Clinical Dx (pyrosis, reflux) **Gold standard**: upper GI endoscopy and Bx Esophogram 24-hr pH recording Impedence plethysmography	**Behavioral Modifications** Elevate head during sleep Smoking cessation Decrease EtOH Reduced fat intake Portion control CI: anticholinergics, BZs, theophylline, CCBs, opioids **Medical Therapy** Antacids H2 receptor antagonists PPIs **Surgical** Nissen Fundoplication Barrett's: Biannual endoscopy to monitor for progression to

	Adult-onset asthma Laryngitis and hoarseness Chronic cough Chest pain Recurrent pneumonia Loss of dental enamel **Provocative Factors** EtoH, caffeine, chocolate, citrus, fat, spices, carbonated drinks, smoking Pregnancy, bending/lifting, meals before sleeping,	**Pathogenesis** May be due to failure of any element in the reflux barrier Main determinant: dysfunctional LES Transient LES relaxation results in initial acid reflux and inflammatory degeneration → leads to increasing sphincter insufficiency TLESRs due to: gastric distension, stress, posture, sleep, pharyngeal stimulation Other causes: hiatal hernia Injury is exacerbated by: ineffective peristalsis, decreased bicarbonate secretion, other caustic ingredients of the refluxate (bile salts, pepsin)		adenocarcinoma
BARRETT'S ESOPHAGUS	Intestinal metaplasia of the esophageal mucosal epithelium			
SQUAMOUS CELL CARCINOMA of the **ESOPHAGUS**	Malignant transformation of the squamous epithelium of the upper esophagus Most common cancer in Asia **RF:** smoking, EtOH, pickled foods, smoked foods, caustic trauma, H/N cancers, Plummer-Vinson Syndrome Tylosis palmaris/plantaris	**Presentation** Dysphagia, GERD, back pain (thoracic), upper GI bleeding, weight loss		
ADENOCARCENOMA of the **ESOPHAGUS**	Most common esophageal cancer Most rapid increase in incidence amongst solid tumors Located at the GEJ **RF:** GERD, Barrett's, middle aged,	**Presentation** Dysphagia, GERD, back pain (thoracic), upper GI bleeding, weight loss **Natural History**	**STAGING** Physical exam for mets to supraclavicular nodes, liver, lungs PET/CT of chest and abdomen for mets Endoscopic U/S + FNA	If Dx via symptoms: Tx is palliative due to poor outcomes **Early**: definitive surgery alone (endoscopic resection)

	Caucasian, male gender, obesity Tobacco (weak associatation) Recurrence due to occult lymphatic spread	Survival at 5 yrs is 12%		**Advanced**: XRT, chemoTx, surgery **Metastatic**: stenting, tumor ablation, PDT, palliative XRT and chemoTx *Surgery*: esophagectomy with gastric pull *ChemoTx*: 5-FU
GASTRIC DYSMOTILITY				
GASTROPARESIS	**Chronic** Delayed Gastric Emptying **Etiologies** DM (20 – 30%; typically insulin-dependent; leading cause) Due to visceral neuropathy incurred during chronic hyperglycemia Idiopathic Upper GI surgery Eating Disorders Scleroderma CKD Amyloidosis Muscular Dystrophy Hypothyroidism PD Medications: anticholinergics, CCBs, opioids, CCBs. Nitrates, PDE	**Pathogenesis** Dysfunction of neurons in the gastric enteric plexus Disruption of the vagus verve Loss of myenteric inhibitory nerons Loss of ICCs Increased serum glucagon Acute hyperglycemia may result in transient gastroparesis **Presenting Symptoms** Nausea, anorexia, fullness, vomiting, weight loss, retained food bolus (bezoar)	**Gastric Emptying Study** Ingestion of radiolabeled scrambled eggs and detection of tracer activity from stomach via scanning gamma camera **Endoscopy** Bezoar (retained food bolus) **DDx:** R/O gastric outlet obstruction Antral stricture PUD Gastric carcinoma Crohn's	If **secondary to DM**: glycemic control **Prokinetic agents**: erythromycin, metocloperamide **Dietary** Small and frequency meals Reduced fat intake Reduced fiber Liquid supplementation **Surgical** Gastric Pacemakers Partial gastrectomy with J-tube COMPLEX GASTROPARESIS

	inhibitors Post-vagotomy Partial gastric resection **Acute** Delayed Gastric Emptying Post-viral infection Acute hyperglycemia			Tricyclics Botulinum toxin inejciton in pyloric sphincter Neurostimulation Surgical management
FUNCTIONAL DYSPEPSIA	Epigastric pain of unknown etiology Gastric motor incoordination Visceral hypersensitivity Psychogenic effects Hp colonization Medications		Dx only if r/o structural and functional abnormalities i.e. diagnosis of exclusion	**Burning epigastric pain**: acid suppression **Abdominal fullness**: prokinetic agents **Abdominal pain**: low-dose tricyclic

PEPTIC ULCER DISEASE

General Features

MICROBIOLOGY OF H. PYLORI
- GNR
- Colonizes the mucus layer within the gastric pits (the organism is rarely found on the ruggae)
- TMX: F/O, salivary; mostly occurs within families with peds
- Virulence: flagellated, urease, adhesins (BabA; allows for antigenic variation), CagA pathogenicity genes (growth factor response), antigenic variation between 32 OMPs, VacA cytotoxin (increased surface bicarbonate)
- Host response is CMI with TH1 predominance: results in gastrin release, atrophic gastritis, and neutrophilic inflammation (IL-8)
  - Note that this is an unexpected response, as the organism is extracellular
- Antibody response does not neutralize

PATHOGENESIS of PUD
- Most mucosal damage is due to active inflammation, NOT acid secretion
- Antral Hp infection results in decreased SS → (endocrine) → increased gastrin → increased HCl
- Decreased active bicarbonate and mucous secretion
- End result is duodenal inflammation progressing to ulcer

Non-atrophic pangastritis: gastric MALT lymphoma OR asymptomatic
- Gastrin and acid production is relatively NML

Antral infection: duodenal ulcer

Body infection: gastric ulcers and adenocarcinoma
- Gastrin secretion is decreased, and there may be achlorhydria

PEPTIC ULCER DISEASE (PUD)	Incidence: DU > GU 10% in males 5% in females Infection rate in U.S: 30% Higher incidence in developing countries **RFs** Hp NSAIDs Increased acid, pepsin, Bile Acids Smoking, EtOH, caffeine Genetic Gastoparesis / delayed emptying Stress Steroids FHx *Highest risk of bleeding*: NSAID + Hp infection	**Presentation** Dyspepsia: epigastric burning, nausea Relieved by eating and antacids GU: exacerbated by food DU: relieved by food, but symptoms increase in severity 1 – 3 hrs post-prandially, as the intestinal phase begins **Complications** Bleeding (10 – 20%) Gastric outlet obstruction (<2%) Inflammation and fibrosis at the pyrlorus and duodenal bulb Perforation (< 2%) Secondary pancreatitis, hemorrhage with free perforation **Duodenal Ulcers** More common variant Little malignant potential If ulceration of distal 2/3 duodenum: suspect hypersecretory state (Zollinger-Ellison) Posteiror bulb ulcers may erode into the gastroduodenal artery → high bleeding risk **Gastric Ulcers** Presumed to be pre-malignant Require re-imaging (endoscopy) after acid-suppression therapy	**Gold Standard**: upper GI endoscopy **Dx Hp Infection** EDG with Bx: direct visualization of organisms and detection of urease (CLO test) Urea breath test: requires radiolabeled carbon Hp stool antigen Serology DO NOT test within 2 wks of acid-suppression or ABx due to poor sensitivity	**With Hp infection** Multiple ABx + acid suppression (PPI + H2R antagonist) Tx 10 – 14 d. **Non-infected PUD** Acid suppression Discontinue NSAIDs Tx 8 wks **Surgery** If refractory outlet obstruction, continual GI bleed, perforation, concurrent malignancy, recurrent ulcers Truncal vagotomy + pyloroplasty Selective vagotomy Antrectomy + vagotomy
GASTRIC CARCINOMA				
GASTRIC ADENOCARCINOMA	95% of gastric malignancies 4th leading malignancy worldwide Dx at age > 50 yrs	**Presentation** Weight loss, anorexia, dyspepsia, bleeding, upper abdominal pain (referred to midline), dysphagia		

	Increasing incidence of tumors in fundus and cardia Decreased incidence otherwise **RF:** chronic Hp, smoking, pickled foods, smoked foods, lower SES, advanced age DISTRIBUTION Antrum (45%; decling incidence), Cardia and Fundus (35%; increasing incidence) Lesser and Greater Curvatures (20%)	**Linitus Plastica** Diffuse infiltration of the gastric wall with loss of distensibility **Cardia Tumors** Associated with intestinal metaplasia at the squamocolumnar interface		
GASTRIC LYMPHOMA	Most common extramedullary of primary lymphoma > 90% of cases are associated with prior Hp infection	Results in diffuse wall thickening with bleeding and/or ulceration		
GASTRIC MALT LYMPHOMA	Associated with Hp May occur throughout the GI tract	Generally a low-rage (indolent) lymphoma May actually occur anywhere in the GI tract 50% of cases are responsive to ABx therapy		Tx Hp infection: this is sufficient
GASTRIC BENIGN NEOPLASMS	Beningn tumors in the submucosa and muscularis propria	**Lipoma** Localized to the submucosal adipose tissue **Pancreatic Rest Tumor** Ectopic pancreatic tissue in submucosa **Leiomyoma** May cause luminal bleeding and ulceration Possible outlet obstruction		

GI STROMAL TUMORS (GIST)	Tumors in the submucosa and muscularis propria	Derived from primitive mesenchymal cells Epithelioid morphology: higher malignant potential		
PANCREATITIS				
ACUTE PANCREATITIS	**Etiology** Gallstones (45%) EtOH (35%) Idiopathic (10%) Post-ERCP Post-operative Sphincter of Oddi Dysfunction ART Blunt trauma Post-operatrive Hypertriglyceridemia Hypercalcemia CF Hereditary Pancreatitis Autoimmune Pancreatitis Ascariasis Pancreas divisum	**Presentation** Epigastric pain with dorsal radiation to mid-back Steady, boring quality Aggravated by supine position Relieved by sitting, truncal flexion, and knee retraction NV due to hypomotility Exam: distension, epigastric tenderness, guarding, hypoactive bowel sounds **Complications** Pancreatic necrosis Pancreatic ascites Edema Pseudocysts (require 4 – 6 wks for development) Abscess formation Splenic vein thrombosis **Necrotizing Pancreatitis** Should be suspected if febrile > 5 d. or no clinical improvement	Parallel elevation of amylase and lipase Amylase is elevated in: CKD, salivary gland lesions, carcinoma of lungs, esophagus, breast, ovaries, DKA, pregnancy, bowel obstruction : so it is quite non-specific **Persistent elevation in lipase** with rapid decline in amylase 3-fold increase in **serum lipase** + classic **pain**: diagnostic of acute pancreatitis U/S, MRI + MRCP, ERCP + EUS, CT: look for stone in common bile duct Imaging is not informative Necrosis not detected for 48 – 72 hrs Will see edematous pancreas, possibly with obstructive lesion CT-guided percutaneous Bx: assess for infection	**Simple pancreatitis**: Analgesia Intake restriction No oral intake status IV hydration Typically self-limiting **Severe**: Surgical debridement of necrotic areas Broad-spectrum ABx if infected (Carbapenems) Nasojejunal feeding **Gallstones**: endoscopic sphincterotomy and stone retrieval May use prophylactic ABx for sterile necrosis

	RF for progression: Ranson Scale At admission: Age, glucose, LDH, WBC, AST In first 48-hrs: dropped Hct, increased BUN, etc CT severity index Glascow score Necrosis on CT Hemoconcentration	**Systemic illness (SIRS)** ARDS, AKI, shock, DIC, GI hemorrhage Hyperglycemia Hypocalcemia The syndrome of extrapancreatic inflammation: SIRS **Pathogenesis** Activation of zymogen granules → fusion → release into interstitium at basolateral membrane → activation of neutrophils → autodigestion → third-spacing → hypoperfusion → perpetuation → necrosis		
CHRONIC PANCREATITIS	**Etiology** EtOH (70 – 80%) Idiopathic (10 – 30%) (hereditary pancreatitis, CF) Autoimmune pancreatitis Obstructive jaundice Increased serum Gammaglobulin Hyperparathyroidism Hyperlipidemia Pancreas divisum	Pathogenesis The *Sentinel Acute Pancreatitis Event* Zyomgen activation via initial insult → early inflammatory phase → neutrophilic infiltrate → activation of pro-fibrotic stellate cells → deposition of collagen with continual injury → periacinar fibrosis **Presentation** Chronic and persistent multifocal (epigastric) pain Low-grade pancreatic inflammation Peri-pancreatic inflammation Intraductal hypertension Malabdosorption Occurs with loss of > 90% of gland Weight loss, vitamin deficiencies, steatorrhea DM (Brittle type) In end-stage pancreatitis with massive fibrosis	Amylase and lipase are only moderately elevated Gold standard: Endoscopic Retrograde Pancreatography (ERP) Endoscopic U/S **Abdominal X-ray**: pancreatic calcificaitons **U/S**: dilated pancreatic duct, heterogenous parenchyma, calcifications CT: same finding as U/S Elevated stool fat Assess for vitamin deficiencies **Abnormal secretin test**: *DECREASED* duodenal bicarbonate, lipase, and trypsin with IV secretin Indicates poor function	**Analgesia** Opioids Pancreatic enzyme analogs: *decrease CCK stimulation* Celiac plexus block Obstruction without dilated duct: endoscopic stricture dilation, stone removal, sphincter ablation **Dilated main duct**: lateral pancreatojejunostomy (Puestow) Allows dfirect drainage into the small bowel **Localized disease in pancreatic head**: distal pancreaticoduodenectomy (Whipple)

				Localized disease in the corpus or tail: Distal pancreatectomy **Restore Absorption** Supplemental Amylase, lipase, protease **Tx DM** Insulin
PANCREATIC NEOPLASMS				
PANCREATIC DUCTAL ADENOCARCINOMA	4th leading cause of cancer mortality in US < 20% with resectable disease at Dx Survival at 1 yr is 20% 95% of tumors from exocrine cells Mostly from the ductal epithelium 2% of tumors from endocrine cells **RFs** Smoking Obesity Sedentary lifestyle Heriditary Pancreatitis Non-heriditary chronic pancreatitis High-fat diets **Genomic abnormalities** K-ras, p16, p53, DPC4	70% of tumors in pancreatic head Present with jaundice and steatorrhea due to biliary obstruction Palpable and non-tender gallbladder May have acute pancreatitis 30% of tumors in the body and tail Present with pain and weight loss Pain is due to invasion of the celiac and superior mesenteric plexi Dull, epigastric, dorsal radiation Other manifestations Gastroparesis New-onset glucose intolerance Migratory thrombophlebitis (Troussaeu) Depression	CT EUS (higher sensitivity is < 2 cm) ERCP Used only with plan for duct stenting CA 19-9 serum test Low sensitivity and specificity	
SEROUS CYSTADENOMA	25% of cystic tumors Predominates in middle-aged females	No malignant potential Symptoms due to mass effect	Microcystic morphology Central fibrosis and calcification Cyst fluid analysis: no malignant cells, NML	

		NVD, distension	tumor markers, decreased amylase and CEA	
MUCINOUS CYSTIC ADENOMA *and* **ADENOCARCINOMA**	9:1 female predominance K-ras and p53 mutations are commonly found	Presumed to be pre-malignant Symptoms similar to serous cystadeneoma	Macrocystic structure (> 1 cm) Septated cuboidal cavitations Heterogenous size Cyst fluid analysis: elevated CEA, depressed amylase	Surgical resection due to malignant risk
INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (IPMN)	Derived from the main pancreatic duct (80%) and major branches (20%)	Presumed to be pre-malignant Excessive mucin secretion results in ductal occlusion This results in pancreatitis (acute and chronic)	Gold standard: ERCP demonstrates active mucin exudation from apices of papillae, diffuse ductal dilation, cystic side branch dilation Cyst fluid analysis: **increased** amylase	
INSULINOMA	90% are benign The most common endocrine tumor of the pancreas	Whipple's Triad Symptoms of hypoglycemia Documented low plasma glucose Alleviation with exogenous glucose Altered mental status		
GASTRINOMA		**Zollinger-Ellison Syndrome** Results in excessive acid secretion Widespread GI ulceration May involve distal duodenum May have diarrhea	Secretin stimulation test Massive increase in serum gastrin levels	
GLUCAGONOMA		Glucose intolerance Weight loss Anemia Necrolytic migratory erythema	Increased plasma glucagon	Octreotide
VIPOMA		**Verner Morrison Syndrome** Severe watery secretory diarrhea		Octreotide

		Dehydration Hypokalemia		

GENERAL FEATURES of HEPATIC HISTOLOGY

HISTOPATHOLOGY OF HEPATIC INJURY

Intracellular Accumulations

- Ballooning Degeneration: expansion of hepatocyte cytoplasm, loss of hexagonal architecture, cellular sphericity
  - Acute Alcoholic Steatohepatitis (ASH)
  - Acute Viral Hepatitis
- Steatosis
  - Microvesicular: multiple small lipid vacuols withoutnuclear displacement
  - Macrovesicular: coalesced vacuole with nuclear displacement
    - HCV hepatitis, DM, Obesity
- Mixed presentation in Alcoholic Steatosis

Necrosis

- Coagulative Necrosis: nucleolysis, preservation of cytoarchitecture, ghosted cells
  - Ischemic infarction due to hepatic artery thrombosis
- Lytic Necrosis: cell lysis due to ballooning degeneration
  - Results in cystic spaces
  - Associated with EtoH
- Centrilobular (Zone 3) Necrosis: necrosis around the terminal hepatic (central) vein
  - Ischemic infarction, shock
  - APAP toxicity
  - Chronic venous congestion (Budd-Chiari)
  - CHF (cardiac cirrhosis)
- Bridging Necrosis and Fibrosis: due to injury to contiguous zones
  - portal:portal bridging is seen in Zone 1 necosis
  - portal:central bridging is seen in Zone 3 necrosis

PATTERNS of HEPATIC INJURY

- **Alcoholic Steatosis:** greasy liver, mixed vescivular steatosis, no inflammation or fibrosis
- **Alcoholic Steatohepatitis (ASH)**: ballooning degeneration, Mallory bodies (cytokeratin), neutrophilic infiltrate; perivenular fibrosis; central hyaline sclerosis; steatosis
- **Alcoholic Cirrhosis**: regenerative nodules with bands of fibrosis, grossly reduced volume
- **Non-alcoholic Steatohepatitis (NASH)**: similar to ASH, EXCEPT for macrovescicular steatosis predominance + lymphocytic lobular inflammation

Non-alcoholic Fatty Liver Disease: virtually identical to Alcoholic Steatosis
Acute Viral Hepatitis: diffuse portal and parenchymal inflammation; lymphocytic; ballooning degeneration + necrosis + apoptotic forms
Chronic Viral Hepatitis: portal and interface inflammation, lymphocytic, steatosis (HSC), inclusions ('ground glass', HBV), varying stages of fibrosis, cirrhosis
Auotimmune Hepatitis: resembles acute or chronic viral hepatitis + may progress to FHF (panlobular necrosis); thus, there will be a spectrum of inflammation (portal to lobular)
Herditary Hemochromatosis: diffuse intracellular iron pigment, fibrosis and cirrhosis, NO INFLAMMATION
Wilson's Disease: features of acute and chronic hepatitis, steatosis, cirrhosis
α1-antitrypsin deficiency: eosinophilic glycoprotein inclusions, fibrosis, cirrhosis
Cardiac Sclerosis: Perivenular (Zone 3) fibrosis, perivenular cirrhosis (nutmeg liver)
Hepatocellular Carcinoma: solitary mass lesion in cirrhotic liver, loss of portal structures, cellular dysplasia

PATTERNS of BILIARY INJURY

Primary Biliary Cirrhosis (PBC): aggregation of lymphocytes and plasma cells around small interlobular ducts; periductal granuloma (florid bile duct lesion), segmental obliteration of ducts, ductopenia
Primary Sclerosing Cholangitis (PSC): may affect any segment of biliary system, concentric (onion skin) periductal fibrosis, segmental sclerosis and intervening dilatation
Cholangiocarcinoma: dysplastic cellular arrangements (glands,sheets, acini), desmopalstic response, perineural invasion

GENERAL FEATURES of LIVER FUNCTION TESTING

HEPATOCELLULAR INJURY

AST: mitochondrial and cytosolic enzyme, found in liver and striated muscle
ALT: more specific to liver
ALT/AST ≥ 2 with ALT, AST < 400 IU/L: suggests alcoholic liver disease [ALT is depressed due to B6 deficiency]
CPK: distinguishes muscle injury from hepatocellular necrosis
LDH: not specific to liver, elevated in **ischemic liver injury**

BILIARY TREE DYSFUNCTION and CHOLESTASIS

ALP: canilicular membrane, bone, placenta, kidney
Increased levels indicate cholestasis due to induction of ALP synthesis by static bile acids
Nay also be elvated in pregnancy, peds (bone turnover), osteodystrophy
Decreased levels indicate zinc deficiency, Wilson's disease + FHF
GGT: cholangiocytes, pancreatic acinar cells
Increased with ALP: specific to hepatobiliary damage
NML with increased ALP: indicates extrahepatic damage
Increased with NML ALP: poor specificity; may be elevated by EtOHM phenytoin, Phenobarbital
5' NT: released from the basolateral membrane of cholangiocytes
Specific to biliary damage
If NML with elevated ALP: supports extrahepatic injury during pregnancy or childhood

LIVER FUNCTION

Direct (Conjugated) Bilirubin: indicates excretory function of both hepatocytes and the bile ducts
Prognostic value in chronic liver disease; **not informative in acute disease**
Indirect (Unconjugated) Bilirubin: hemolysis and Gilbert's syndrome
PT and **INR**: sensitive for hepatocellular dysfunction due to short half-life of Factor VII
However, must r/o malabsoption and VitK deficiency; assess normalization of INR with IM VitK injection
Factor VIII level: used to differentiate DIC from liver failure [it is the only clotting protein not synthesized in the liver]
Albumin: Not useful in acute liver failure; prognostic in chronic disease and cirrhosis
Serum Bile Acids: indicates excretory function; higher sensitivity and specificity than direct bilirubin
Ammonia: increased levels indicate hepatocellular dysfunction or portal-systemic shunting
May also be elevated following **massive GI hemorrhage**

END-STAGE LIVER DISEASE

END-STAGE LIVER DISEASE *is* **DECOMPENSATED CIRRHOSIS**

There are two broad pathophysiologic mechanisms
Hepatocellular Insufficiency
Portal HTN

ETIOLOGY of CIRRHOSIS
EtOH
Chonic HBV/HDV, HCV
Wilson's, Hemochromatosis (hereditary and secondary), AIAT deficiency
NAFLD and NASH
Chronic Autoimmune Hepatitis
PBC, PSC, Biliary Atresia, Alagille's Syndrome, Caroli's Syndrome
Secondary Biliary Cirrhosis
May be due to cholelithiasis, PSC, cholangitis
Chronci Budd-Chiari Syndrome, Cardiac Sclerosis
Idiopathic

HEPATOCELLUALR INSUFFICIENCY
Coagulopathy
Echymossis, Epistaxis, Gingival bleeding, minor anorectal bleeding
Exacerbates varaceal bleeding
Hepatocytes synthesize: all Factors EXCEPT VIII, HMWK, Proteins S + C, AT-III
Lack of hemostasis is due to impaired Factor synthesis *and* VitK deficiency due to cholestasis

May present as hypercaogulable state: DVTs and PE
This is due to depletion of Proteins C and S, AT-III

Hypoalbuminemia

May simply be due to oncotic dilution via fluid retention
Contributes to ascites
Cirrhotic hydrothorax, peripheral edema, SBP

Hyperbilirubinemia

Increasing jaundice
Malabsoption of ADEK: xeropthalmos, osteodystrophty, coagulopathy

PORTAL HYPERTENSION
Portal venous pressure > IVC pressure (5 mmHg)

Complications are seen when PVP > 10 mmH
Acute Portal HTN: late stages of AHF (submassive hepatic necrosis), acute Budd-Chiari, venocclusive disease

Post-hepatic: IVC occlusion, Budd-Chiari
Intrahepatic: VOD (post-sinusoidal), Schistosomoasis (presinusoidal), Cirrhosis
Prehepatic: portal venous thrombosis

Ascites

DDx: portal HTN, diffuse peritoneal malignancy (carcinomatosis), peritoneal TB
Serous exudates in peritoneum
Presentation: Increased girth, rapid weight gain, right-sided cirrhotic hydrothorax
Dx: shifting dullness, fluid wave, paracentesis

Paracentesis: **SAAG** (albumin gradient) > 1.1 mg/dL
Not that high SAAG may be seen in ASH, CHF, hepatic mets, FHF, venous occlusion

Portal HTN → shunting away from portal circulation → decreased clearance of endogenous vasodilator (NO) → splanchnic vasodilation → decreased preload → decreased ECV → systemic hypotension → activation of RAAS and sympathetics → increased Na+ retention, increased contractility → overflow of hepatic lymphatics → ascites
Also: aldosterone is cleared by the liver
TX: salt restriction,aldosterone antagonists (potassium sparing diuretics) and Loop Diuretics, parecentesis, TIPS

Hepatorenal Syndrome

Pre-renal AKI
Due to massive renal arterial constriction

May be triggered by infection, SBP, diuretics, paracentesis

Resembles pre-renal azotemia: FENa+ < 1%, urine N+ < 10 mEq/L, CrU/CrP > 30

BUT Does **NOT** respond to ECV re-expansion (due to continual third-spacing into ascites)

May convert to frank ATN if the kidnys are subjected to severe ischemia or toxicity

Hypovolemia (diuretics, variceal hemorrhage), Infection (SBP, pneumonia, UTI), IV contrast, aminoglycosides, NSAIDs
DDx: r/o hemorrhage, COX-inhibitors, IV contrast, ABx, septic shock, ATN, glomerulonepritis
Thus, requires urinalysis and kidney U/S
Tx: MAINTAIN VOLUME (IV infusions), avoid nephrotoxins, octretide, albumin, TIPS
The prognosis is very poor, and survival may be < 2 wks

Varices

If PVP-IVCP gradient > 12 mmHg: high risk of of rupture of esophageal varices
Other sites: stomach, rectum, mesentery, abdominal cutaneous veins
Acute bleeding: hemoclips, band ligation, sclerotherapy, octreotide, antibiotics, vasopressin, ABx
Prophylaxis for recurrence (secondary): continued band ligation, beta-antagonists, TIPS, transplantation

Hepatic Encephalopathy

Rapidly reversible changes in cognitive function
Early: reversal of diurnal rhythm
Progresses to agitation, confusion, delirium, somnolence, seizures, STM deficits
Motor findings include: dysarthria, asterixis, hyperreflexia, decerebrate posturing, seizures
Due to shunting (secondary to Portal HTN or TIPS) OR decreased hepatocellular function
The proposed toxins: NH3 (produced by gut flora), Aromatic amino acids, GABA and BZ analogs
Excess NH3 Results in astrocyte dysfunction and swelling
Triggered by increased gut Nitrogen load (hemorrhage, infection), or depressed encephalopathy threshold (sedatives, hypokalemia, dehydration)
TX: treat the underlying provocative factors (GI bleed, toxins, hypokalemia, hypoxia), lactuloase (NH3 trapping), ABx (glut flora clearance; rifaxamin or metronidazole)
Generally, protein is restricted only if comatose

Splenomegaly (Hypersplensim)

Portal HTN leads to increased splenic arterial flow and splenomegaly
This leads to thrombocytopenia → leucopenia → anemia

Hepatopulmonary Syndrome

Decreased hepatic clearance of endogenous vasodilators results in blotchy dilation of intrapulmonary capillaries
This results in V/Q mismatch and profound hypoxemia
Symproms: dyspnea, platypnea
Note: some mild hypoxemia is expected with large ascites due to restricted discursion of the diaphragm
Dx via triad: liver disease, pulmonary vasodilation (bubble echo), increased A-a gradient on room air (ABGs)

Hepatic Hydrothorax

Efflux of ascites fluid through defects in the diaphragm
No evidence of CHF

Pleural fluid: transudate with SAAG > 1.1

Portopulmonary Hypertension

Occurs in portal HTN, but the PAP does not correlate to the portal venous pressure

ENDOCRINE DISODERS

The stigmata of ESLD (erythema and angiomata) are due to hyperestrinism (normally conjugated by hepatocytes)

In males: hypandrogenism and feminization

- Decreased libido and/or impotence
- Testicular atrophy and hypoganadism
- Gynecomastia
- Corporeal alopecia
- Spider angiomata and palmar erythema

In females: dysregulated pituitary-gondal axis

- Decrease libido
- Anovulation
- Amenorrhea
- Spider angiomata and palmar erythema

HEPATIC OSTEOPENIA

VitD deficiency (decreased absorption *and* decreased synthesis)

Pathologic fracture of long bones

Vertebral collapse

INFECTION

Cirrhosis → decreased macrophage function, shunting with portal HTN, increased gut permeability →increased frequency of infection and inability to clear portal bacteremia → predisposition to sepsis

Spontaneous Bacterial Peritonitis

Infection of the ascitis fluid

Common organisms: GN aerobes (*E. coli*, *Klebsiella*), pneumococcus

May complicate cirrhotic hydrothorax

In 50% of SBP, no organism can be recovered; but suspect if neutrophils > 250 per mL

ACUTE LIVER FAILURE

ACUTE HEPATIC INJURY	Sudden loss of hepatocyte mass Abrupt increase in aminotransferase levels (> 10 – 25-fold above NML) **Natural History** There are three outcomes Convalescence without complications Chronic hepatitis progressing to cirrhosis Mortality due to FHF **ETIOLOGY** **Viral Hepatitis** Hepatotropic, EBV, CMV, VZV, HSV **APAP** **Medications:** amoxicillin + clavulanate, volatile anesthetics, INH, Me-DOPA, valproate, MAOIs **Vascular:** Acute obstruction of hepatic veins (typically due to thrombosis; Budd-Chiari Syndrome), Shock **Alcoholic hepatitis** Elevation in AST/ALT is moderate Typically superimposed on Cirrhosis and end-stage liver disease	May result from acute hepatitis, medications, ischemia, and malignancy **Perivenular (Zone 3) Necrosis** Shock Hepatic ischemia due to arterial occlusion (thrombosis, cocaine toxicity) APAP toxicity (CYP450 is preferentially expressed near the central vein) Thus, this is a particular pattern of injury seen with APAP and ischemia **Pathogenesis of APAP Toxicity** 10% of APAP is converted to NAPQI Typically, NAPQI is neutralized by conjugation with glutathione Toxicity occurs with Excessive APAP → NAPQI (result in saturation of glutathione pool) Depletion of **glutathione** (malnutrition) Induction of CYP450 (chronic EtOH, some medications) NAPQI forms adducts with intracellular proteins → hepatocyte cell death	Increased amintransferase levels without evidence of hepatocellular insufficiency INR NML No Hyperbilirubinemia (Note that albumin is not a good indicator of AHI)	**APAP toxicity**: N-acetyl Cysteine

	Autoimmune Hepatitis Rarely presents as AHI **Other RARE causes** Wilson's Disease Mushroom toxicity Acute Fatty Liver of Pregnancy Reye's Syndrome Lymphomas Galactosemia, Tyrosinemia Hereditary Fructose Intolerance			
ACUTE HEPATIC FAILURE	AHI + evidence of hepatic dysfunction e.g. elevated INR, hyperbilirubinemia Thus, the etiologies are equivalent to AHI	AHF is due to dysfunction in hepatocyte protein synthesis Thus, the most common anomalies are coagulopathy and elevated direct bilirubin AHF is NOT due to biliary damage or reduced clearance of ammonia	Prolonged PT Deep jaundice Pruritis Hyperbilirubinemia (Bilirubin is not a good prognostic index of AHF, but it is elevated)	
FULMINANT HEPATIC FAILURE	AHI + Hepatic Encephalopathy within 8 wks of symptomatic failure in **previously healthy subject** The Dx of FHF cannot be assigned to acute encephalopathy in the background of chronic liver disease or cirrhosis **RFs** for **poorer prognosis:** Slow onset Extremes of age Drugs EXCEPT APAP Idiopathic Acidosis Severe global liver failure	**Complications** Cerebral edema R/O hypoglycemia This may be seen in APAP FHF and microvesicular failure (Reye's, AFL of pregnancy, valproate) Changes in cerebral perfusion are provoked by positional change Bleeding From IV sites and GI	Stages of Encephalopathy 1. Subtle changes in behavior and higher cognitive function; may have asterixis 2. Disorientaiton, somnolence, asterixis 3. Confusion, incoherent speech, roused by vocal command 4. Comatose, posturing	

	Leading causes: APAP, Acute HAV infection			
ALCOHOLIC LIVER DISEASE				
ALCOHOLIC LIVER DISEASE	**EtOH Abuse** Excessive drinking without personal or social consqueuences **EtOH Dependence** Excessive drinking with negative physical and social consequences Notice that these definitions differ from those of DSM-IV	**Pathogenesis** Oxidation of EtOH to acetaldehyde and acetate generates excess NADH → inhibit fatty acid oxidation and TCA cycle → increased lipogenesis and storage Chronic EtOH → increased GI mucosal permeability → increased translocation of GNOs (LPS) → activation of Kupffer cells → hepatic cytokine cascade → alcoholic hepatitis → activation of stellate cells → production and deposition of collagen → fibrosis and cirrhosis **Alcoholic Steatosis** May result from acute alcohol use over a few days Reversible with abstinence **Alcoholic (Steato)hepatitis** Requires sustained EtOH use Presentation: fever, jaundice, hepatomegaly, anorexia Thus, the presentation is similar to that of acute viral hepatitis **Cirrhosis** The end-stage of ALD Will present as chronic liver failure	**Alcoholic (Steato)hepatitis** Ballooned hepatocytes Mallory bodies (cytokeratin) Neutrophilic inflammation (lobular) Perivenular fibrosis (filamentous) Mixed vescicular steatosis Indications of AHF Prolonged PT Moderate aminotransferase elevation AST:ALT ~ 2 AST, ALT < 400 IU (10-fold NML) Elevated total bilirubin Signs of cirrhosis: angiomata, ascites, encephalopathy, gynecomastia, palmar erythema	**The main treatment**: abstinence May Tx alcohol dependence with BZs, disulfiram, acomprosate, naltrexone, topiramate, baclofen Emergent Tx for **alcoholic hepatitis:** corticosteroids This is indicated for severe hepatitis Other therapies: Anti-TNF agents (pentoxifylline, infliximab, etanercept), caspase inhibitors Tx **complications of alcoholic cirrhosis** Tx **concurrent HBV and HCV infection** **Inhibit rate of liver fibrosis** Propylthiouricil (PTU), colchcine, SAME

NON-ALCOHOLIC LIVER DISEASE

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) *and* **NON-ALCOHOLIC STEATOHEPATITIS (NASH)**	Both disorders are associated with: Morbid obesity Truncal obesity Metabolic Syndrome DMII OSA PCOS	**Pathogenesis** Insulin resistance → NAFLD → oxidative stress → NASH Adipocytes secrete leptin → activate stellate cells → increased fibrosis Decreased adiponectin activity (normally anti-fibrotic) → increased intrahepatic fibrosis **Presentation** Very similar to the syndromes of alcoholic liver injury (ASH and AS) Thus, cirrhosis is the ultimate manifestation of end-stage NAFLD	Mild elevation in AST and ALT Bright liver on U/S **Liver Bx** NAFLD: Bland macrosteatosis NASH: identical to ASH Perivenular filamentous fibrosis Mixed vesicular triglyceride deposition (mainly macrovesicular) Lymphocytic infiltrate throughout the lobule Uncommon: ballooned hepatocytes and Mallory bodies Cirrhosis: no vesicles apparent due to loss of TG content	**Lifestyle Modification** **Tx insulin resistance** Metformin Thiazolidinediones **Tx dyslipidemia** Fibrates, Niacin, Statins **Tx HTN** **Bariatric Surgery** **Hepatoprotection** Anti-oxidants TNF-α inhibitors Inflixumab, Pentoxyfylline UDCA Tx HCV infection **Transplantation**

VIRAL HEPATITIS

HEPATITIS A	Naked SS+ve RNA enterovirus **TMX**: F/O 50% of cases are sporadic Point source epidemics due to contaminated water or food (shellfish) **Natural History** AHF in < 1% of cases **RF:** concurrent HCV infection	**Pathophysiology** Hepatic injury is due to the host response CD8+, NK, IFN-γ **Presentation** Peds: most infection is asymptomatic Adults: more likely to develop jaundice and AHF Prodrome: fatigue, myalgia, RUQ pain Hepatic failure: jaundice, bilirubinuria,	Acute: anti-HAV IgM May be detected for 6 mos. following Inoculation Convalesced: anti-HAV IgG Detectable within 4 – 8 wks	No antivirals Supportive therapy with rehydration Transplantation for acute liver failure **Vaccination** Vaccinate all peds in U.S Vaccinate risk groups: chronic liver disease,

	Chronic hepatitis (rare)	acholic stool Viral shedding occurs before onset of symptoms **Extrahepatic Manifestations** Optic neuritis Arthritis		immunocompromised, nursing homes, travel to endemic area, IV drug abuse **Post-Exposure Prophylaxis** HAV vaccine for patients with NML liver function HepA immunoglobulin if > 40 yrs + chronic liver disease or medical illness **Hygiene**
HEPATITIS E	Pregnant: increased risk of AHF in third trimester **TMX**: F/O via contaminated water and food	Similar clinical presentation as HAV	Serology HEV RT –PCR from serum or stool	**Acute:** supportive Tx HEV immune globulin for PEP
HEPATITIS B	Enveloped dsDNA **TMX** Percutaneous (requires membrane lesions) Vertical TMX at birth (does not cross placenta) Leading mode in developing Countries Sexual From chronic carriers with HBsAG+ve; typically Asymptomatic	**Pathophysiology** Hepatic injury is due to CD8+ inflammation CMI against HBcAG and HBeAg expressed by hepatocytes Chronic inflammation also increases the risk of cirrhosis **Viral Biology** Replicaiton via RNA intermediate Generation of quasi-species A single reading frame encodes HBcAg and HbeAg	**SEROLOGY** HbsAg: the earliest indicator of acute infection If detectable > 6 mos.: chronic HBcAg: Not detectable in serum Accurate replication index HBeAg: peak serum levels at maximal infectivity (3 – 6 wks) Persistence of Ag indicates chronic infection and infectivity Anti-HBs: neutralizing Ab; appears after 1 – 4 mos. and indicates viral clearance, vaccination, or immunity Anti-HBc: dual class (IgG and IgM); non-	**TX acute HBV** Supportive Oral antiviral therapy AHF: liver transplant **TX chronic HBV** IFN-α + Antivirals **Vaccination** Derived from the HBsAg May be used as PEP May prevent vertical TMX if given with HBIG to neonate

	1/3 of chronic HBV also associated with cirrhosis or HCC Risk of **conversion to chronic HBV** is inversely related to age at initial infection 90% if infected at birth 25 – 50% if infected at 1 – 5 yrs < 5% in peds and adults 10% of adults with acute HBV develop chronic HBV < 1% of cases progress to FHF > 100-fold increased risk of HCC Mean latency of 35 yrs **RF**: higher HBV DNA copy titre, infection in early childhood, male gender, cirrhosis, tobacco, exposure to Alfatoxin	HBV DNA may integrate into the cellular genome Thus, HBV acts as a chronic cancer virus Infants and peds: typically asymptomatic Adults: icteric illness in 30 – 50% **Presentation** Prodrome: NVD, anorexia, headache, low-grade fever Occurs during incubation period (6 – 24 wks) Progression to jaundice **Extrahepatic Manifestations** Glomerulonephritis Polyarteritis Nodosa Cryoglobulinemia	Neutralizing IgM: early, IgG: chronic OR convalescent Anti-HBe: seroconversion indicates resolution of acute infection [HBsAg, Anti-HBs Ab, Anti-HBc Ab] +/-/- : early acute HBV +/-/+: acute or chronic HBV Distinguish with IgM and IgG titres -/+/+: Previous infection, but cleared -/+/-: vaccination **Screen for HCC** Regular U/S with serum AFP Recommended in HBsAg carriers with cirrhosis	Recommended: All neonates Adults with risk factors Immunosuppresed, HIV Chronic liver disease
HEPATITIS D	Partial virus-like particle Closed RNA plasmid genome Humans are only natural host Ubiquitous in environment **TMX**: similar to HBV	Requires coinfection or superinfeciton with HBV to complete viral life-cycle Superinfection is more likely to cause chronic HDV and cirrhosis Both infective patterns may result in AHF	**Serology** Anti-HD IgM and IgG	HBV vaccination prevents infection with HDV **Tx**: high-dose IFN The antiviral polymerase inhibitors are **NOT EFFECTIVE** against HDV

HEPATITIS C	Enveloped SS+ve RNA 6 genotypes with 15 subtypes 70% infected with Genotype 1 Genotype does not correlate with progression of chronic infection Genotype determines sensitivity to IFN-α Generation of quasi-species allows for immune evasion Leading cause of chronic liver disease in US Leading cause of transplantation in US Highest prevalence in China Declining incidence due to transfusion screening Increasing detection due to latency between infection and cirrhosis Progression to cirrhosis: 20 yrs Progression to HCC: 30 yrs **RF** for infection: IV drugs (strongest risk; 60%) Sexual TMX Transfusion (prior to screening) Fomites Hemodialysis Vertical TMX (occurs during	Enters hepatocyte via LDL/VLDL receptor No genomic integration Life cycle is exclusively cytoplasmic Most (>75%) of infections are asymptomatic Acute Hepatic Failure is RARE! Hepatic injury is due to CD8+ inflammatory response Acute HCV infection: self-limited hepatitis Nausea, fever, abdominal pain, Progression to jaundice Corresponds to highest RNA titres and replication phase **Extrahepatic Pathology** Mixed essential cryoglobulinemia Glomerulonephritis Sjogren's Increased lymphoma risk	Acute: anti-HCV IgM, -ve HCV RNA (PCR) The Ab only appears > 10 wks after hepatitis syndrome Chronic: HCV RNA detectable > 6 mos. after infection Moderate elevation in aminotransferases 30% have NML AST and ALT **Liver Bx** Portal and interface inflammation Lymphoid aggregation Occasional steatosis	**No vaccine** **Combination therapy** IFN-α + Ribavirin Requires longer duration of Tx for Genotype I IFN-α: SC injection, ARs include cytopenias, flu-like illness, depression, thyroid disease Reduces conversion to acute HCV to chronic infection Ribavirin: ARs include teratogenicity and hemolytic anemia **Vaccinate** for HBV and HAV

	viremia only) **Natural History** Acute HCV converts to chronic HCV in 70% of cases Chronic HCV converts to cirrhosis in 20% of cases **RF**: male sex, EtOH, > 40 yrs at initial infection, HIV co-infection Cirrhosis may convert to HCC at 1 – 6 % per yr Risk only increases with development of cirrhosis			
METABOLIC LIVER DISEASES				
HEREDITARY HEMOCHROMATOSIS	Clinical disease is apparent in C282Y homozygotes and C282Y/H63D heterozygotes	**IRON OVERLOAD** Cirrhosis and HCC DMII Cardiomyopathy, Conduction Block Arthropathy Bronzing of skin Hypogonadism Mutation of HFE (Cys282Tyr) → dysfunctional signal transduction → no upregulation of hepcidin with increased transferrin saturation → increased iron absorption Increased intracellular iron generates ROSs via the Fenton reaction → lipid peroxidation → activation of stellate cells + mitochondrial instability + activation of Kupffer cells → fibrosis and regeneration → cirrhosis	Increased transferrin saturation Increased serum ferritin Common HFE mutations detected by molecular analysis **Liver Bx: iron quantitation**	**Phelobtomies** **Iron Chelation** **Transplantation**

		DNA damage+ cirrhosis → HCC		
WILSON'S DISEASE (HEPATOLENTICULAR DEGENERATION)	Mutation in ATP7B copper transporter protein (the Wilson ATPase)	ATP7B mutation → defective secretion of copper in excretory vesicles (into caniliculi) and loading (via secretory vesicles) onto ceruloplasmin → increased intracellular copper and decreased serum ceruloplasmin → necrosis of hepatocytes → increased plasma copper concentration → deposition in cornea, basal ganglia, kidney, RBC membrane Liver: acute *and* chronic hepatitis, FHF, cirrhosis Optic: Kayser-Fleischer rings CNS: gliosis of basal ganglia (lenticular degeneration), EPS, psychosis Renal: Fanconi syndrome (uric acid wasting) RBCs: hemolysis	Decreased serum ceruloplasmin Increased urinary copper Kayser-Fleischer rings **Increased copper on Liver Bx**	**Copper Chelation** Penicillamine, Trientine **Liver Transplant** Advanced cirrhosis and FHF
α-1 ANTI-TRYPSIN DEFICIENCY (A1AT)	Mutation in serine protease inhibitor Typically PiZZ type Co-dominant expression	PiZZ variant → accumulation in the rER → mitochondrial damage → cell death and fibrosis → cirrhosis In lung, lack of normal A1AT results in excessive activity of neutrophilic elastase → emphysema Liver: hepatitis and **cholestasis** (neonates), increased aminotransferases, cirrhosis, HCC Lung: premature emphysema	Low serum A1AT level Abnormal Pi variant **Liver Bx: intracellular globular inclusions**	**Liver:** transplant if severe **Lung:** smoking cessation, exogenous A1AT
AUTOIMMUNE LIVER DISEASE				

AUTOIMMUNE HEPATITIS	F > M **Type 1** (80%) ANA + ASMA (actin, troponin) **Type 2** (4%) Anti-LKM1p (CYP2D6) **Type 3** (3%) Anti-SLA (cytokeratin 8, 18) **Cryptogenic** (13%) No autoantibodies characterized	May be asymptomatic Fatigue, polyarthralgia, jaundice Associated with other immune diseases Thyroiditis (Hashimoto's) RA UC Grave's IDDM Sicca PSC Vitiligo, collagen-vascular disease, ITP, MG, hemolytic anemia, pernicious anemia, myositis	Circulating autoAbs Polyclonal hypergammaglobulinemia Liver Bx: lobular infiltration of T cells, plasma cell influx	**ISD**: prednisone + azathioprine Generally food response May recur after transplantation
PRIMARY DISEASE *of the* BILIARY SYSTEM				
PRIMARY SCLEROSING CHOLANGITIS (PSC)	Fibrosis and stricture formation along the biliary tract in entirety Intrahepatic + Extrahepatic ducts are involved Occurs in males < 45 yrs Etiology maybe remote portal bacteremia with dysregulated immune response and loss of competence Associated with IBD (UC and Crohn's) 75% with UC 5% with CD 2 -.5 – 7.5% of pts with UC have co-morbid PSC 90% symptomatic at Dx	**Pathogenesis** Chronic portal bacteremia → activation of Kupffer cells → progressive fibrosis Symptomatic in late disease stages **Cholestasis**: jaundice, pruritis, ascending Cholangitis (rare) Cholelithiasis (cholesterol and pigment type) Dominant stricture Liver failure + portal HTN This is due to secondary biliary cirrhosis Fatigue, weight loss, abdominal pain Note that cholestatic injury is not usually expressed clinically at time of Dx	Hypergammaglobulinemia pANCA positive (80%) HLA DRw52a isotype (50%) Circulating immune complexes Avidity for the biliary and colinic epithelium Elevated ALP (> 2 x NML) With progression: elevated AST, ALT, bilirubin, PT, decreased albumin **Gold standard**: ERCP demonstrates mutiple focal structures (segmental) with intervening dilation; may have biliary diverticulae Liver Bx is not informative: onion skin fibrosis around the duct in 10%; ductopenia of the portal tracts Active inflammation is rarely seen, since the	**Refractory to all ISDs** Supportive Tx Dilation of strictures Stone removal Transplantation UDCA

	10 – 30% develop colangiocarcinoma		underlying pathology is an increased fibrotic response of stellate cells	
PRIMARY BILIARY CIRRHOSIS (PBC)	Inflammation of small intrahepatic ducts Slowly progressive course (extremely variable natural history) Symptomatic within 2 – 4 yrs of Dx Survival is 10 – 12 yrs Best indicator: bilirubin (total) Highest post-transplant survival 9:1 female predominance Occurs between 60 – 79 yrs 50% are symptomatic at Dx Associated with other **autoimmune disease** Sjogren's, scleroderma, thyroiditis Bilirubin is highly prognostic Survival is < 2 yrs if TB > 10 or liver is cirrhotic Survival is 10 – 12 yrs after onset of symptoms	**Pathogenesis** B-cell chronic inflammation against bile duct antigens Loss of regulator T-cell function Choestatic injury → hepatocellular injury → intrahepatic fibrosis → cirrhosis Late jaundice (< 25% at presentation) Pruritis (significant distress, > 50%) Fatigue Steatorrhea Hypercholesterolemia ADEK deficiency Osteomalacia Late disease may lead to liver failure Hepatosplenomegaly Cirrhosis Portal HTN Cholestatic failure	ERCP is NML Increased serum IgM Anti-mitochondrial antibodies No immune complexes (antigens are fixed) Elevated ALP Moderately elevated AST, ALT Liver Bx: patchy obliteration of intragepatic ducts + periductal (portal) lymphocytic infiltrate + granulomas, ductopenia Thus, it resembles chronic viral hepatitis	**UDCA** Increases bile flow Stabilize hepatocte membranes Reduce synthesis of toxic bile acids Delays time to transplantation + increased survival **Transplantation** **Tx vitamin deficiencies** **Tx pruritis**

CHOLANGIOCARCINOMA	**RF**s PSC (30% of cases) Clonorchiosis (flukes) Choledochal cyst Caroli's Dx Chonic cholelithiasis Peak incidence in 60 – 79 yrs in absence of risk factors M > F Intrahepatic masses Lowest incidence Poor respectability BUT highest survival (at 5 yrs) Perihilar masses Highest incidence Fair resectibility Low survival at 5 yrs Distal masses Optimal respectability (90%) Low survival	**Pathogenesis** Neoplasia due to chronic bile duct inflammation Cholestasis: jaundice, **dark urine, acholic stool** Abdominal pain, weight loss, anorexia Tumors may occur throughout the biliry system Bifurcation of L and R hepatic ducts (**Klatskin** tumor) Intrahepatic mass lesion Extrahepatic mass	Elevated CEA CA 19 – 9 > 100 IU/mL Gold standard for imaging of intrahepatic mass lesion: CT of abdomen In a background of longstanding PSC, it may be extremely difficult to detect a mass Gold standard for CCA: ERCP Permits Bx	20 – 30% of proximal tumors are resectable 60 – 70% of distal tumors are resectable Resectable: median survival of 4 yrs Unresectable: median survival < 1 yr Invasion of bothhepatic lobes or major vessel ChemoRx and XRT are not effective **Klatskin**: liver transplantation + post-operative chemoRx and XRT Improved survival **Palliation**: endoscopic/percutaneous stenting to re-establish bile flow

CHOLELITHIASIS *and* ASSOCIATED BILIARY DISEASE

GENERAL FEATURES

The constituents of bile: mainly BAs and PLs; < 5% is bilirubin

95% of Bas are reabsorbed in the terminal ileum in the ionized cojnugated form

There are five major underlying mechanisms of hyperbilirubinemia and jaundice

- Hemolysis
- Decreased hepatocellular uptake (increased enterohepatic cycling)
- Defective conjugation

Defective secretion (hepatocellular injury)
Biliary obstruction

RISK FACTORS for Cholesterol Stones
5F: 'fat', forties, female, fertile, family history
Rapid weight loss with low fat intake
Increased TGs
Decreased HDL
Ileal Crohn's
DM
Muliple Pregnancies

PATHOPHYSIOLOGY

Increased biliary cholesterol : obesity, age, OCs, estrogen, rapid weight loss, high PUF intake
Increased lipoprotein uptake
Stimulation of HMG CoA Reductase
Decreased 7α-Hydroxylase activity
Decreased ACAT activity

Decreased biliary BAs : age, ileitis (Crohn's), ileal bypass or resection, PBC
Hypersensitive feedback
Impaired synthesis: 12α-hydrozylase deficiency, cholestatic injury
Decreased ileal reabsorption

Decreased gallbladder contractility : progestins, increased cholesterol, cholecystitis

Biliary Colic: obstruction of the cystic duct
Characteristic sharp, intervallic, epigastric + RUQ pain
Afebrile, Non-icteric
AST, ALT are NML

Cholecystitis: infection or inflammation, usually associated with cystic duct obstruction
Biliary colic + radiation to scapula and flank
Febrile, Non-icteric
AST and ALT are elvated; leukocytosis expected on CBC

Choledocholithiasis: obstruction of the distal common bile duct
Biliary colic
Afebrile
Jaundice
Elevated GGT and ALP, increased direct bilirubin
May result in acute pancreatitis and brittle diabetes

Ascending Cholangitis: ascending infection of the bilirary system with duodenal bacteria, often due to distal obstruction

Charcot's Triad I: febrile/rigors, RUQ pain (biliary colic), jaundice All enzymes are elevated				
CHOLELITHIASIS	**RF** *Cholesterol Stones* Estrogens, age, obesity, rapid weight loss, OC, ileal bypass/resection, Crohn's disease *Black Pigment Stones* Hemolysis, Liver Disease with cholestatic injury *Muddy Pigment Stones* Infection of bile ducts Cholesterol: > 50% cholesterol 80% of all stone disease Pigment: 20% of all stone disease	Asymptomatic in 60 – 80% of cases Biliary cholic develops in 1 – 4 % of cases Non-colicky pain (no large variation in intensity) RUQ and epigastrium Crescendo – Maintained – Decrescendo pattern with period of 30 min. Occurs at night Associated with NV **Complications** Acute cholecystitis: results from obstruction of the cystic duct may actually perforate Ascending Cholangitis: bacterial infection within the biliary tree, secondary to obstruction Acute Pancreatitis These are nearly universally preceded by biliary colic, EXCEPT Elderly Immunocompromised DM Chronic Renal Failure **Pathogenesis** Cholesterol supersaturation → crystal nucleation (bacterial nidus or aggregated glycoproteins) → sludge trapping within the gallbladder mucus → biliary stasis → microlithiasis → macroscopic stones	ERCP	**Cholecystitis** Open or laproscopic cholecystectomy **Choledocholithiasis** Endoscopic sphincterotomy and extraction via ERCP Not effective for stones located proximal to structures **Stenting** if failed extraction by ERCP **Percutaneous Extraction** **Dissolution**
CHOLECYSTITIS	Inflammation of the gallbladder Typically due to cystic duct obstruction	Febrile Non-jaundiced RUQ and epigastric biliary colic	Elevated AST and ALT	
ASCENDING CHOLANGITIS	Infection of the biliary system Typically due to distal	Charcot's Triad	All enzymes are elevated Hyperbilirubinemia	

	common bile duct obstruction	May progress to bacteremia and sepsis		

NEONATAL JAUNDICE

GENERAL FEATURES

EPI: jaundice occurs in 60% of full-term infants, 80% if premature
RFs for neonatal jaundice
- Jaundice within < 24 hrs
- Positive Coombs Test (suggests immune hemolysis)
- Known blood dyscrasia: G6PDH deficiency, hereditary spherocytosis
- Exclusive breast feeding with ongoing weight loss
- East Asian race
- Cephalohematoma
- 35 – 36 wks at gestation

WORKUP of JAUNDICE
Further assessment is necessary if
- Develops < 36 hrs post-partum
- Duration > 10 d.
- Total bilirubin > 12 mg/dL
- Durect bilirubin > 2 mg/Dl

The jaundice progresses cranio-cadually with increasing bilirubin
- Scleral icterus is seen with TB > 2.5 mg/dL
- Palmar and plantar jaundice is seen with TB > 12

Examine for active bleeding (cephalohematoma) and obtain the feeding and elimination (I/O) history
- (Exaggerated) physiologic jaundice may be due to dehydration

Coomb's test, CBC, Reticulocyte Count
Total bilirubin
Bilirubin fraction
- If infant seem ill, dysmorphic, has HSMegaly, LBW, acholic stooling, bilirubinuria, or persistent jaundice
- If direct bilirubin is elevated: LFTs and INR, U/S for presence of gallbladder

Kernicterus: deposition of biliruib in the periventricular white, esp. basal ganglia
- Early: lethary, hypotonia, poor sucking reflex
- Late: hyperteonia, opisthotonos (axial muscle spasms), high-pitched cry
- Sequelae: SN hearing loss, athetosis, dental dysplasia, upward gaze paresis, developmental delay

UNCONJUGATED (INDIRECT)	**ETIOLOGY** (ranked by prevalence)	**Physiologic Jaundice** Onset > 36 hrs of life		**Phototherapy** Results in covalent

HYPERBILIRUBINEMIA	**Physiologic Jaundice** **Breast-feeding jaundice** **Breast milk jaundice** **Hemolysis** **Decreased conjugation** Gilbert Syndrome Crigler-Najjar I and II: deficiency or absence of UGT Thus, there is defective glucuronidation	Increases < 5 mg/dL/d Peaks within 3 – 5 d Maximal levels 12 – 15 mg/dL Resolves within 1 wk: term 2 wks: pre-term No other abnormalities **(**Lack of**) Breast-Feeding Jaundice** Poor milk intake → decreased enteric clearance → increased enteroheaptic cycling This can exacerbate physiologic jaundice **Breast Milk Jaundice** The breast milk contains some inhibitors of UDPGA glucuronyl transferase Immaturity of the neonatal gut flora results in brush border deconjugation and absorption		linking of bilirubin into water-soluble form **Formula Trial**: breast milk jaundice **Exchnage Transfusion**: when high risk of kernicterus, bilirubin > 20 mg/dL
CONJUGATED (DIRECT) HYPERBILIRUBINEMIA	**ETIOLOGY** (ranked by prevalence) **Biliary Atresia** **Idiopathic Neonatal Hepatitis** **Inborn Errors** A1AT deficiency Galactosemia Tyrosinemia Defective hepatocyte excretion Dubin-Johnson Syndrome Rotor Sybdrome **Intrahepatic Cholestasis** Alagille Syndrome			**Biliary Atresia** Exploratory laparotomy + cholangiogram Portoenterostomy (the Kasai procedure) The duodenum is directly anastamosed with the haptic portal vein to restore bile flow Liver Transplantation

	Coroli Syndrome **Neonatal Infection** TORCH: congenital toxoplasmosis, rubella, CMV, HSV, other (HBV, VZV, HIV, PVB19) **Endocrine** Hypothyroidism Hypopituitarism **TPN cholestasis**			
EXTRAHEPATIC BILIARY ATRESIA	The leading cause of conjugated hyperbilirubinemia in infants Untreated: fatal at 1 yr	Progressive fibrosis of the extrahebatic bile ducts Cholestasis → intrahepatic ductal fibrosis NML at birth Progressive jaundice at 2 months due to ongoing duct obstruction **Natural History** Progressively acholic stooling Choluria HMS	Elevated ALP and GGT U/S: absence of gallbladder Liver Bx: bile duct plugs, ductal hyperplasia and proliferation	**Kasai Procedure**

SMALL BOWEL DISORDERS and ANALYSIS of DIARRHEA

GENERAL FEATURES

CELL TYPES of the SMALL BOWEL
Enterocytes: at the apex of the villus, cells are absorptive; in the crypts, cells are secretory
Paneth cells: release lysozyme
Goblet cells: secretemucin (usually found in the upper crypts)
ECF cells : secrete *serotonin* (and VIP); the cellular substrate of carcinoid tumors
M cells: these are essentially APCs
Acinar cells of Brunner's Glands: in the proximal duodenum; these cells secrete alkaline mucus, necessary for neutralization of gastric flow-through

TRANSPORT of MAJOR IONS

Absorption

Occurs through the trancellular route (tight junctions have a minimal contribution to total absorption)
Apical membrane contains: Na+/H+ exchanger, Na+/glucose co-transporter (SGLT), Cl-/HCO3- exchanger
Serosal membrane contains the Na+/K+ ATPase
Thus, Na+ and Cl- are absorbed 1:1 along with water

Secretion

The luminal membrane contains CFTR (conducts Cl-)
    The permeability of this transportedis regulated by cAMP. Cholera toxin causes constitutive activation of Gs and excess Cl- secretion
The serosal membrane contains N+/2Cl-/K+ cotransporter (conduct inwards), Na+/K+ ATPase

ANALYSIS

Osmotic diarrhea

Output < 1 L in 24 hrs; ceases with 48 hr fast
Fecal fluid: total osmolality is **assumed** to be 290 mOsm (~ serum)
Solute gap = serum (equivalent to fresh stool osm) – 2 x [Na + K (stool)]: increased
Decreased stool Na+ (and anions)
    Total Na+ may in fact be NML, but it is diluted by hypotonic transudate

Secretory Diarrhea

Output > 1 L in 24 hrs; continues with 48 hr fast
Fecal fluid: total osmolality is **assumed** to be 290 mOsm
Solute gap: decreased

Note: the solute gap is normally NEGATIVE, since feces are more concentrated than serum!

Approach to Chronic Diarrhea

Always look for stool ova and parasites

If stool output < 200 g/d: colonoscopy + Bx
If stool output > 200 d/d: suggests upper (small bowel) origin (would expect low leukocyte esterase)
  NML fecal fat
    No solute gap: secretory
    Elevated solute gap: osmotic
  Increased fecal fat (steatorrhea)
    Small bowel Bx, culture, UGI series, Hydrogen Breath Test (HBT)
      Positive: establish Dx
      Negative: empiric pancreatic enzyme supplementation

ACUTE MESENTERIC ISCHMEIA	ETIOLOGY Embolus (50%) Post-MI or atrial flutter Severe PVD	"Pain incongruent to exam" Severe acute abdominal pain Often with lactic acidosis		**Thrombolysis** or angioplasty
CHRONIC MESENTERIC ISCHEMIA (INTESTINAL ANGINA)	**RFs** Vascular disease DM II HTN Hyperlipidemia	Occlusion of the mesenteric arteries results in chronic hypoperfusion Pain is post-prandia, and may be severe May lead to sitophopbia	Abdominal arteriography CT/MR Angiography	**Angioplasty**
DIARRHEA MIMICS	**PSEUDODIARRHEA** IBS, hyperthyroidism **FECAL INCONTINENCE**	**PSEUDODIARRHEA** Increased frequency of stools without change in consistency Stool output < 200 g in 24 hrs **FECAL INCONTINENCE** : overflow, reservoir, rectosphincteric, IAS dysfunction		
DYSMOTILE DIARRHEA	ETIOLOGY Amyloidosis Sarcoidosis Autonomic neuropathy (e.g. secondary to DM)	Small bowel stasis → commensal bacterial overgrowth → replacement of small bowel aerobes by colonic anaerobes → cdeconjugation of bile salts → bloating, **diarrhea,** malabsorption **RF** for overgrowth Blind-Loop Syndrome: formation of small static pockets secondary to diverticulosis or surgical anastamosis		
SECRETORY DIARRHEA	Occurs when secretion > absorption ETIOLOGIES Bacterial enterotoxin Circulating secretogogues Long-chain FAs Some laxatives (diphenylmethanes,	**Pancreatic Cholera** (VIPoma) Due to tumor secreting VIP Profuse watery diarrhea Hypokalemic metabolic acidosis Hypochlorhydria **Zollinger-Ellison Syndrome** Due to tumor secreting gastrin	**VIPoma:** Increased serum VIP **ZES**: increased fasting gastrin Positive secretin test Increased acid output **Cholera**: stool culture	

	anthraquiones)	Peptic ulcers (extensive and refractory) Secretory diarrhea **Asiatic Cholera** Bacterial enterotoxin results in massively increased Cl- secretion		
OSMOTIC DIARRHEA	**Ingestion** Magnesium sulfate Lactose and Other Carbohydrates The colonic bacteria generate SCFA as an intermediate to end-products → osmotically active **Malabsorption** (Chronic) Pancreatic insufficiency Biliary obstruction Celiac disease Whipple's disease (chronic mucosal infection) Lymphoma (lymphatic obstruction) Sort Gut Syndrome (resection)			
INFLAMMATORY DIARRHEA	ETIOLOGY *Shigella, Salmonella,* Amebic Dysentery, *Campylobacter, Yersinia,* EIEC, EHEC, *C. difficile*	The organisms may infect the large *and* small bowel	Positive fecal leukocytes Positive lactoferrin Bloody and prurulent diarrhea (dysentery) Typically smaller volumes	
NON-INFLAMMATORY DIARRHEA	ETIOLOGY Viral, *Vibrio*, *Giardia*, ETEC, foodborne gastroenteritis (*S. aureus* toxin)	Infection is usually limited to the small intestine	Negative fecal leukocytes Negative lactoferrin Voluminous watery diarrhea	
FACTITIOUS DIARRHEA	ETIOLOGY Laxative abuse (eating disorders)		The stool osmolality must be measured Osm << 290 mOsm This implies that the stool has been	

	Polle Syndrome		exogenously diluted Stool cannot be diluted to < 290 osm by a normal GI tract	

CELIAC DISEASE

1:133 prevalence in U.S F > M Classic presentation in < 5% of cases	PATHOGENEISIS This is an autoimmune disease that is driven by exogenous antigens (wheat gluten, rye and barley prolamine) Tissue damage is due to intraepithelial T-cells 10% develop associated GI malignancy 10% develop DH Celiac Disease is seen in 80% of DH cases **Environmental** α-gliadin (subtype of wheat gluten) is the most irritating antigen Similar to E1b antigen of adenovirus Ad12 → chronic inflammation Prolamines also incite reactions **Genetic** Mich higher prevalence of HLA-DQ2/DQ8 alleles, relative to general population tTG binds to gluten and increase affinity to MHC on APCs → increased T-cell activation **Mechanical** The small bowel rush border becomes permeable Celiac: increased expression of zonulin → increased leak and trafficking PRESENTATION **Classic**: weight loss, watery diarrhea, steattorhea **Latent** Positive serology without tissue changes	**Serology** Anti –tissue transglutaminase Ab IgA This is the preferred test IgA deficiency seen in2% of pts : so obtain total serum IgA If low, use anti-gliadin IgG **Endoscopy and Bx** Flattened plicae, scalloped edges Hsitology: villus atrophy, crypt hyperplasia, mucosal inflammation, increased intraepithelial lymphocytes Changes are seen from the duodenum to the upper jejunum **Physcial Exam** Emaciation Doughy abdomen Clubbing Peripheral edema Ecchymosis Bone tenderness Angular stomatitis, glossitis, cheilosis Peripheral neurpathy	**GLUTEN-FREE DIET** No wheat, rye, barley, farina, splelt Initally no oat gluten, milk/lactose These may be re-introduced Substitute: rice, corn, potato, soybean, starch, millet

	Silent Positive serology, inflammation on Bx, BUT *asymptomatic* **Minimal** Iron and folate deficiency without anemia VitD and Ca2+ deficiency: osteogenic bone disease Abdominal Cramping, bloating: previous Dx of IBS **Severe** Megaloblastosis Neurologic deceits due to B12 defifiency Profuse diarrhea Weight loss Infertility and menstrual irregularity Tetany and cramps (hypocalcemia) Easy bruising and bleeding Short stature Miscarriage COMPLICATIONS **Malignancy** Increased risk of GI lymphoma, adenocarcinoma (mouth, oropharynx, esophagus, small bowel), esophageal SCC **Ulcerative Jejunoileitis** Refratory to GFD; requires immunomodulation Multiple ulcers in the distal small bowel; may actually perforate **Refractory Sprue** Not responsive to GFD; requires immunomodulation or bowel rest with TPN Collagenous subtype: the submucosa is fibrosed		

INFLAMMATORY BOWEL DISEASE

GENERAL FEATURES

EPIDEMIOLOGY
Preferentially affects Caucasians (esp. Ashkenazi Jewish)
Prevalence of IBD are equivalent amongst M and F
Overall, there is a bimodal incidence: peak onset in early adulthood (18 – 35 yrs; major peak) and 30 – 55 yrs
There seems to be a preference for northern climates (US > UK > Canada > Scandanavia)

RFs for CD
- Tobacco: DECREASES the risk of UC but INCREASES the risk of CD
- NSAIDs : Increases severity of disease (paradoxical), but not the incidence
- OCs: may increase risk of CD
- Environment: IBD is more prevalanet in the developed world (hygiene hypothesis)
- NOD2 mutation and defects in autophagy

RFs for UC:
- NSAIDs
- Environment: developed world

PFs for IBD:
- Tobacco: DECREASES risk of **UC**
- Breastfeeding
- IL-23R mutation
- Appendectomy < 20 yrs: DECREASES risk of UC

PATHOGENESIS
The underlying event Is hypersensitivity to normal gut flora
Some **genetic susceptibility**
- **NOD2:** a RF for ileal and fibrostenosing CD (RR > 40)
  - The WT protein activates NF-κβ → regulates expression of IL-1, IL-6, IL-8, and TNF-α : these are involved in **innate** immunity
  - Mutations result in increased synthesis of cytokines **in response to LPS**
  - Thus, the end-result in unregulated inflammation triggered by bacterial LPS
- **IRGM**: a RF for CD
  - Mutations results in decreased autophagy → decreased intracellular killing → decreased clearance
- **IL-23R**: a **protective** factor in *both* CD and UC
  - Mutations results in decreased TH17 activation

SCREENING for CRC
Begins 7 – 8 yrs after Dx
Initial screening colonoscopy for current extent of colitis; extensive Bx
    No dysplasia + extensive colitis: repeat colonoscopy q 1 – 2 yrs, then q. 1 – 3 yrs if 2 x benign
    No dysplasia + proctosigmoiditis (< 35 cm) : does not require additional screening

TREATMENT
A stepped-up approach, depending on severity
Limited: 5-ASAs and ABx
Moderate: 6-MP/Azathiprine, Methotrexate, Corticosteroids, Budesonide (CD only)
Severe: Anti-TNF agents, α4 integrin antagonists (CD), CSA (UC; rarely used)
Fulminant: Surgical resection

Strategy specific to CD
    Maintenance of surgical remission in CD: 5-ASA
    Induction *and* **maintenance** of remission in moderate **CD**: **methotrexate**
    Fistulizing CD: ABx and 6-MP
    Perianal disease: ABx
Strategy specific to CD
    Induction of remission in limited UC: 5-ASA
Strategy common to both CD and UC
    Induction of remission in moderate disease: **corticosteroids (systemic)**; BUT NOT effective for maintenance
    Maintenance of remission: **6-MP**

MAJOR ADVERSE EFFECTS
5-ASA: myelosuppression, hepatitis, interstitial nephritis, ND, rash, headache
Steroids: DM, Cushing's, depression
ABx: peripheral neuropathy
6-MP: hepatotoxocicity, myelosuppresion, pancreatitis, neutropenia, GI distress
Methotrexate: hepatotoxicity (fibrosis), myelosuppression, pulmonary fibrosis, teratogenicity, alopecia
Infliximab: hypersensitivity, serum sickness, hepatotoxicity, heart failure, infections, demylenation, SLE
CSA: nephrotoxicity, hirsutism
α4-integrin antagonists: PML

The 5-Aminosalicylates (5-ASAs)

Mesalamine (active moiety of sulfasalazine)

TX: limited UC and CD

UC: induction and maintenance of remission

CD: maintenance of surgical remission; poor control of medical remission

Pharm: oral and topical formulation, depending on extent of disease

Mech: free radical scavenger ; inhibitor of PG synthesis

AR: rash, headache, ND, myelosuppression, hepatitis, interstitial nephritis

Corticosteroids

Can be used to **convert to remission**, with <50% maintenance once discontinued

Thus, they are not effective in maintaining remission

Topical (enema, foam, suppository): proctitis and L-sided colitis

Oral: moderate and severe UC, CD

Parenteral: severe and toxic UC, CD

Antibiotic Therapy (CD)

Metronidazole

TX: fistulizing CD, perianal CD, ileocolonic CD (may actually convert to remission)

AR: peripheral neuropathy, GI distress

Ciprofloxacin

Ileocolonic, colonic, and perianal CD

Thiopurines (azathiprine, 6-MP)

TX: maintain remission in UC and CD; generally not used for induction
fistulizing CD

AZA → non-enzymatic degradation to 6-MP → converted to 6-MMP by TPMT
6-TU by Xanthine Oxidase
Thiosinic acid by HPRT → 6-TG (active)

6-MMP causes hepatotoxicity and 6-TG causes myelosuppression

Requires 12 wks for maximal effect

AR: pancreatitis, GI distress, heaptotoxicity, myelosuppression

Methotrexate

Inhibits DHFR

TX: induction and maintenance of CD (IM)

AR: hepatic fibrosis, myelosuppression, pulmonary fibrosis, alopecia, teratogenicity, abortion

Anti-TNF Agents

Infliximab

AR: hypersensitivity, serum sickness, demyelination, drug-induced SLE, hepatotoxicity, NHL, heart failure, infections

α4-integrin Antagonists
Mech: inhibit chemotaxis of inflammatory cells
TX: CD refractory to anti-TNF
IV: PML

Cyclosporine
TX: rarely used for fulminant UC
AR: HTN, renal failure, hirsutism

CROHN'S DISEASE	Inflammation affects all layers of the GI wall (Transmural) May occur anywhere (oral cavity to cloaca) Usually manifests as discrete skipped lesions 45% ileocolitis 30% ileitis or jejunoileitis 20% colitis 5% gastroduodenitis Other location are rare F > M Onset during 20s – 40s	PRESENTATION Abdominal pain Nob-bloody (typically) diarrhea Weight loss Fatique Iron deficiency anemia (bleeding and decreased absorption) *Ileocolitis* RLQ pain, diarrhea Looks like acute appendicitis *Ileitis* and *Jejunitis* Diarrhea, bloating Small bowel obstruction (adhesions) *Colitis* **Hematochezia**, diarrhea *Perianal Disease* Skin tags, fitulas, perirectal abscess, anal canal stenosis Perianal Disease (20% in CD) **Extraintestinal Manifestations** Erythema nodosum Pyoderma gangrenosum Iritis, uveitis, spiscleritis Sacroiliitis, ankylosing spondylitis, peripheral arthritis	**Physical Exam** Tachycardia RLQ tenderness, distension, or palpable mass Perianal disease Extraintestinal signs **Capsule Endoscopy and Colonoscopy** Stellate and apthous ulcers Mucosal cobblestoning **Tissue Bx** Non-caseating granulomas Longitudinal and stellate ulceration **Serology** Positive ASCA (60%) Positive OmpC (50%) These indicators are not diagnostic, but may support CD in low-prevalence populations	Medical Therapies Bowel rest and TPN Elemental Diet Surgical resection or stricturoplasty

		COMPLICATIONS Vitamin deficiencies: B12, VitD Iron deficiency and anemia Fistulae Enteroenteric, enterocutaneous, enterovescicular, rectovaginal Perforation and Sepsis Abscess formation (occurs after perforation) Stricture (may result in obstruction of the small bowel, where the lesion is most common) Increased risk of CRC With involvement of > 1/3 of colon Requires very vigilant screening Gallstones: due to bacterial overgrowth or malabsoprtion Renal stones: due to enteric hyperoxaluria PATHOGENESIS Excessive T-cell predominant inflammation (TH1 and TH17 arm: IL-12, IFN-γ, TNF-α)		
ULCERATIVE COLITIS	M > F Inflammation in the superficial mucosa only Involves colon only (rectum → proximally)	PRESENTATION Fecal urgency Tenesmus Hematochezia Abdominal pain Fever Iron Deficiency and Anemia (more likely than in CD, due to chronic blood loss)	**Physical Exam** Tachycardia Abdominal tenderness and distension Blood in rectal vault Extraintestinal signs **Serology** Increased p-ANCA (> CD)	Topical ASA and corticosteroids fro limited diseaseof trhe distal colon Combined oral and topical ASAs Severe: Continue mesalamine + add immunomodulator or

	Proctitis: 20% L-sided colitis: 50% (including limited rectosigmoiditis) Pancolitis: 30%	*Pancolitis* Severe bloody diarrhea, diffuse abdominal pain, anemia *Proctitis* Fecal urgency, tenesmus, hematochezaia COMPLICATIONS Toxic megacolon Seen in background of fulminant pancolitis with microperforations TX: emergent colectomy Refractory GI Bleeding Increased risk of CRC With L-sided disease and pancolitis PSC PATHOGENESIS Excessive B-cell (humoral) and T-cell response (TH2 arm: IL-4, IL-5, IL-13)	**Colonoscopy** Friable mucosa with erythema **Colonic Bx** Expanded laminal propria Neutrophilic infiltration Crypt abscesses	biologic agent If fulminant: parenteral steroids, bowel rest, ABx **Surgery** A total colectomy is preferred for severe disease at any location Indication: toxicity, perforation, anemia, fatigue, hemorrhage, refractory disease, dysplasia

FUNCTIONAL GI DISEASE (FGID) *and* IBS

IRRATABLE BOWEL SYNDROME	The leading from of FGID (> 90%) Prevalence is 15 – 21% 3:1 F predominance 80% with concurrent psychiatric illness	PATHOGENESIS Involves disruption of normal homeostasis between CNS, GI function, GI sensation, GI flora, and inflammation The dysregulation may be triggered by remote acute gastroenteritis and persistent changes	ROME III Model Abdominal pain > 3d/mo in > 3 mos. Symptom onset > 6 mos. before Dx Requires ≥ 2 of these symptoms: Alleviated by defecation Change in stool frequency Change in stool consistency	The only therapeutics with demonstrated relief of global symptoms: Probiotics Psychoterapy Antidepressants **Dietary Fiber** (Psyllium, bran) May have some placebo effect

		Genetic BDNF, SNPs → affect CNS sensory perception **Diet** Affects all areas **Environment** Stress May be instigated by **ACUTE GASTROENTERITIS** **Inflammation** Increased lymphocyte density (per ganglion) Inflamed myenteric plexus Increased cytokines: TNF, IL-1, IL-6, IL-8 Increased mast cell density in antrum, terminal ileum, and colon → degradulation → visceral hypersensitivity The inflammation may progress to loss of ganglion cells **Altered Gut Flora** **RFs** during acute gastroenteritis Female gender Severe diarrheal illness Weight loss > 10 lbs Bloody diarrhea **Dysfunction ENS** Increased visceral hypersensitivity to stretch (pain is reported at lower volumes of balloon distension) PRESENTATION There are three forms of IBS IBS-Diarrhea IBS-Constipation IBS-mixed	**EXCLUDE the following alarm signs:** Rectal bleeding Weight loss Iron deficiency anemia Nocturnal symptoms FHx of PMHx of CRC, IBD, Celiac Onset > 50 yrs Guiac +ve stool Other features (supports the Dx) **Abdominal tenderness**: due to visceral hyperalgesia Tenesmus Incomplete stooling: rectal dissatisfaction Passage of mucus Bloating Distended sensation **Screening** IBS-D or IBS-M Screen for celiac disease Typical IBS without alarm signs No routine testing Age < 50 yrs + typical IBS without alarm signs No routine colon imaging Age > 50 yrs or alarm featrures Routine colonospcpy Thus, routine colonoscopy recommended for age > 50 or alarm symptoms Otherwise, no further screening	AR: increased bloating **Anticholinergics** (dicyclomine, hyocysamine) Used intermittently Reduces pain and bloating **Antidepressants** (tricyclics, SSRIs) Global relief of IBS symptoms (including pain) **ProBx** (*Bifidobacterium*) Global relief of IBS symptoms **Psychotherapy** (CBT, hypnotherapy, IPT) Global relief of IBS symptoms **ABx** (rifaxamin) Temporary reduction in bloating **Prokinetics** No efficacy EXCEPT cisapride **Antidiarrheals** Decreases stool frequency without relief of other symptoms WITHDRAWN from market **5-HT4 agonist** (tegaserod) AR: CV events Effective in IBS-C **5-HT3 antagonist** (alosetron) AR: ischemic colitis Effective in IBS-D in females

DISORDERS OF SMALL BOWEL MOTILITY

GENERAL FEATURES

INNERVATION and NORMAL MOTILITY
ICC in the myenteric plexus generate slow waves (BER) throughout the small bowel
NML migration of food bolus requires 2 hrs
The primary mode of transit is via ring contractions
  These occur at spike potentials; 7 – 12 cycles/min (decreasing frequency distally); localized peristaltic effect

Excitatory NTs: Ach, Substance P
Inhibitory NTs: NO, VIP
Excitatory endocrine substances: CCK, gastrin, motilin, 5-HT, T3/T4
Inhibitory endocrine substances: secretin, glucagon

Fed State: segmentation predominant
Isolated ring contraction (5 s in duration) involvement of sort tracts (1 – 5 cm)
Propagated contractions are rare, and occur over short distances

Fasting State: propulsion predominant
Occurs 4 – 6 hrs after most recent meal and is maintained until next
There are three phases
  Phase I: no activity
  Phase II: irregular ring contractions (may occur as signlets, doublets, or triplets)
  Phase III: MMC
    Ring contractions occur at the maximal; frequency (12 cycles/min) and are very large in amplitude
    Contractions begin at any point along the small bowel and migrate caudally (90 min. from duodenum to terminal ileum)
  Propagates at 6 – 8 cm/min

ILEUS	Acute failure of intestinal contraction Reversible ETIOLOGY Post-surgical (abdominal) Electrolyte abnormalities Medications: opioids, diltiazem, anticholinergics, CCBs Pancreatitis Peritonitis	Obstructive symptoms: abdominal pain, NV, fullness, distension, loss of flatus and stool May occur as a result of decompensated chronic pseudo-obstruction	R/O mechanical obstruction Exam: distended abdomen, diffuse tenderness, no guarding or rebound CT: dilated loops of small bowel, decreased colonic gas, no cut-off sign	**NG tube**: suction gas and fluid proximal to the obstruction **No ingestion** **Discontinue causative medication** **Encourage ambulation** to increase endogenous

	Mesenteric ischemia Sepsis			motility **Restore electrolytes**
SMALL BOWEL PSEUDO-OBSTRUCTION	Chronic failure of intestinal contraction Irreversible **RF** Neurotropic medications **ETIOLOGY** Loss of ICC Progressive neuromuscular disease Dermatomyositis Scleroderma Roux-en-Y gastric bypass Gastroenteritis Paraneoplastic neuropathy Medications Post-surgical Thyroid disease Electrolyte abnormalities	Obstructive symptoms: abdominal pain, bloating, distension, NV, constipation May have lack of flatus and stool	X-ray: Dilated bowel > 3 mos, air-fluid level CT: R/O obstruction	**Dietary modification** **TPN** **ABx rotation** for diarrhea **Decompression** with venting tubes and ostomies **Pro-kinetics**
SMALL BOWEL OBSTRUCTION	Adhesions Tumors Hernia Intussusception	May result in ischemic necrosis and perforation		**Monitor for 24 hrs**

COLONIC *and* **ANORECTAL DISORDERS** (CONSTIPATION and INCONTINENCE)

GEENRAL FEATURES

INNERVATION

The L and proximal transverse colon receive DUAL parasympathetic innervaiton (vagus + pelvic splanchnic from S2 – S4)

The R and distal transverse colon receive single innervations from the splanchnic nerve

MYOGENIC REGULAITON

Slow waves are generated by the Interstitial Cells of Cajal (ICC)

In L colon: propagation is cuadad
In R colon: propagation in orad
Thus, with spike potentials, the progation of contractions will generally be towards the rectum

NON-AUTONOMIC REGULATION
CCK, motilin, 5-HT, gastrin, substance P, neurotensin, GABA: excitatory
Secreetin, glucagon, VIP, neuropeptide Y, NO: inhibitory
NO is the major non-autonomic NT in the colon and rectum

The gastrocolic reflex: Meal → presentation of fat to duodenum → CCK release → increased mass movements in colon
there is an elevation in the resting luminal tone → reduced storage

Motor activity is maximal at waking and after meals

COLONIC INTERTIA	Colonic pseudo-obstructiion with NML caliber (non-dilated) Due to decreased density of enteric neurons F >>M Onset 15 – 40 yrs	Infrequent defection or excessive straining No response to laxatives and fiber.	Marks are diffused throughout the colon and move slowly	
OUTLET DELAY	Disorder of the rectum and/or sphincter complex Thus, it represents a disorder of defecation		Marker transit through the colon in SML, but they are retained in the rectum and sigmoid	
ACUTE MEGACOLON (OGILVIE'S SYNDROME)	Colonic pseudo-obstruction with acute dilation r/o mechanical obstruction Due to disruption of autonomic input to the colon myenteric plexus Symp >> Parasymp Seen in hospitalized patients following Surgery (orthopedic, GYN,	Occurs 4 – 5d. after uncomplicated surgery	Dilated colon on abdominal plain film	**Neostigmine (IV)** **Colonoscopic** **Decompression**: if refractory to medical therapy **Surgical Decomopression**: with evidence of ischemia or perforation

	abdominal) Sepsis Cardiac/Neurologic disease			
DIVERTICULOSIS	Herniation of the colonic mucosa through muscularis Usually between the mesenteric and interarterial taenia, where the longitudinal and circular muscle layers are interrupted Nearly always found in the sigmoid and descending colon Prevalence is 1/3 by 50 yrs **RF:** age, dietary fiber insufficiency (increases motor activity and luminal pressure)	Brisk and painless bleeding Due to ruptured adjacent arterioles or direct erosion into vessels at the sac neck		
DIVERTICULITIS	Occurs in 10 – 25% cases of diverticulosis over 10 yrs	Diverticulum → obstruction with stool → microperforation → inflammation **Complications** Peridiverticular abscess Fibrosis → large bowel obstruction Fistulae: to bladder, vagina, small bowel Free perforation → peritonitis and sepsis Bleeding	Palpable mass + fever + leukocytosis + tenderness (direct or rebound) Usually presents as suprapubic tenderness + flu-like illness	
HIRSCHPRUNG'S DISEASE	Defect in NML migration of neural crest cells to the GI tract There is an absence of ganglions in the plexi of the	Neonatal constipation Massively dilated NML colon proximal to the effected tract	Barium plain film Anorectal manometry Pneumatic distension normally results in reflex inhibition of the IAS	**Surgery**

	large bowel The IAS is always affected, and spasticity extends rostrally AR and AD inheritance Mutation in RET proto-Oncogene: tyrosine kinase receptor encoded by neural crest cells Sporadic M > F	Hypertonic distal bowel Inability to relax the IAS	Rectal Bx > 3 cm from the anal outlet AChE staining demonstrates excess of cholinergic neurons in the submucosa	
DYSSYNERGIC DEFACATION	Acquired behavior	Failure to relax the EAS and PRM	Anal manometry Inaprorpateincrease in canal pressure and EAS EMG during the Valsalva maneuver	**Biofeedback techniques**; effective in adults, but not in peds
OVERFRLOW INCONTINENCE	**RFs** Peds Elderly in institutions Dementia and Psychosis	Fecal impaction → megarectum → blunted rectal sensation → overflow of semi-liquid stool around impacted bolus	Digital rectal exam Abdominal plain film	Disimpaction and cleansing
RESERVOIR INCONTINENCE	**RFs** IBD with proctitis Pelvic XRT Rectal surgery	Decreased rectal compliance and storage	Clinical Sigmoidoscopy	Decrease dietary fiber Tx inflammation Anti-kinetic drugs: loperamide, diphenoxylate Colostomy
IAS INCONTINENCE	**RF** Middle-age and ederly Scleroderma Shhincterotomy	IAS injury → autonomic degeneration → atonia	Slow seepage	Loperadmide Plug
RECTOSPHYNCTERIC INCONTINENCE	Occurs in middle-age and elderly women with no prior Hx of anorectal disease		IAS weakness: decreased resting pressure EAS trauma : decreased active contractile pressure	

	ETIOLOGY DM MS Cord Injury		Peipheral Neurogenic : decreased active contractile pressure and PRM strength Central Neurogenic: same as Peripheral + decreased rectal sensation	