MANAGEMENT OF GALLSTONE DISEASE

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Learning Objectives:

After this presentation, participants will understand:

1. The epidemiology and risk factors for the development of gallstones.
2. The natural history of gallstones and clinical features of gallstone disease.
3. The optimal therapeutic options for gallstone disease.
4. The significance of gallbladder emptying in the pathogenesis of gallstones and gallbladder disease.
MANAGEMENT OF GALLSTONE DISEASE

Cholelithiasis is a common occurrence in Western societies. An estimated 15 million women and 5 million men in the U.S. have gallstones, with approximately 1 million cases diagnosed annually. 500,000 cholecystectomies are performed each year in the U.S. at an annual cost of 4 billion dollars. Six-thousand people die each year from gallstone disease. The magnitude of this problem, in terms of both its morbidity and cost, has led to the development of non-operative techniques for treating and perhaps preventing gallstone disease.

I. Epidemiology

- 80% of gallstones in U.S. are pure cholesterol or mixed stones with at least 50% cholesterol; 20% of gallstones are pigment and/or calcified stones.

- Pigment stones (e.g. Calcium-bilirubinate) major risk factors:
  
  Chronic hemolysis
  Alcoholic cirrhosis
  Biliary infection
  Age
  Demographic characteristics: Far East more than West, rural more than urban

- Cholesterol stones major risk factors
  Obesity
  Female sex hormones
  Bile acid malabsorption
  High calorie diet (high polyunsaturated fat) clofibrate, gemfibrozil, cholestyramine, rapid weight loss,
  Demographic characteristics: Northern European, North and South America, American Indians, family history

*Note - "healthy" activities such as diet high in polyunsaturated fats, rapid weight loss or taking a cholesterol lowering drug may increase the risk of cholesterol gallstone disease.

II. Pathophysiology of Cholesterol Gallstones

- Genetic or metabolic predisposition
- Supersaturation of bile with cholesterol (biliary cholesterol vs. bile acids or lecithin)
- Nucleation and crystal growth
- Development of macroscopic stones (poor gallbladder emptying)
III. Natural History of Gallstones

- 80-85% of gallstones cause no symptoms and can be managed conservatively without treatment
- Typical symptoms: indigestion, biliary colic (75%)
- Major complications: acute cholecystitis, jaundice, cholangitis, pancreatitis, gallbladder carcinoma
- Risk factors to develop symptoms: large stones (> 2.5 cm), non-functioning gallbladder, calcified gallbladder wall (carcinoma)
- Stone duration before symptoms develop: 12-14 years
- Asymptomatic gallstones natural history: 15-20% develop symptoms in 15-20 years; 90% develop biliary colic before major complications
- Symptomatic gallstones natural history; 50-75% continue to have symptoms; usually within one year often with symptoms of increasing severity.

IV. Diagnosis

- Abdominal ultrasound: 95% sensitive and specific
- Oral cholecystogram: assesses calcification and density of stones; assesses gallbladder function.
- Abdominal CT scan: poor sensitivity; best test to assess density and type of stone (Hounsfield units)
- ERCP - best test for common bile duct stones
- Duodenal drainage for cholesterol crystals of controversial significance.
- Radionuclide biliary scan (HIDA): most useful for diagnosis of acute cholecystitis.

V. Treatment

- Treatment depends upon presence of symptoms, likelihood of complications, morbidity of complications (or treatment) and cost.
- Treatment options currently available in U.S.:

1) Cholecystectomy (routine vs laparoscopic)
2) Gallstone dissolution with bile acids (slow dissolution)
   - Chenodeoxycholic acid (CDC or Chenodiol)
   - Ursodeoxycholic acid (UDC or Ursodiol)
3) Contact dissolution
   - Methyl tert-butyl ether (MTBE)
   - Monooctanoin (common bile duct stones)
4) Extracorporeal shock wave (lithotripsy) (ECS)
1) Surgical treatment - cholecystectomy
   - Only definitive treatment, relieves symptoms in 75-90%
   - Mortality is low - 0.17% for elective surgery without COMMON BILE DUCT exploration; age and COMMON BILE DUCT exploration increase risk
   - Cholecystectomy is treatment of choice for most symptomatic patients
   - Laparoscopic cholecystectomy (with or without ERCP to clear COMMON BILE DUCT) is now the preferred surgical technique because of rapid recovery time.

2) Gallstone dissolution with bile acids (Chenodiol, Ursodiol)
   - Bile acid dissolution is useful only for cholesterol gallstone
   - CDC and UDC act by:
     a) Depressing secretion of cholesterol into bile (low cholesterol-solubility capacity due to hydrophilic property) - Major effect
     b) Expands the bile acid pool and increases bile acid secretion - Minor effect

A) Chenodiol (CDC)
   - Approved by FDA in 1983
   - Criteria for treatment: cholesterol stones, small stones, functioning gallbladder (opacifies on OCG), thin patient
   - Contraindications for treatment: pigment stones, calcified stones, large (> 1.5 cm) stones, liver disease, pregnancy, disabling symptoms
   - Optimal dosage and duration: 15 mg/kg day for up to two years.
   - Results: 13.5% complete dissolution at two years, 40% partial dissolution at two years;
   - Recurrence rate of 10%/yr (to 50% at five years) following dissolution; low dose CDC does not prevent recurrence.
   - Predictors of successful dissolution: floating stones on OCG; less than 3 stones; less than 1.5 cm diameter; high plasma cholesterol; weight < 100% of ideal body weight
   - Chances of complete dissolution in this ideal setting: 60-90%
   - Complications: diarrhea (33%); increased plasma cholesterol by 20 mg/dl; increased liver enzyme (AST)

B) Ursodiol (UDC)
   - Approved by FDA in 1988
   - Criteria for treatment and efficacy; essentially the same as CDC
   - Optimal dosage and duration: 10-13 mg/kg/d
   - Advantages: no hepatotoxicity; no alteration in plasma cholesterol; no diarrhea.
   - Stone recurrence may be prevented with low dose UDC
   - Ursodiol has replaced CDC as bile acid of choice for gallstone dissolution
   - Combination CDC-UDC regimens have been used with comparable safety to UDC alone.
3) Contact dissolution (fast dissolution) - **cholesterol stones only**

**A)** Methyl Tert-butyl ether (MTBE) - experimental
- Percutaneous placement of pigtail catheter into gallbladder (through skin, liver and into gallbladder)
- Empty bile from gallbladder, then 5-10 ml MTBE infused for 5-10 min, then repeat until dissolved.
- Dissolution takes minutes (up to 90), successful in > 90% of cholesterol stones.
- Side effects: invasive procedure; sedation, hemolysis or duodenitis occur if MTBE overflows out of gallbladder; bile peritonitis
- Gallbladder ablation following dissolution may be a promising technique in the future.

**B)** Monoctanoin (glycerol-1-monooctanoate)
- For cholesterol common bile duct stones only
- Perfusate monoctanoin via t-tube into COMMON BILE DUCT for days to weeks
- Side effects; diarrhea, abdominal pain, nausea
- Most retained COMMON BILE DUCT stones can be removed by endoscopic retrograde cholangiopancreatography or T-tube extraction

4) Extracorporeal Shock Wave Lithotripsy of Gallstones (ECS)
- Experimental in U.S.
- All European Clinical Trials combine ECS with bile acid dissolution therapy, resulting in complete dissolution of 90% at 12-18 months.
- Criteria for treatment: 1-3 stones; all stones less than 3 cm in diameter; patent cyst duct (gallbladder visualizes on OCG);
- Effectiveness for calcified/pigment stones is unknown (exclusion criteria in most trials)
- Minimal complications: cutaneous petechiae, hematuria, biliary colic
- Minimal or no anesthesia; outpatient treatment
- Often requires multiple treatments for fragmentation

VI. Functional Biliary Tract Syndromes

1. Biliary dyskinesia (sphincter of Oddi dysfunction; SOD)
   - Differential diagnosis of post-cholecystectomy pain includes: common bile duct stones, strictures, biliary leak, IBS and SOD
   - SOD may require biliary manometry (during ERCP) for diagnosis
   - Suspect SOD when liver tests or pancreatic enzymes transiently increase with pain
   - Endoscopic sphincterotomy is treatment of choice

2. Gallbladder Dyskinesia (poor gallbladder emptying)
   - Abnormal GB emptying is a risk factor for stones
   - Abnormal GB emptying occurs in: DM, vagotomy, pregnancy, IBS
   - Normal GB emptying* by CCK cholescintigraphy: GBEF > 35-40%
   - Correlation of low GBEF with success of cholecystectomy for acalculous cholecystitis is high variable
   - RUQ pain in patient without gallstones is reproducible with balloon distension of the intestines (IBS)
SELECTION REFERENCES


