Pediatric Medical Liver Disease

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PRESENTATION OUTLINE:

I. Cholestatic Liver Disease
   A. Neonatal hepatitis
   B. Progressive familial intrahepatic cholestasis
   C. Paucity of intrahepatic ducts/Alagille syndrome
   D. Extrahepatic biliary atresia
   E. $\alpha$-1 Anti-trypsin deficiency
   F. Ductal plate malformations/ARPKD
   G. Wilson’s disease
what is it, gall bladder? can't you see I have a lot to do?

I maked these

you made STONES?

YOU'RE JUST SUPPOSED TO HOLD WHAT I GIVE YOU!

GET OUT! GO ON!

I maked these

theAwkwardYeti.com
I. Examples of cholestatic diseases:

<table>
<thead>
<tr>
<th>Mechanical obstruction</th>
<th>Non-obstructive intrahepatic cholestasis</th>
<th>Systemic illness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extrahepatic</strong></td>
<td><strong>Intrahepatic</strong></td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>Malignant</td>
<td></td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>Metastatic malignancy</td>
<td></td>
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<tr>
<td>Pancreatic carcinoma</td>
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<tr>
<td>Ampullary carcinoma</td>
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<td>Gall bladder carcinoma</td>
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<tr>
<td>Metastases to lymph nodes in porta hepatitis</td>
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</tr>
<tr>
<td><strong>Benign</strong></td>
<td>Benign</td>
<td></td>
</tr>
<tr>
<td>Choledocholithiasis</td>
<td>Abscess</td>
<td></td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>Suppurative cholangitis</td>
<td></td>
</tr>
<tr>
<td>AIDS cholangiopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital</td>
<td>Congenital fibrosis</td>
<td></td>
</tr>
<tr>
<td>- Choledochocele</td>
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</tr>
</tbody>
</table>

**Small bile ducts/canalicular**
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Vanishing bile duct syndrome
  - Chronic rejection in liver transplants
  - Sarcodeiosis
  - Drugs
- Inherited
  - Benign recurrent cholestasis
  - Progressive familial intrahepatic cholestasis
    - Gilbert's syndrome
    - Crigler-Najjar syndrome
    - Dubin-Johnson syndrome
    - Rotor syndrome
- Cholestasis of pregnancy

**Hepatocellular**
- Viral
- Alcoholic hepatitis
- Drug induced
- Autoimmune
- Malignant infiltration
- Vascular occlusion
  - Budd-Chiari syndrome
  - Portal vein thrombosis
- Metabolic/Hereditary
  - NAFLD/NASH
  - Iron overload
- Wilson's disease
- Alpha1-antitrypsin deficiency
- Galactosaemia
- Tyrosinaemia
- Cystic fibrosis

AIDS = acquired immunodeficiency syndrome; NAFLD = non-alcoholic fatty liver disease; NASH = non-alcoholic steatohepatitis.
A. Neonatal Hepatitis
   --Multifactorial disorder with myriad pathogenetic mechanisms

   --Diagnosis of exclusion based on adjunct testing:
     Laboratory investigation
     Electron microscopy
     Imaging studies
     Infectious disease work-up
     Clinical features
     Etc.
**TABLE 12.2. Conditions Associated with Neonatal Hepatitis.**

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic neonatal hepatitis</td>
</tr>
<tr>
<td>Infections, including cytomegalovirus, herpes virus, enterovirus (coxsackie B- and echovirus), rubella, hepatitis B, varicella, reovirus, paramyxovirus, parvovirus B19, toxoplasmosis, syphilis, toxoplasmosis, and bacterial sepsis (Escherichia coli and Listeria)</td>
</tr>
<tr>
<td>Metabolic conditions (see Table 12.3)</td>
</tr>
<tr>
<td>Endocrine, hypopituitarism</td>
</tr>
<tr>
<td>Obstructive, including biliary atresia, choledochal cyst</td>
</tr>
<tr>
<td>Chromosomal, including trisomy 17-18 syndrome, 21, and Monosomy X</td>
</tr>
<tr>
<td>Immune and hemolytic disorders (ABO and Rh incompatibility, spherocytosis, neonatal lupus erythematosus)</td>
</tr>
<tr>
<td>Total parenteral nutrition</td>
</tr>
<tr>
<td>TABLE 12.3. Metabolic Causes of Hepatitis (Neonatal or Acute).</td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td>Alpha-1-antitrypsin deficiency</td>
</tr>
<tr>
<td>Tyrosinemia</td>
</tr>
<tr>
<td>Bile acid synthesis disorders (oxysterol 7α hydroxylase deficiency, 3β hydroxy steroid dehydrogenase deficiency and oxosteroid 5β reductase deficiency)</td>
</tr>
<tr>
<td>Alagille syndrome</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Peroxisomal disorders (Zellweger syndrome, Refsum disease, di- and trihydroxycholestanoic acidemia)</td>
</tr>
<tr>
<td>Familial intrahepatic cholestatic syndromes (progressive familial intrahepatic cholestasis II, North American Indian childhood cirrhosis)</td>
</tr>
<tr>
<td>Fructosemia</td>
</tr>
<tr>
<td>Galactosemia</td>
</tr>
<tr>
<td>Mitochondrial mtDNA depletion</td>
</tr>
<tr>
<td>Neonatal hemochromatosis</td>
</tr>
<tr>
<td>Gaucher disease</td>
</tr>
<tr>
<td>Niemann–Pick disease type C</td>
</tr>
<tr>
<td>Wilson’s disease(^1)</td>
</tr>
<tr>
<td>Indian childhood cirrhosis(^1)</td>
</tr>
<tr>
<td>Ornithine transcarbamylase deficiency(^1)</td>
</tr>
</tbody>
</table>

\(^1\)Acute hepatitis pattern.
Common Histological Features of Idiopathic Neonatal Hepatitis (INH):

-- Pronounced giant cell transformation

-- Portal and lobular inflammatory infiltrates

-- Apoptotic bodies

-- Bile ductular reaction
INH: Giant cell transformation, portal/periportal infiltrate with lobular spill (H&E x 4)
INH: Feathery degeneration of hepatocytes, canalicular cholestasis and inflammation (H&E x 10).
INH: Mixed acute/chronic inflammation with eosinophils. Note neutrophil in bile duct epithelium (arrow) (H&E x 40).
INH: Canalicular and cytoplasmic cholestasis (arrows), extramedullary hematopoiesis (star), and giant cell transformation (H&E x 20)
INH: Moderate ductular proliferation (CK7 x 2) but no fibrosis
(Masson trichrome x 2)
INH: Microvesicular steatosis (H&E x 10).
INH: Canalicular and cytoplasmic cholestasis, apoptotic body, and feathery degeneration with focal giant cell transformation (H&E x 20).
Stage 2 fibrosis (Masson trichrome x 4).
INH: As possible causes are numerous, diagnosis often descriptive with suggestions for additional testing to determine etiology.

Helpful ancillary tests:
--Special stains:
  iron, copper;
  infections (CMV/HSV/Adenovirus) immunostains as CK7/CKAE1/AE3)
--Electron microscopy
--Quantification studies (iron/copper)
--Viral RT-PCR
--Serology
B. Progressive Familial Intrahepatic Cholestasis (PFIC):

--Originally described in 1965 in Byler kindred of Pennsylvania Amish
--Different subtypes classified on molecular profile

--All 3 types are caused by recessive mutations in different genes

--Benign recurrent intrahepatic cholestasis also described in 1965, now recognized as milder form of PFIC
PFIC I often shows ductopenia on histology
PFIC II may display a hepatitic pattern
PFIC III may present with cirrhosis
All three types may lead to neoplasia.
Canalicular membrane surface proteins, their substrates, and known associations with pediatric disease.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Biliary Transporter</th>
<th>Clinical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphatidylcholines</td>
<td>MDR3</td>
<td>Progressive familial intrahepatic cholestasis type 3</td>
</tr>
<tr>
<td>Aminophospholipids</td>
<td>FIC1</td>
<td>Progressive familial intrahepatic cholestasis type 1; Benign recurrent intrahepatic cholestasis type 1</td>
</tr>
<tr>
<td>Bile acids</td>
<td>BSEP</td>
<td>Progressive familial intrahepatic cholestasis type 2; Benign recurrent intrahepatic cholestasis type 2</td>
</tr>
<tr>
<td>Conjugated bilirubin</td>
<td>MRP2</td>
<td>Dubin-Johnson syndrome</td>
</tr>
</tbody>
</table>

Hepatocyte → Canalicular membrane

David Brumbaugh, and Cara Mack Pediatrics in Review 2012;33:291-302

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PFIC I: Portal inflammation and ductopenia (H&E x 10)
PFIC I: Pale canalicular bile (arrow) (H&E x 40).
PFIC I: Mild to moderate portal and lobular fibrosis (Masson trichrome x 4); CK7 highlights ductular proliferation and hepatocytes (x 10).
Ultrastructural feature of normal bile
Granular (Byler) bile in PFIC I liver found on electron microscopy.
PFIC III: Chronic active hepatitis with brisk inflammation and portal-portal bridging (H&E x 4).
PFIC III: Ductular hyperplasia and interface hepatitis (H&E x 20).
PFIC III: Ductular proliferation highlighted by CK7 (x 10); bridging fibrosis on Masson trichrome (x 4).
Applicable Antibodies:

<table>
<thead>
<tr>
<th>BSEP</th>
<th>MDR3</th>
<th>GGT</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="BSEP Image" /></td>
<td><img src="image2" alt="MDR3 Image" /></td>
<td><img src="image3" alt="GGT Image" /></td>
</tr>
</tbody>
</table>
C. Paucity of Intrahepatic Bile Ducts

Two general groups:

1. Syndromic
   -- Alagille syndrome (arteriohepatic dysplasia)

2. Non-syndromic
   -- Diseases in which paucity is associated with another identifiable condition:
     -- Infection (CMV, HSV, rubella)
     -- Immune abnormality, e.g. GVHD
     -- Hepatotoxicity
     -- Metabolic diseases (Zellweger syndrome, bile acid metabolism)
     -- Chromosomal abnormalities (45XO; trisomy 17, 18, 21)
     -- Extrahepatic biliary atresia
     -- Sclerosing cholangitis
     -- Langerhans cell histiocytosis
     -- Primary biliary cirrhosis
C. Paucity of Intrahepatic Bile Ducts: Alagille syndrome epidemiology:

| Etiology                                      | • Autosomal dominant genetic disease  
|                                              | • Mutations in the JAG-1 gene on chromosome 20p12 are responsible for AGS in more than 90 percent of patients; others have mutations in NOTCH-2 |
| Incidence                                    | • Approximately 1/100,000 live births |
| Gender Ratio                                 | • There is equal gender distribution |
| Age Predilection                             | • The majority of patients present before six months of age |
| Risk Factors                                 | • Mutation in the Jagged1 (JAG1) or NOTCH2 gene |
| Treatment                                    | • Currently no curable treatment exists and medical management depends on diagnosing and treating disease in each affected organ system |
| Prognosis                                    | • Predicting prognosis is difficult; however, it is dependent on the severity of liver damage and cardiac complications |
| Findings on Imaging                          | • ERCP: Narrowing of the extrahepatic biliary ducts and uniform narrowing of the intrahepatic ducts with reduced arborization  
|                                              | • Cholescintigraphy: Delayed visualization of gastrointestinal tract  
|                                              | • MR: Peripheral pulmonary stenosis. Structural abnormalities of the liver, with a combination of tumor-like nodules centered on a hypertrophic portal vessel and areas of major atrophy  
|                                              | • CT: Peripheral pulmonary stenosis; Butterfly vertebrae |

Table 1: Summary table of syndromic Alagille syndrome
Features of Alagille Syndrome:

A | Slit-lamp eye exam with posterior embryotoxon (arrow).
B | Classical cardiac abnormalities with frequency.
C | MRI of ren arcuatus.
D | Cerebral angiogram with moyamoya disease.
E | Trichrome stain on liver demonstrating paucity of bile ducts.
F |Characteristic facies: broad forehead, pointed chin, deep-set eyes.
G | Butterfly vertebral bodies (arrow).
Alagille syndrome (AS): Cholestasis and giant cell transformation (H&E x 10).
AS: Portal tract with no bile ducts (H&E x 20).
AS: Portal tracts with CK7 and H&E demonstrating proliferating ductules but no bile ducts (each x 10).
AS: No bile ducts in portal tracts (H&E x 20).
AS: CK7 in hepatocytes and one possible bile duct in portal tract (x 20).
Non-syndromic paucity of bile ducts: intense periportal inflammation (H&E x 4)
Non-syndromic paucity of bile ducts (H&E x 20).
Non-syndromic paucity of bile ducts: Cytoplasmic and canalicular cholestasis with plugging (H&E x 40).
Non-syndromic paucity of bile ducts: Ductular proliferation highlighted on CK7; portal fibrosis on Masson trichrome (each x 10).
## D. Extrahepatic Biliary Atresia:

<table>
<thead>
<tr>
<th>Gene</th>
<th>IHBD</th>
<th>EHBD</th>
<th>Gallbladder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jagged/Notch pathway</td>
<td>Abnormal</td>
<td>No findings</td>
<td>No findings</td>
</tr>
<tr>
<td>Hes1</td>
<td>No findings</td>
<td>Hypoplasia</td>
<td>Agenesis</td>
</tr>
<tr>
<td>HNF6</td>
<td>Ductal plate malformation</td>
<td>Abnormal</td>
<td>Agenesis</td>
</tr>
<tr>
<td></td>
<td>IH biliary cysts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HNF1β</td>
<td>Rarefaction of small IHBD</td>
<td>Undefined</td>
<td>Abnormal epithelium</td>
</tr>
<tr>
<td></td>
<td>Dysplasia of large IHBD</td>
<td></td>
<td>Dilated cystic duct</td>
</tr>
<tr>
<td>Foxf1</td>
<td>Normal</td>
<td>Undefined</td>
<td>Small or absent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Without epithelial cells</td>
</tr>
<tr>
<td>Foxm1β</td>
<td>Agenesis</td>
<td>Undefined</td>
<td>Undefined</td>
</tr>
</tbody>
</table>
Type I: Obliteration of common bile duct with patent proximal bile ducts.
Type IIa: Atresia of hepatic duct with cystic bile ducts at porta hepatis.
Type IIb: Atresia of cystic duct, common bile duct, and hepatic ducts.
Type III: Atresia of extrahepatic biliary tree and intrahepatic ducts of porta hepatis.
Common bile duct biopsy in biliary atresia. Left: Markedly fibrotic stroma with small ductular structures displaying pinpoint lumens. Right: CK7 stain (each x 4).
Biliary atresia: Liver wedge biopsy with bridging fibrosis. Left, H&E x 2; Right, trichrome x 2.
Biliary atresia: Ductal bile plugging; ductular proliferation on CK7 (H&E x 10, CK7 x 4).
Liver resection after failed Kasai procedure.
Probes demonstrate no luminal connection of intrahepatic biliary tree with small intestine anastomosis.
Macronodular cirrhosis with diffuse cholestasis and fibrosis.
EHBA: Portal fibrosis and proliferating ductules with ductal plugging and mild interface inflammation; hepatocytes have cytoplasmic cholestasis (right side) (H&E x 10).
Biliary atresia: Portal fibrosis and proliferating ductules with ductal plugging and mild interface inflammation; hepatocytes display cytoplasmic cholestasis (H&E x 10).
Treatment for Extrahepatic Biliary Atresia: 
--Kasai hepatopportoenterostomy:
Complications after Kasai procedure:

1. Ascending cholangitis (most common)
2. Portal hypertension
3. Intrahepatic biliary cavities
4. Poor growth and malnutrition

**Biliary atresia is most common reason for pediatric liver transplant in the US**
E. α-1 Anti-trypsin Deficiency

--Common cause of neonatal cholestasis

--Autosomal recessive disease causing low serum levels of alpha-1-antitrypsin (AAT) and leading to emphysema (80%, usually 20-39 years) and liver disease

--α1AT: 394 amino acid plasma glycoprotein synthesized predominantly by hepatocytes and encoded by gene at 14q31.3

--α1AT: Protease inhibitor (Pi) that inhibits neutrophil elastase released at sites of inflammation; also inhibits trypsin
Conditions Associated with Alpha-1 Antitrypsin Deficiency

Skin
- Necrotising Panniculitis
- Systemic Vasculitis
- Psoriasis
- Urticaria
- Angioedema

Liver
- Cirrhosis
- Neonatal Hepatitis
- Hepatocellular Carcinoma

Kidneys
- Proliferative Glomerulonephritis
- IgA Nephropathy

Intestines
- Inflammatory Bowel Disease

Lungs
- Chronic Obstructive Pulmonary Disease (Panacinar Emphysema)
- Bronchiectasis
- Asthma

Vascular
- ANCA-positive Vasculitis
- Abdominal and Intracranial aneurysms
- Arterial fibromuscular Dysplasia
α1AT: Liver displays bright intracytoplasmic eosinophilic globules in hepatocytes (arrows) near the limiting plate (H&E x 20).
α1AT: H&E (left) and PAS-Diastase (right) demonstrating accumulations of α-1 antitrypsin material (each x 20).
α1AT: Liver with α-1 antitrypsin deficiency showing marked fibrosis on reticulin (left) and Masson trichrome (right) (each x 2).
α1AT: Electron micrograph with accumulations of α-1 antitrypsin (arrows).
## Diagnostic Tests for Alpha₁-Antitrypsin (AAT) Deficiency and Associated Disease Risks

<table>
<thead>
<tr>
<th>Inherited Genetic Variants†</th>
<th>Protein Phenotype‡</th>
<th>Serum Protein Level§</th>
<th>Molecular Genotype¶</th>
<th>Risk of COPD</th>
<th>Risk of Liver Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZZ</td>
<td>Z</td>
<td>Very low</td>
<td>ZZ</td>
<td>Very high</td>
<td>High</td>
</tr>
<tr>
<td>ZNull</td>
<td>Z</td>
<td>Very low</td>
<td>Z/non-S, non-Z</td>
<td>Very high</td>
<td>Unknown</td>
</tr>
<tr>
<td>MZ</td>
<td>MZ</td>
<td>Intermediate</td>
<td>Z/non-S, non-Z</td>
<td>Possibly increased</td>
<td>Possibly increased</td>
</tr>
<tr>
<td>MNull</td>
<td>M</td>
<td>Intermediate</td>
<td>Non-S, non-Z/non-S, non-Z</td>
<td>Unknown</td>
<td>None</td>
</tr>
<tr>
<td>SZ</td>
<td>SZ</td>
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<td>SZ</td>
<td>Increased</td>
<td>Possibly increased</td>
</tr>
<tr>
<td>NULL</td>
<td>None</td>
<td>None</td>
<td>Non-S, non-Z/non-S, non-Z</td>
<td>Very high</td>
<td>None</td>
</tr>
</tbody>
</table>
α1AT treatment:

--Augmentation therapy or infusion of purified α-1 anti-trypsin from pooled human plasma

--Liver transplantation
F. Ductal Plate Malformation & Polycystic Kidney Disease:

A. Small interlobular ducts
   --Congenital hepatic fibrosis, ARPKD
   --Biliary hamartomas

B. Medium interlobular ducts
   --AD Polycystic Liver Disease
     --Isolated form caused by 2 genes:
       --SEC63 and PRKCSH
     --Associated with ADPKD caused by 2 genes:
       --PKD1 and PKD2

C. Large-sized intrahepatic ducts
   --Caroli’s disease

D. Large extrahepatic ducts
   --Choledochal cysts
Normal bile duct development

References: Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University Graduate School of Medicine - Kyoto/JP
Fig. 2: Types of ductal plate malformation depending on duct size affected. References: Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University Graduate School of Medicine - Kyoto/JP
Liver ultrasound showing dilated intrahepatic ducts.
ARPKD/CHF: Cirrhosis with ductal plate malformation. Note macronodular architecture of parenchyma and grey bands of fibrosis (x 2).
ARPKD/CHF: Dense bands of fibrosis, inflammatory infiltrates, and marked ductular proliferation (H&E x 4).
ARPKD/CHF: Dilated enlarged ducts at edge of limiting plate (H&E x 20).
ARPKD/CHF: CK7 positive in florid proliferation of small, intermediate and large ducts (x 4).
ARPKD features:
--Early mortality most common due to pulmonary complications: 30-50% perinatal mortality, 80-95% 5 year survival after the first month of life

--1:20,000 births

--Usually no cysts other than kidney/liver, but liver is always affected with ductal plate malformation and congenital hepatic fibrosis

--Caused by mutations in PKHD1 gene at locus 6p12
ARPKD: External and cut surfaces of kidney. Note effacement of entire cut surface and perpendicular orientation of cysts to renal capsule.
ARPKD: Kidney histology with multiple cystic structures (H&E x 2). Note presence of few glomeruli (circled).
G. Wilson Disease (Hepatolenticular degeneration)

--AR disorder, 1:30,000; causes toxic copper accumulation in liver, brain and eyes

--Genetic abnormality on 13q14 producing ATP7B, a transmembrane copper-transporting ATPase

--Diagnosis: serum ceruloplasmin <20 mg/dL (<5), increased copper on liver biopsy, urinary copper excretion >50μg/24 hr, liver copper quantification >250 μg/g dry weight
Wilson disease: Abnormal $ATP_{7B}$ functionality leads to failure of conversion of apoceruloplasmin to ceruloplasmin and failure of conjugated copper to be excreted in bile. Results in toxic accumulation of copper in hepatocytes.
Kayser-Fleischer rings in eyes result from copper accumulating in Descemet’s membrane at corneoscleral junction (limbus).

The ‘Giant panda face’ is typical on MRI when copper accumulates in midbrain.
Wilson disease: Liver explant from WD patient with fulminant hepatic failure.
Wilson disease: Macronodular cirrhosis with scattered necrosis (arrows).
Wilson disease: Necrosis surrounded by hemorrhage (H&E x 2).
Wilson disease: Effacement of normal architecture with bands of fibrosis containing proliferating bile ductules (Right: H&E x 4; Right, CK7 x 4).
Wilson disease: Steatosis, proliferating bile ductules and hepatocytic cholestasis (H&E x 10).
Wilson disease: Reticulin (left) and Masson trichrome (right) demonstrate dense bands of fibrosis (each x 2).
Wilson disease: Red-brown accumulations of copper in hepatocytes and Kupffer cells. (arrows) (rhodanine x 20).
Wilson disease: Electron-dense deposits (arrows) of copper.
Treatment for Wilson’s Disease:

Long-term copper chelation therapy and/or liver transplantation
Acknowledgement:
Sincere thanks to Steve Taylor, MHS, PA<sup>CM</sup> (ASCP) for assistance in creating this lecture.