Ascites and Related Disorders

Luis S. Marsano, MD
Professor of Medicine
Director of Hepatology
University of Louisville
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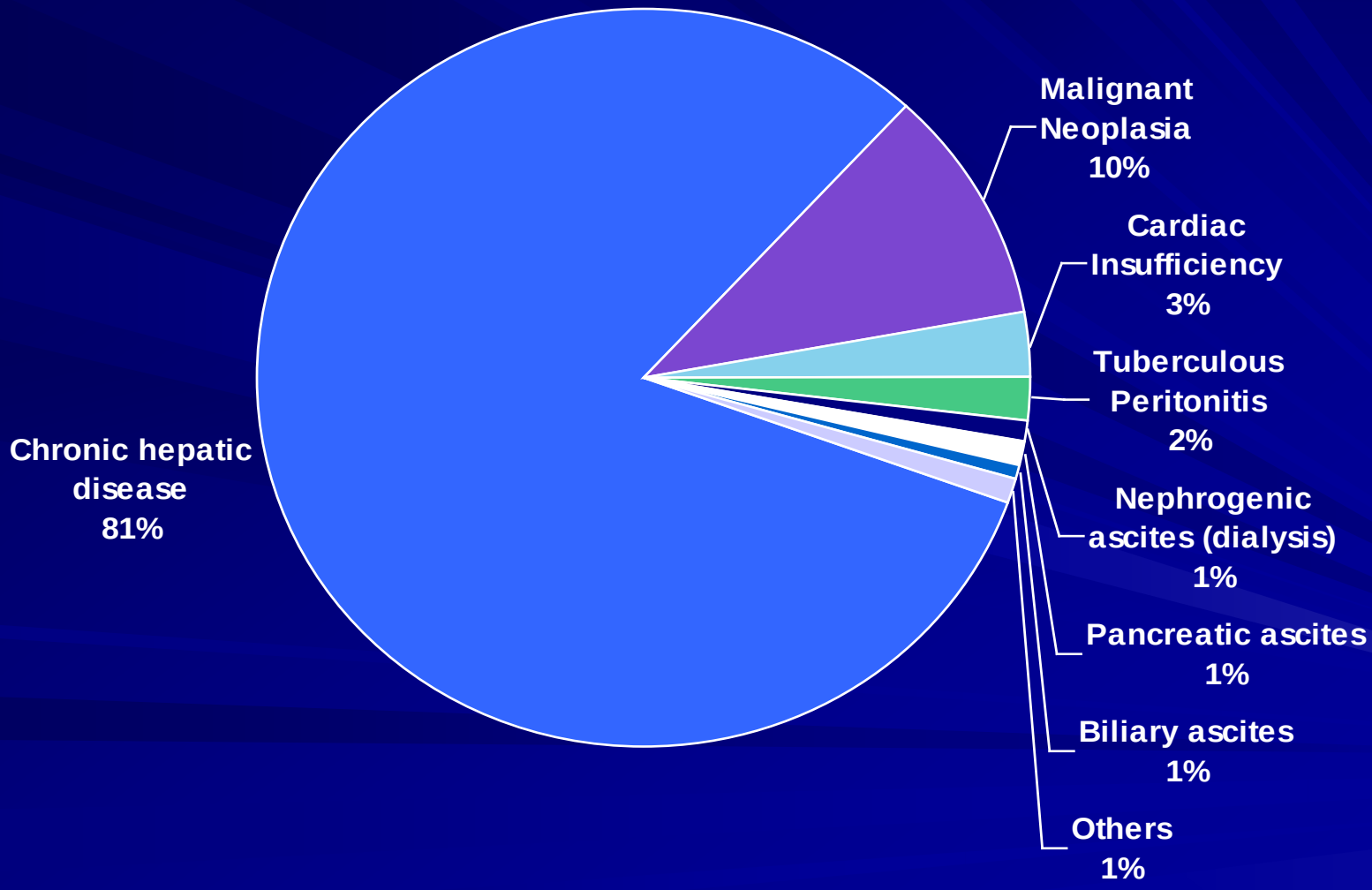
Causes of Ascites



Pathophysiology of Cirrhotic Ascites

↑ Hepatic sinusoidal pressure

↓

Activation of hepatic baroreceptors

↓

Compensated

Peripheral arterial vasodilation with hypervolemia, (normal renin, aldosterone, vasopressin, or norepinephrine)

↓

↑ Peripheral arterial vasodilation (“underfilling”)

↓

Decompensated

Neurally mediated Na+ retention, (with elevated renin, aldosterone, vasopressin, or norepinephrine)

Classification of Ascites

- Serum-ascites albumin gradient (SAAG)
- SAAG (g/dl) = $albumin_s$ – $albumin_a$
- Gradient $\geq$1.1 g/dl = portal hypertension
- Serum Beta-type Natriuretic Peptide > 365 pg/mL supports diagnosis of ascites due to CHF.

- Serum globulin > 5 g/dl:
  - SAAG correction = (SAAG mean)(0.21+0.208 serum globulin g/dl)

Ascites with High SAAG

≥1.1 g/dl = portal hypertension

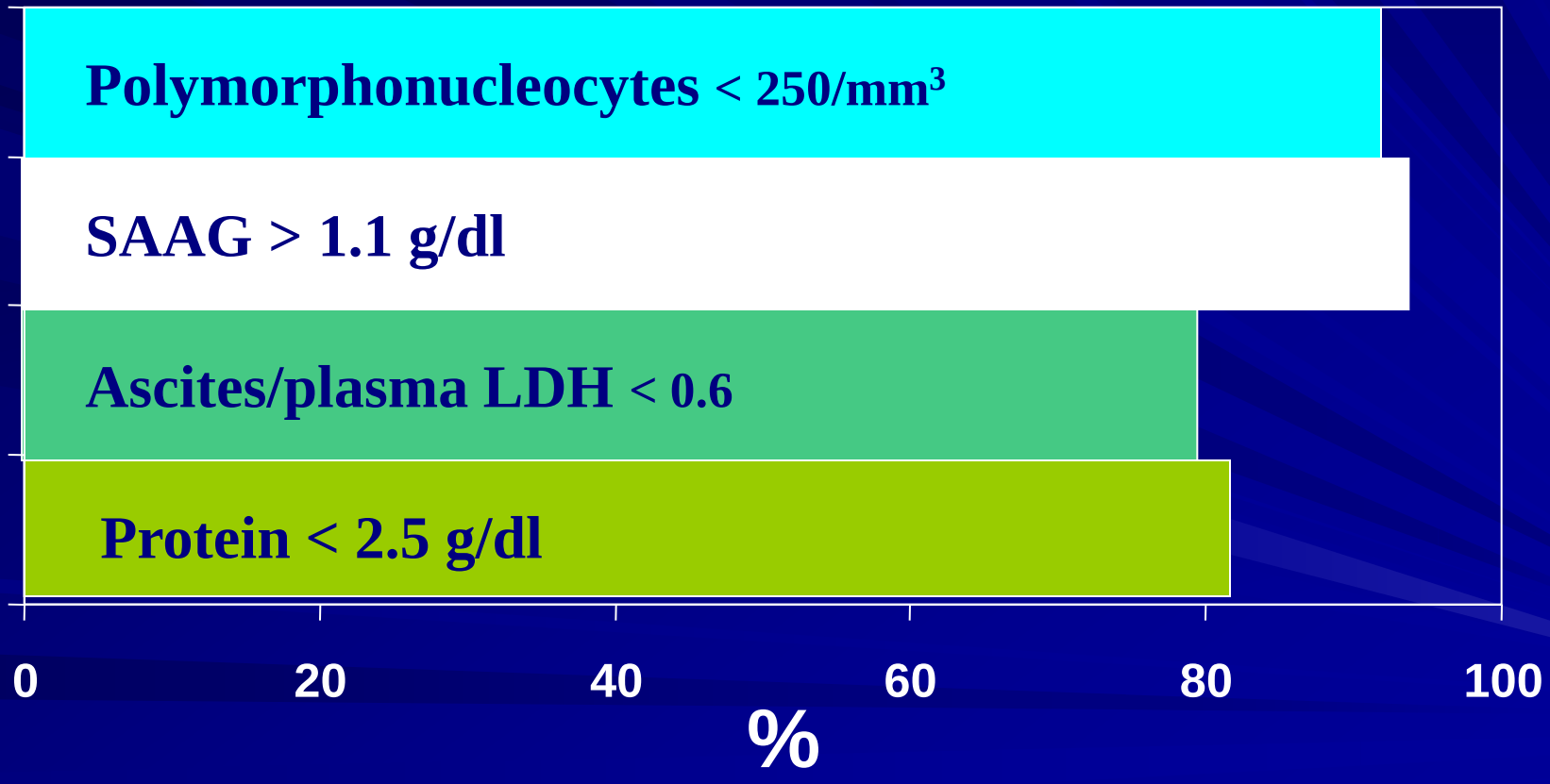
- Cirrhosis
- Alcoholic Hepatitis
- Cardiac ascites
- Massive hepatic metastasis
- Fulminant hepatic failure
- Budd-Chiari syndrome
- Portal vein thrombosis
- Veno-occlusive disease
- Acute fatty liver of pregnancy
- Myxedema
- Mixed ascites

Low SAAG
<1.1 g/dl

- Peritoneal carcinomatosis
- Tuberculous peritonitis (without cirrhosis)
- Biliary ascites (without cirrhosis)
- Pancreatic ascites (without cirrhosis)
- Nephrotic ascites
- Connective tissue disease
- Intestinal obstruction/infarction
- Ovarian Hyperstimulation Syndrome
- POEMS Syndrome
- Chylous Ascites
- Urine ascites

Survival of Cirrhotics with Ascites

Characteristics of Uncomplicated Cirrhotic Ascites



Ascites/plasma amylase ~0.5

Leucocytes < 300/mm^3; intense diuresis 1100/mm^3

Treatment of Ascites with High SAAG (≥ 1.1 mg/dl)

- ***Treat primary disease*** (alcoholism, Wilson's, autoimmune hepatitis, cardiac insufficiency, …)
- ***Na+ restriction***:
  - Inpatient: 250-1000 mg (11-44 mEq) depending on urinary loss
  - Outpatient: 1-2 g (44-88 mEq) of Na/day with diuretics for 0 or slightly negative balance

Treatment of Ascites

- ***Diuretics***
  - **General therapeutic goal**
    - Maximum ascites absorption is 930 mL per day (Shear L et al. N Engl J Med 1970;282:1391-1396)
    - Without edema : 1 lb/d weight loss
    - With edema : 1-2 lb/d weight loss
    - If urine Na/K ratio 24 h after diuretics is > 1, then 90% of patients will loose at least 88 mEq Na/day (Na balance: 0 or negative).
    - any Random spot urine Na/K > 0.97 has similar value (PPV 84%; NPV 90%) and if Na/K >/= 3.5, PPV is 100% (Liver Int. 2012;32(1):172-3).

Treatment of Ascites

- **Spironolactone**: more effective than loop diuretics. Can produce hyperK and acidosis
  - Dose: 100, 200, or 400 mg QD
- **Furosemide**: produces hypoK and alkalosis
  - Dose: 40, 80, or 160 mg QD
- **Metolazone**: added when maximal spironolactone 400 + Furosemide 160 is not controlling ascites. Causes severe hypoK
  - Dose 2.5-10 mg QD

Treatment of Ascites with High SAAG

- **Water restriction**
  - If serum Na < 126-130 mEq/L
  - Restrict to 0.8-1.5 liters/day
  - If water restriction fails: Tolvaptan (Samsca) 15 mg po q day; increase to 30 mg po qd if serum Na fails to increase by 5 mMol in 24 h, and to 60 mg po qd if Na fail to increase by 5 mMol after 30 mg x 1 day.
    - Goal: correct Na by 8 mMol/d (never > 12 mMol/d)
    - Correct hypothyroidism and adrenal insufficiency.
    - Contraindications: MI, ventricular arrhythmia, PCWP < 5 mmHg, BPs < 90 mmHg, severe pulm. HTN, Creat > 3.5, Serum Na < 120 with neuro impairment, uncontrolled DM.
- **Aggressively correct malnutrition**

Treatment of Ascites

- ***Therapeutic paracentesis:*** done in patients with stable cirrhosis with or without edema
  - Single large volume paracentesis (4-6 L): with or without colloid infusion
  - Serial LVP (4-6 L/Day): Colloid infusion (40 g albumin) need is controversial
  - Total paracentesis (6-22 L over 1 hr) with IV albumin (6-8 g/L removed), or Dextran 70 (8 g/L removed), or Midodrine 5-10 mg p.o. TID with goal to increase baseline MAP by 10 mmHg x 72 hours (Am J Gastroenterol 2008;103:1399-1405)

Treatment of Refractory Ascites

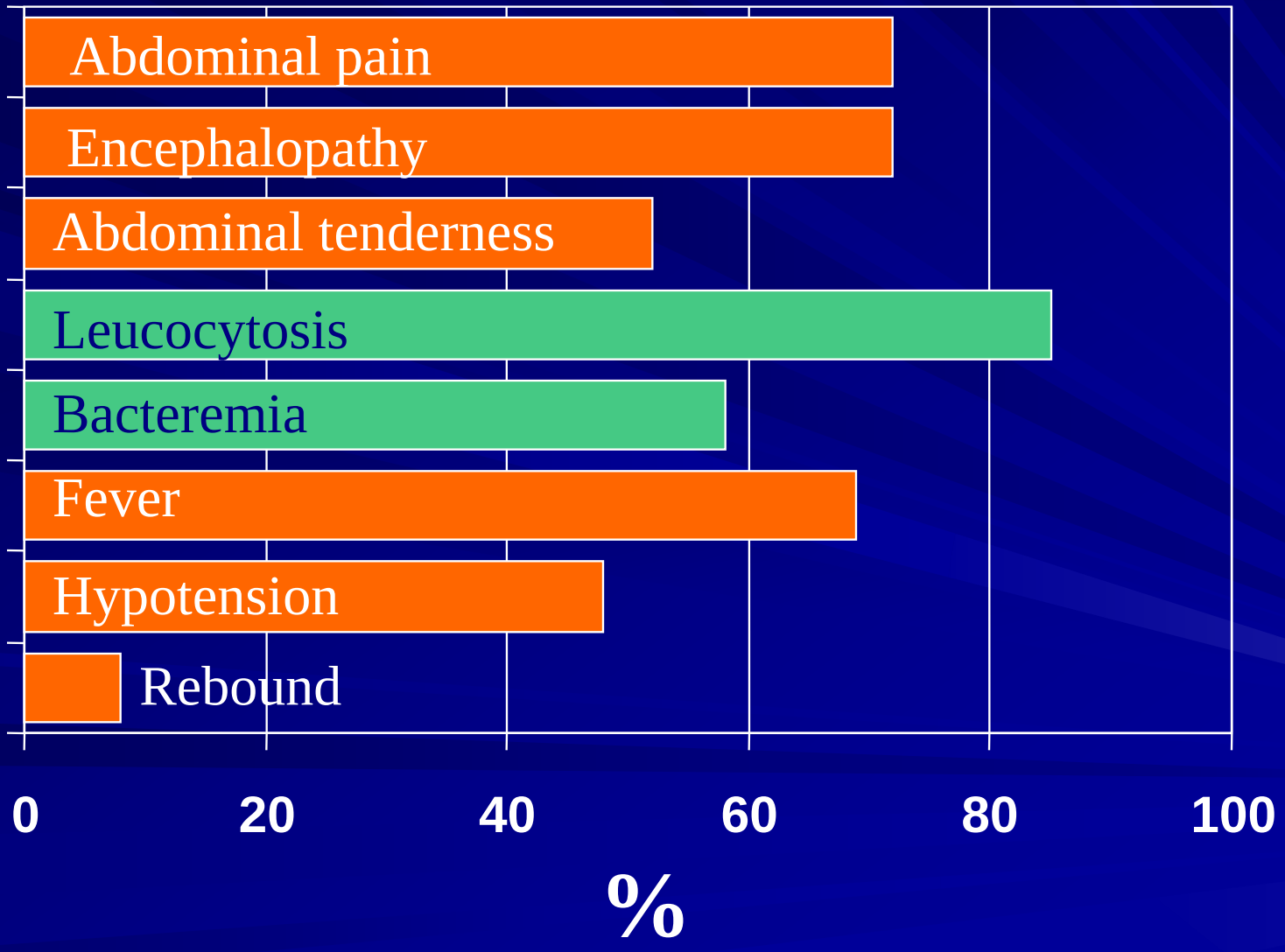
- **Definition**: Ascites that can not be controlled on a 2 g Na diet with Spironolactone 400 mg + Furosemide 160 mg, without causing azotemia.
- **Treat as HRS**: Albumin + Midodrine + Octreotide
- **TIPSS**
- **Non-selective surgical Shunt**

Spontaneous Bacterial Peritonitis (SBP) and Culture Negative Neutrocytic Ascites (CNNA)

- ***Prevalence*** 10-27% in hospitalized patients with cirrhotic ascites

- ***Pathogenesis***: distant bacteremia (UTI, URI, etc.) or translocation of bacteria from intestinal lumen

Signs and Symptoms of SBP



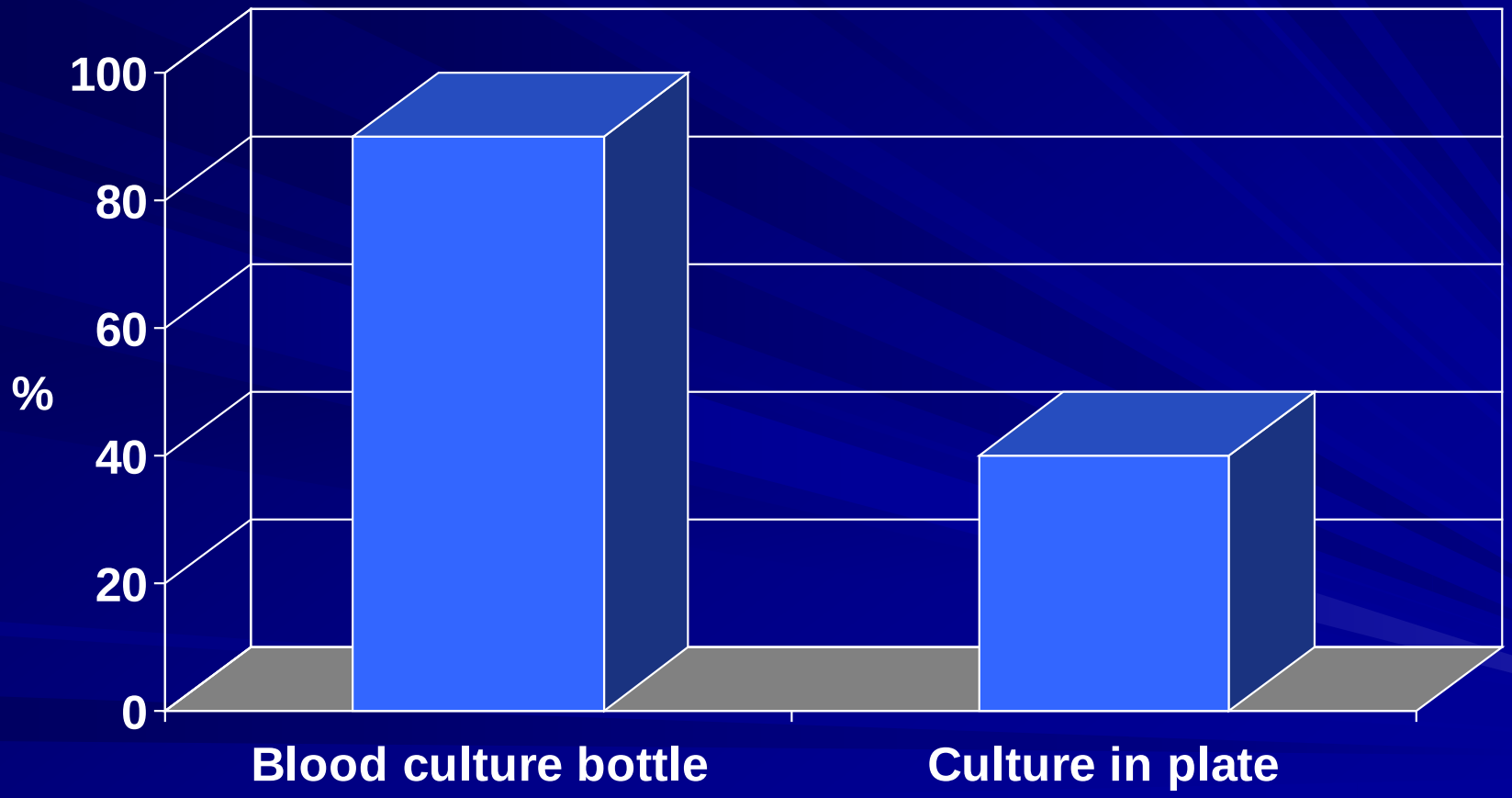
Diagnosis of SBP and CNNA

- ***SBP*** = PMN >250/mm^3 with (+) culture (> 90% monobacterial)
  - Other predictors:
    - ascites WBC > 1000/uL;
    - ascites pH < 7.35;
    - blood-ascites pH gradient =/> 0.1
- ***CNNA*** = PMN >250/mm^3 with (-) culture (without previous antibiotics nor other causes of increased PMN [bleeding, cancer, TB, pancreatitis])

Bacteriology of SBP

- ***Gram-Negative Bacilli*** ***70%***
  - Escherichia coli
  - Klebsiella spp.
- ***Gram-Positive Cocci*** ***20%***
  - Streptococcus pneumonia
  - Enterococcus spp
  - Staphylococcus spp
- ***Anaerobes, Microaerophils & others*** ***10%***

Ascites Culture



SBP and CNNA

- ***Morbidity and Mortality***
  - **Mortality without treatment: 78-100%**
  - **Mortality w. Cefotaxime: 30% (HRS= 33%)**
  - **Mortality w. Cefotaxim+albumin: 10% (HRS=10%)**
  - **Recurrent SBP in 69%**

- ***Treatment***
  - **Cefotaxime 2g TID x 5 days + Albumin 1.5 gm/Kg @ day 1 & 1 gm/Kg @ day 4**
  - **Re-paracentesis at 48hrs (50% reduction in WBCs)**
  - **Nosocomial SBP is often due to MDR gram (+) and (-) bacteria; use albumin and piperacillin/tazobactam, or meropenem + daptomycin (Hepatology 2016; 63:1299-1309)**

Recommended empirical antibiotic treatment for community-acquired and nosocomial bacterial infections in cirrhosis

J Hepatol 2014; 60: 1310-24

Type of Infection	Community Acquired	Nosocomial
SBP, SBP, or Spontaneous Bacteremia	Cefotaxime **or** ceftriaxone **or** amoxicillin/clavulanic acid	Piperacillin/tazobactam **or** meropenem ± vancomycin **or** meropenem + daptomycin
Urinary Infection	**Uncomplicated:** **or** co-trimoxazole **or** ciprofloxacin **If sepsis:** cefotaxime **or** ceftriaxone **or** amoxicillin/clavulanic acid	**Uncomplicated:** nitrofurantoin **or** fosfomycin **If sepsis:** piperacillin/tazobactam **or** meropenem ± vancomycin
Pneumonia	Amoxicillin/clavulanic acid **or** ceftriaxone + macrolide **or** levofloxacin, **or** moxifloxacin	Piperacillin/tazobactam **or** meropenem/ceftazidime + ciprofloxacin +/- vancomycin vancomycin should be added in patients with risk factors for MRSA
Cellulitis	Amoxicillin/clavulanic acid **or** ceftriaxone + oxacillin	Meropenem/ceftazidime + oxacillin **or** vancomycin

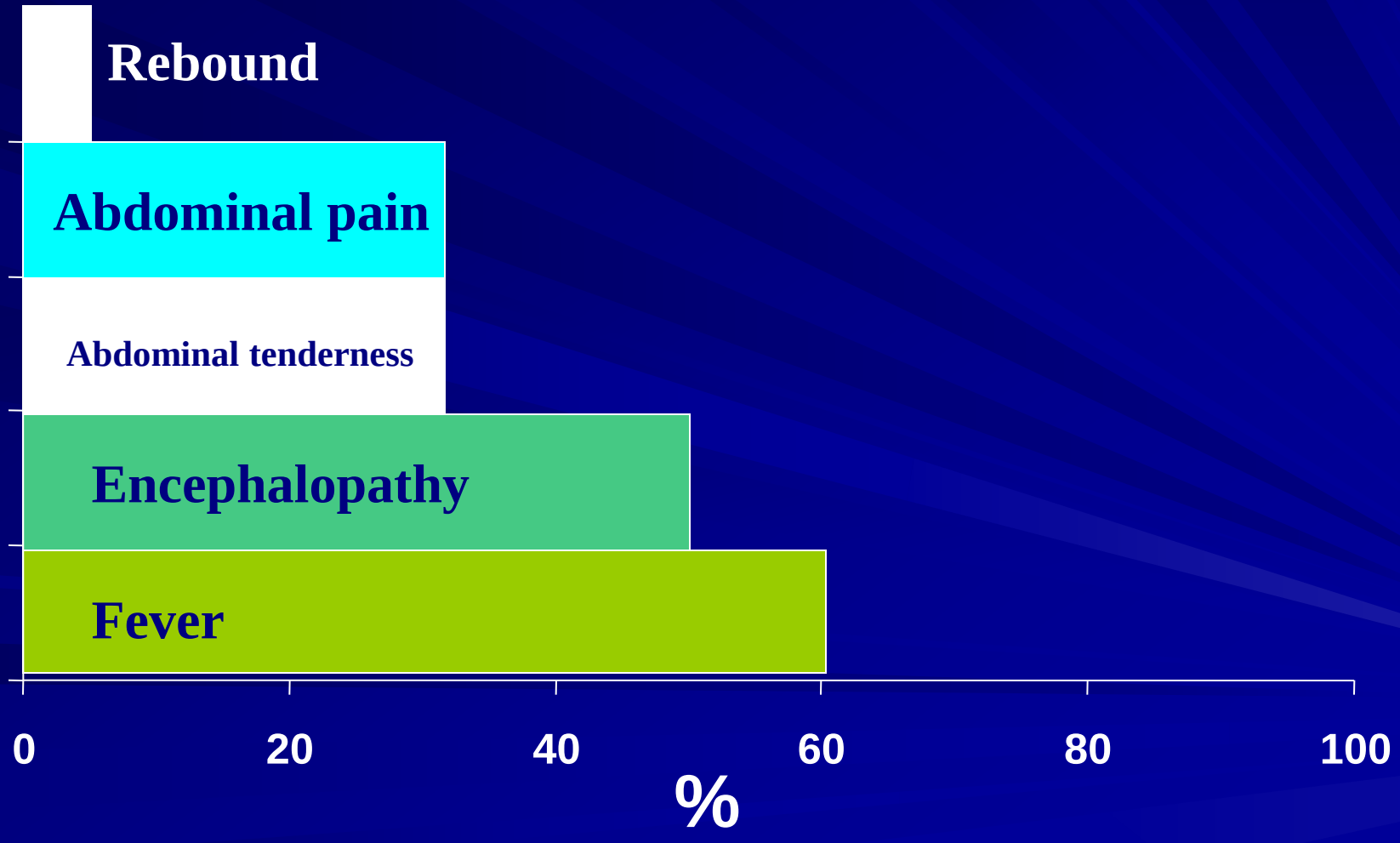
SBP & CNNA

- ***Prophylaxis***
  - **Cirrhotic with total protein < 1.5 g/dl;**
    - Norfloxacin 400 mg/d po or Bactrim DS 5 days/week during hospitalization
  - **Cirrhotic with GI bleed**
    - Norfloxacin 400 mg po BID x 7 days

Monomicrobial Bacterascites

- Diagnosis
  - (+) ascites culture with PMN < 250/mm^3 and without surgically treatable intra-abdominal source of infection

Signs and Symptoms of Monomicrobial Bacterascites



Monomicrobial Bacterascites

- Mortality: 40%
- Treatment
  - Cefotaxime 2 g TID as per antibiotic susceptibility
  - Repeat paracentesis in 48 hr

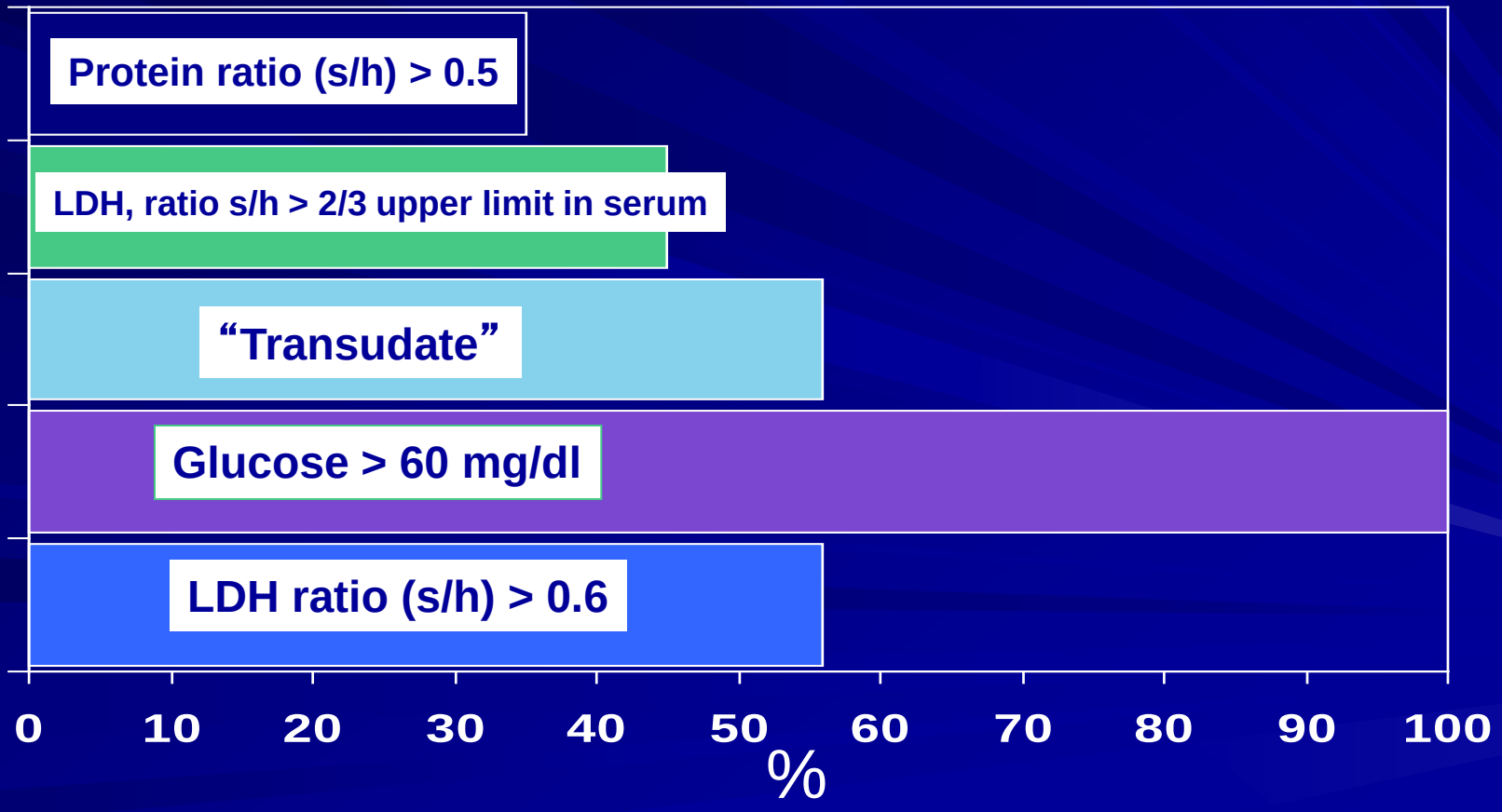
Ascites Management

- **EVALUATE:**
- Paracentesis post-adm, PSE, Azotemia, Fever
- Check: Prot, Alb, WBC, Glu, LDH in serum & ascites
- Bedside Culture in Blood Culture bottle

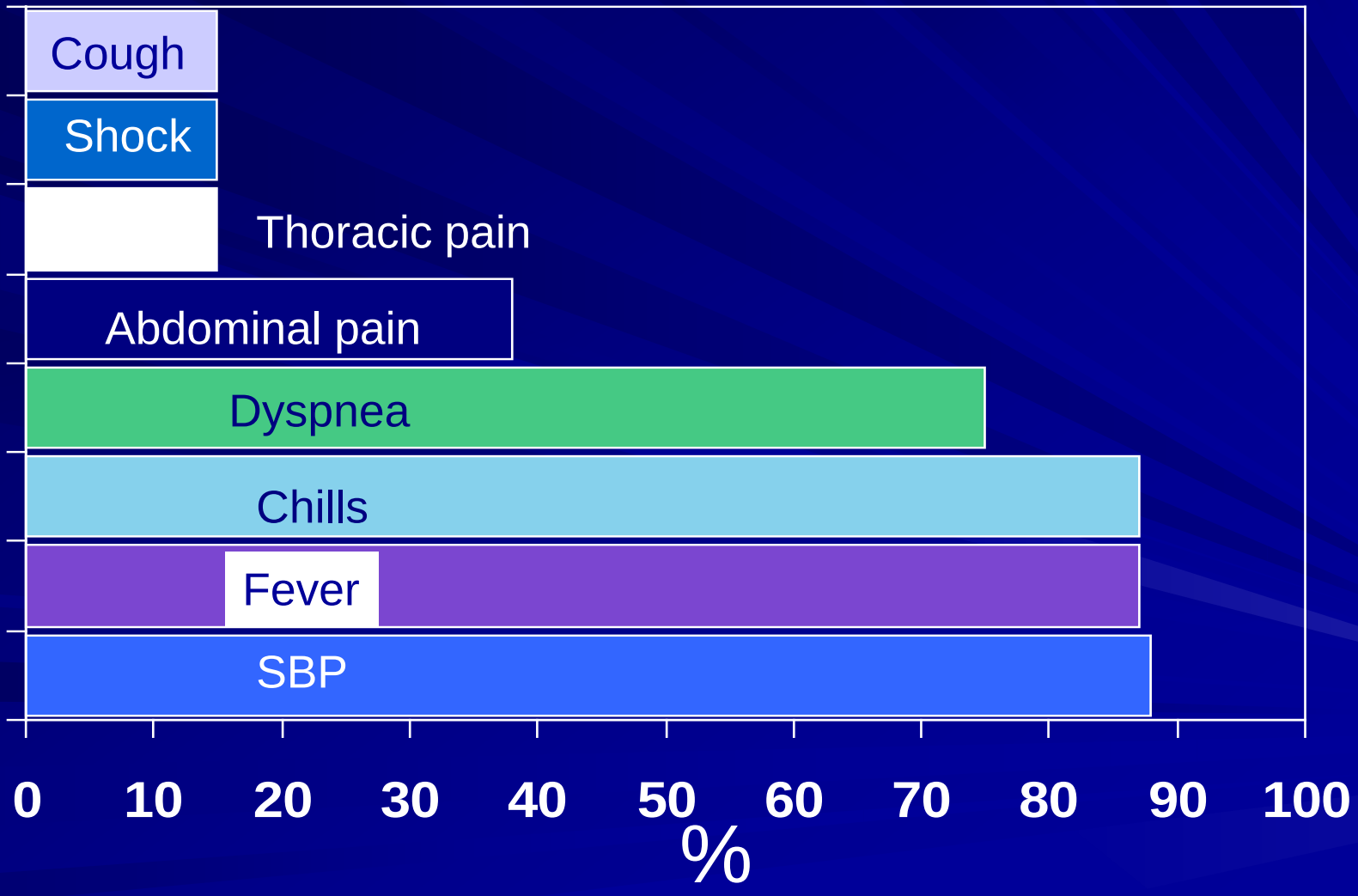
- **TREAT:**
- Na restrict + LVP + diuretics
- PMN>250: Cefotaxim + Albumin
- Prot < 1.5g: Norfloxac
- GI Bleed: Norfloxacin

Hepatic Hydrothorax

- In 10% of patients with ascites
- Usually right sided
- T. protein in hydrothorax > ascites by 0.75-1 g/dl



Signs and Symptoms: Spontaneous Bacterial Empyema



Spontaneous bacterial empyema

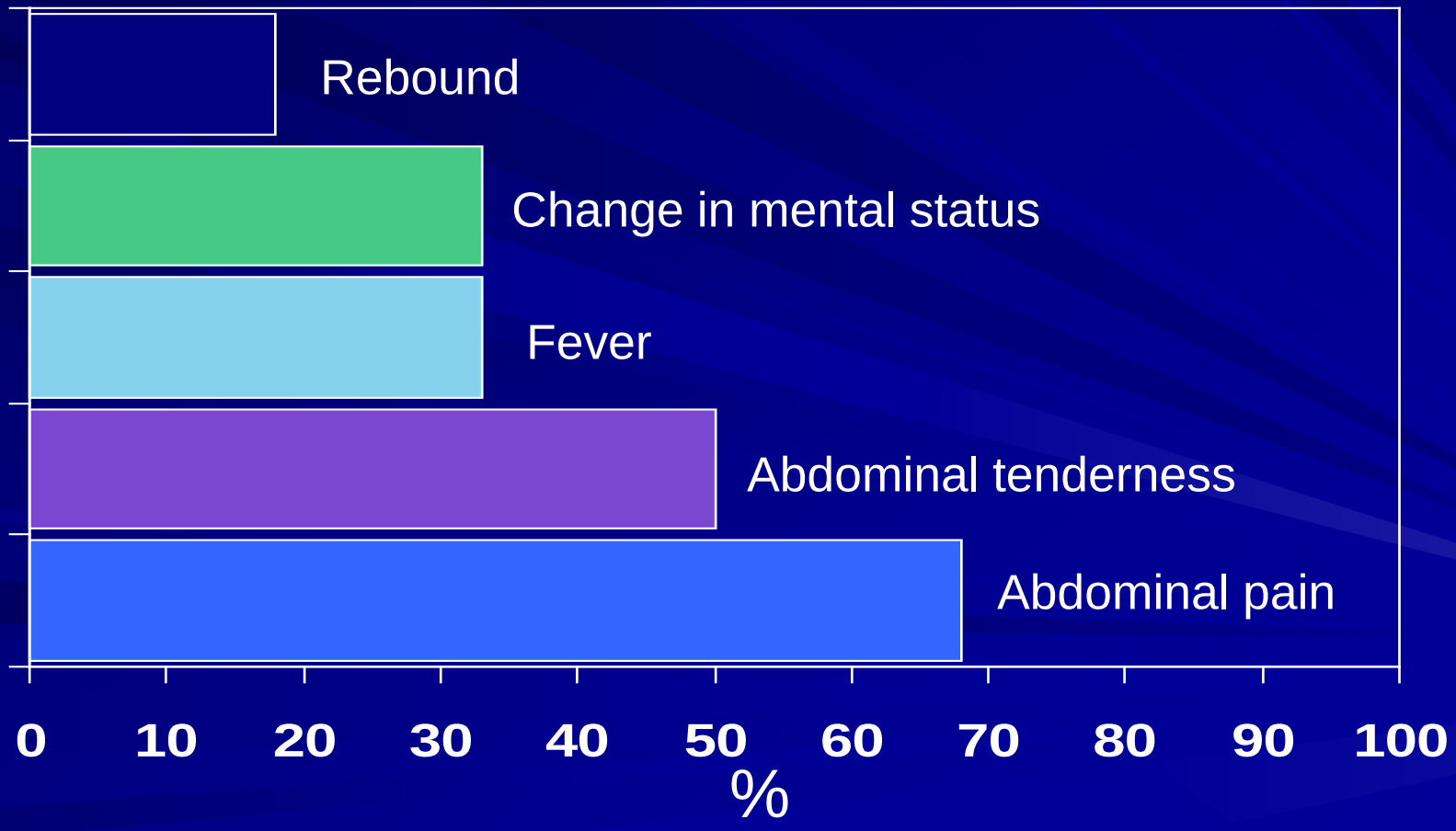
- **Diagnosis**:
  - **A)** culture (+) (in blood culture bottle), or
  - **B)** PMN > 500/mm^3 in patients with known hepatic hydrothorax and CXR without pneumonia
- **Bacteriology**: single bacteria (E.coli, K. pneumonia, C. perfringes)
- Bacteremia in 36%
- **Mortality**: in culture (+) = 50%; in general = 27%
- **Relapse rate**: 38% at 1 year; mortality at 1 year =50%
- **Treatment**:
  - Cefotaxime (or as per antibiotic susceptibility) + albumin expansion.
  - Nosocomial SBE is often due to MDR gram (+) and (-) bacteria; use albumin and piperacillin/tazobactam, or meropenem + daptomycin (Hepatology 2016; 63:1299-1309)
- **Response to therapy** = 72%

Suspect Secondary Peritonitis in:

- Multiple organisms or fungi in culture
- Ascitic infection in peritoneal carcinomatosis or cardiac ascites
- Increased PMN count after 48 hr therapy of SBP
- Two of the following (sensitivity 100%; specificity 45%):
  - Ascites glucose < 50 mg/dl (67%)
  - Ascites protein > 1 g/dl (83%)
  - Ascites LDH > upper normal in serum (100%)
- Other markers: Alkaline phosphatase > 240 U/L, or CEA > 5 ng/mL (sensitivity 92%; specificity 88%).

Secondary peritonitis

Pathogenesis: perforation/microperforation on hollow viscus or contamination from intraabdominal abscess



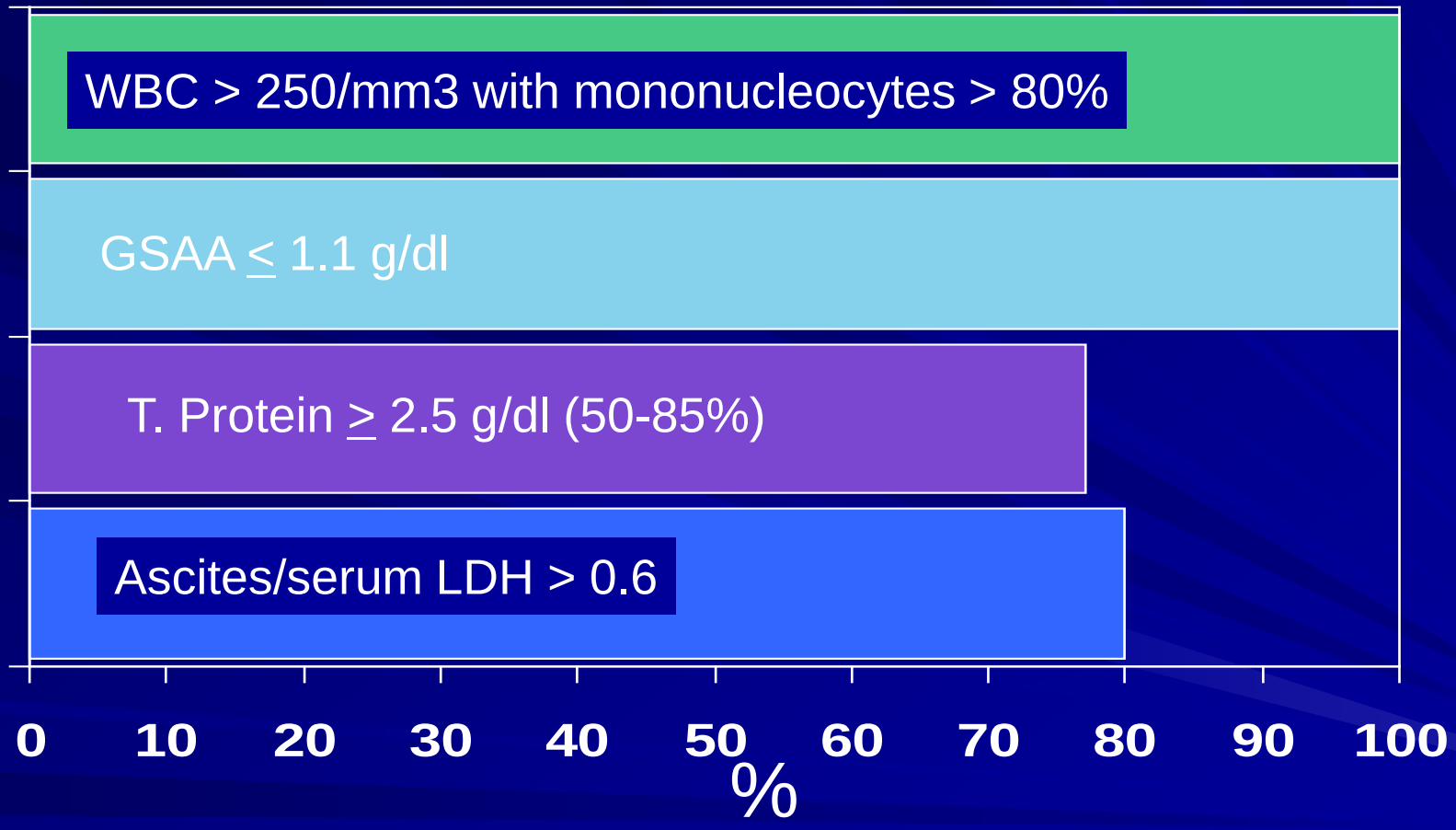
Secondary peritonitis

- **Evaluation**: look for perforation (extravasation of contrast) or loculated pus.
- **Treatment**:
  - Surgery (if perforation or abscess found)
  - Antibiotics (Cefotaxime + metronidazol) + albumin expansion

Tuberculous Peritonitis

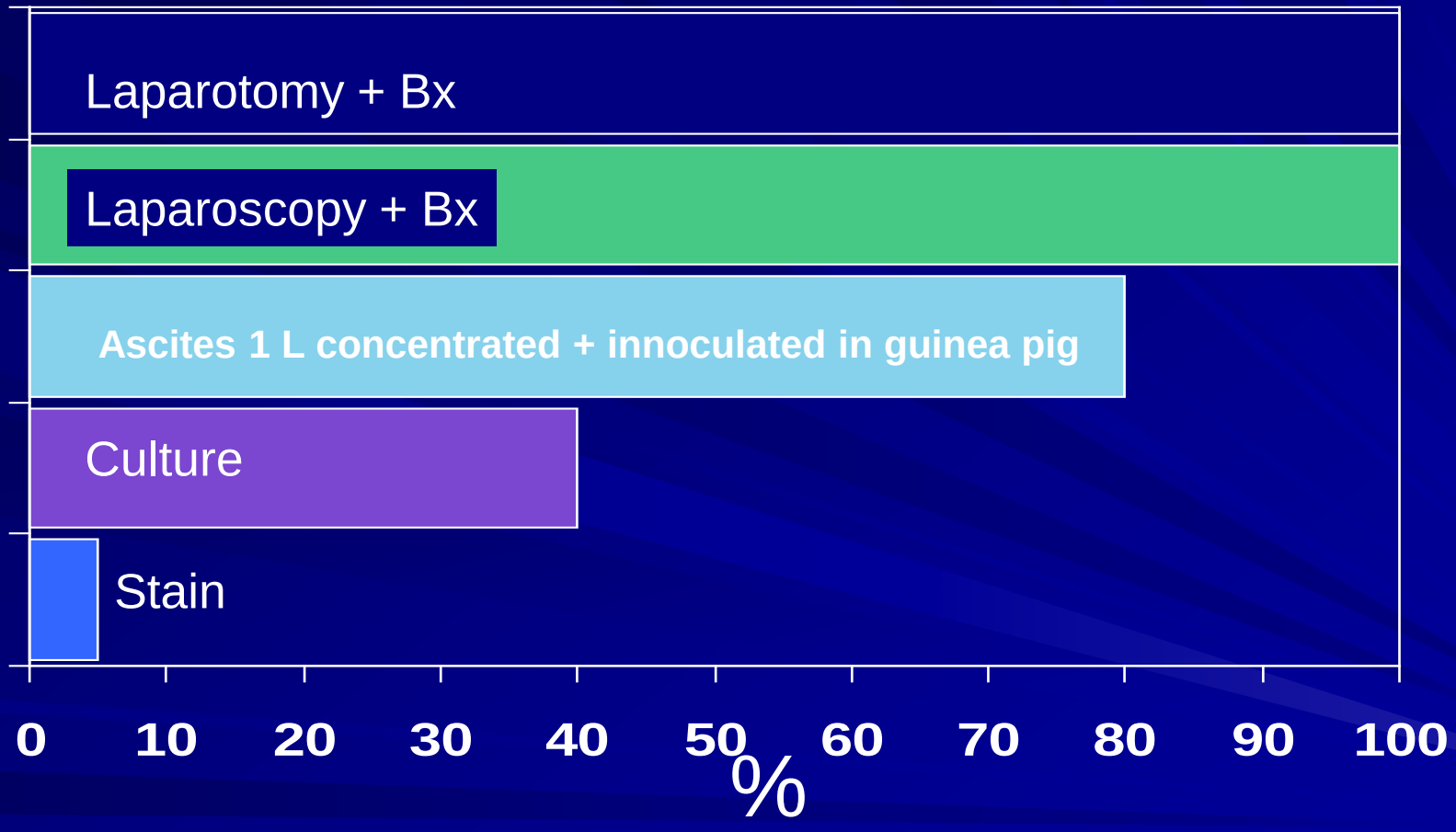
- **Pathophysiology**: infection of peritoneum causes exudate of protein which “pulls” fluid for oncotic balance;
- Classically SAAG is < 1.1 g/dl, and many patients have underlying cirrhosis
  mixed ascites (SAAG ≥ 1.1 g/dl)

Characteristics of Tuberculous Peritonitis



- 78% serum glucose < 100 mg/dl
- 5-10% bloody

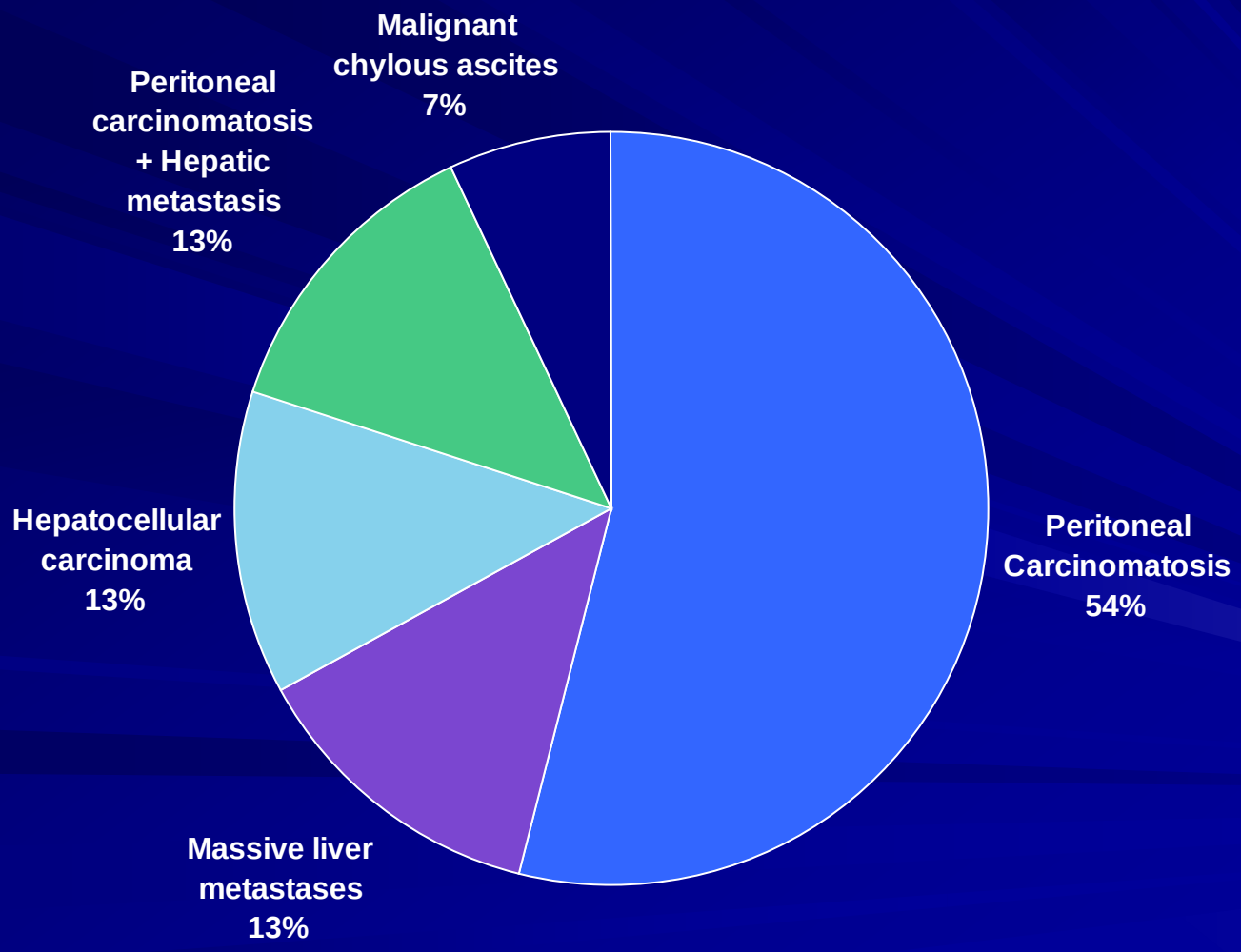
Diagnosis of Tuberculous Peritonitis



Tuberculous Peritonitis

- Mortality without therapy: 60%
- Treatment:
  - –Anti-tuberculous agent
  - –Anti-fungal agent

Causes of Malignant Ascites



Peritoneal Carcinomatosis (54%)

- Peritoneal protein exudate pulls fluid : SAAG < 1.1
- Other characteristics:
  - WBC >500
  - T. protein > 2.5 g (usually – 4.0)
  - LDH > 225 (usually – 1000 IU/L)
  - Glucose < 100 in 71%
- Cytology (+)

Massive hepatic metastases (13%)

- Portal hypertension : SAAG > 1.1g/dl
- Bloody in 10%
- Cytology negative

Peritoneal Carcinomatosis + liver metastases (13%)

- Mixed ascites : SAAG >1.1g/dl
- Bloody in 10%
- Cytology (+)
- WBC > 500 with dominant lymphocytes

Hepatocellular carcinoma (13%)

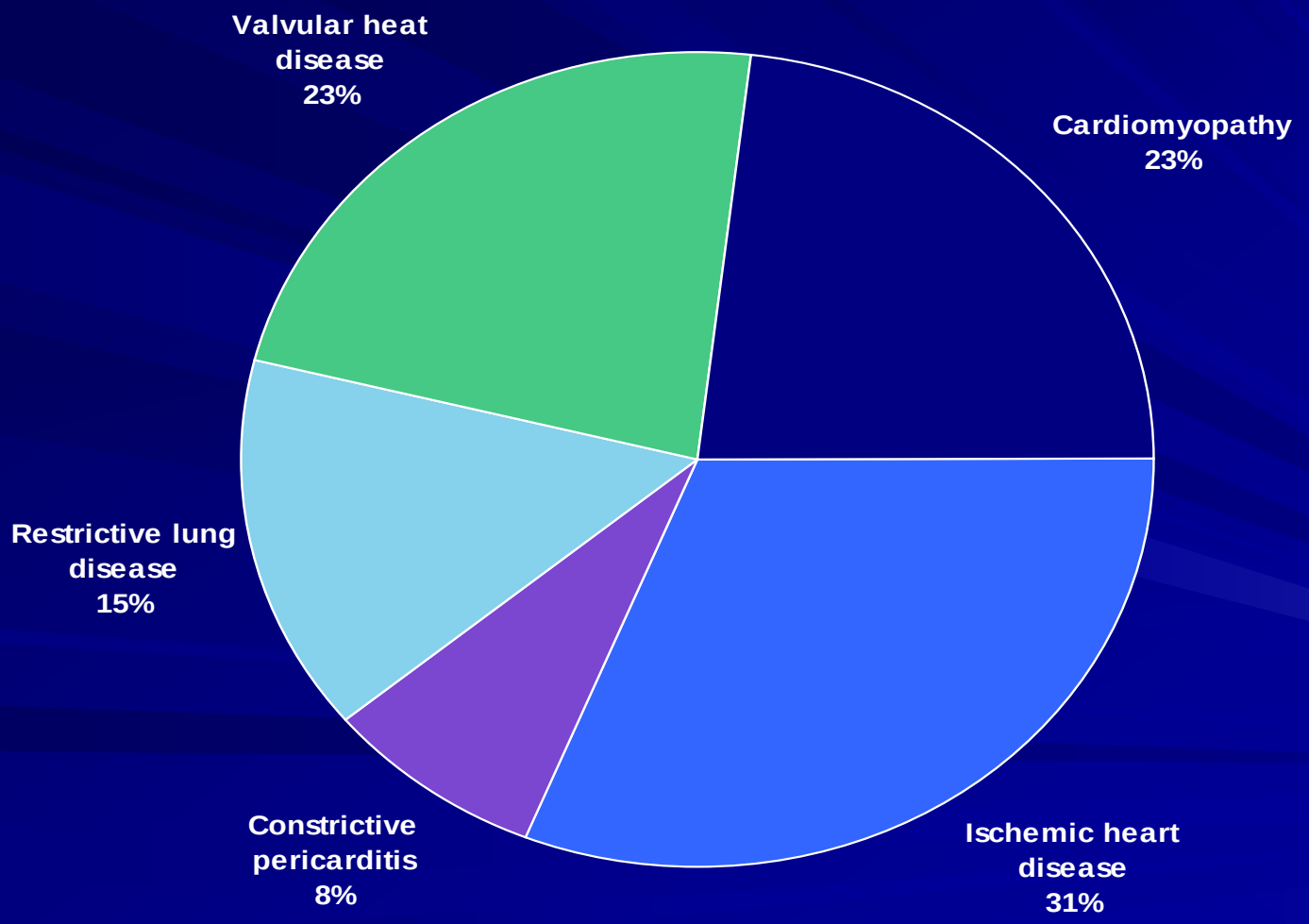
- Portal hypertension (cirrhosis +/- portal vein thrombosis)
- SAAG > 1.1g/dl
- Bloody in 50%
- Alpha-fetoprotein high (serum > ascites)
- Cytology negative

Malignant chylous ascites (7%)

- Lymph leak due to invasion of lymph nodes with rupture of lymphatic vessels
- Characteristics: SAAG < 1.1g/dl, triglycerides > 81 mg/dl or > plasma triglycerides (usually > 1000 mg/dl)
- Bloody in 10%
- Cytology is variable

Cardiac Ascites

Passive congestion causes portal hypertension : SAAG ≥1.1g/dl (100%), Serum Beta-type Natriuretic Peptide > 365 pg/mL



Cardiac ascites

- Characteristics:
  - SAAG > 1.1 g/dl (100%)
  - T. protein > 2.5 g/dl (100%)
  - LDH < upper limit of normal (100%)
  - WBC is variable 480 $\pm$ 490/mm^3
  - PMN < 250/mm^3
  - **Serum:** Beta-type Natriuretic Peptide > 364 pg/mL (sensitivity 98%; specificity 99%);
    - Values of </= 182 pg/mL rule out cardiac ascites.
- Treatment: underlying disease

Pancreatic Ascites

- Pancreatic duct or pseudocyst rupture in chronic alcoholics
- Up to 50% with cirrhosis (SAAG $\geq$1.1 mg/dl)
- Characteristics
  - Amylase > 1000
  - SAAG < 1.1 mg/dl
  - T. protein > 2.5 g/dl (100%)
  - High LDH (~2000 IU/L)
  - High WBC (~4000/mm^3)
  - High PMN (~3000/mm^3)
  - Glucose variable
- Secondary infection occurs in 25%
- Treatment: stenting, surgery, octreotide, bowel rest

Nephrotic ascites

- Hypoalbuminemia ⇨ decreased effective arterial blood volume ⇨ activation of renin/aldosterone/vasopressin/norepinephrine ⇨ renal Na and water retention ⇨ edema + ascites
- Characteristics
  - SAAG < 1.1g/dl
  - T. protein – 0.6 g/dl
  - Glucose - 100 mg/dl
  - LDH ascites/serum < 0.5
  - WBC < 250/mm^3
  - PMN few
- Treatment: Na restriction and diuretics

Nephrogenous ascites

- Unknown etiology
  - Patients on hemodialysis
  - 50% have cirrhosis
- Characteristics
  - SAAG < 1.1 g/dl in 50%
  - Protein > 2.5 g/dl (100%)
  - LDH < upper limit of normal 100%
  - Glucose > 100 mg/dl
  - WBC < 500/mm^3 in 75% (350$\pm$225), mostly lymphocytes
  - PMN < 250/mm^3
- Laparoscopy + bx to rule out cirrhosis + TB
- Treatment: vigorous dialysis

Biliary ascites

- Perforation of gall bladder, bile duct or proximal gut produces bile leak
- Characteristics
  - Bilirubin in ascites > 3 mg/dl and ascites/serum bili > 1
  - SAAG < 1.1 g/dl but variable (1.2±0.5)
  - LDH – 2500 IU/L
  - T. protein > 2.5 g/dl (2.6±0.2)
  - Glucose variable (90±85 g/dl)
  - WBC – 3400
  - PMN – 3000
  - Amylase usually not elevated (except in intestinal perforation)
- Usually monomicrobial
- Treatment: stenting, surgery