INFECTIOUS COMPLICATIONS IN PATIENTS WITH CIRRHOSIS: *WHAT SHALL WE DO?*

Jenny Lim Limquiaco, MD

Epidemiology

- present in about 30% of patients with cirrhosis at admission or during hospitalization
- 60% are community-acquired
- 30% exhibit acute on chronic liver failure
- Mortality reaches 38%

Clin Gastroenterol Hepatol 2010;8:979–985

Gastroenterology 2013;144:1426-37

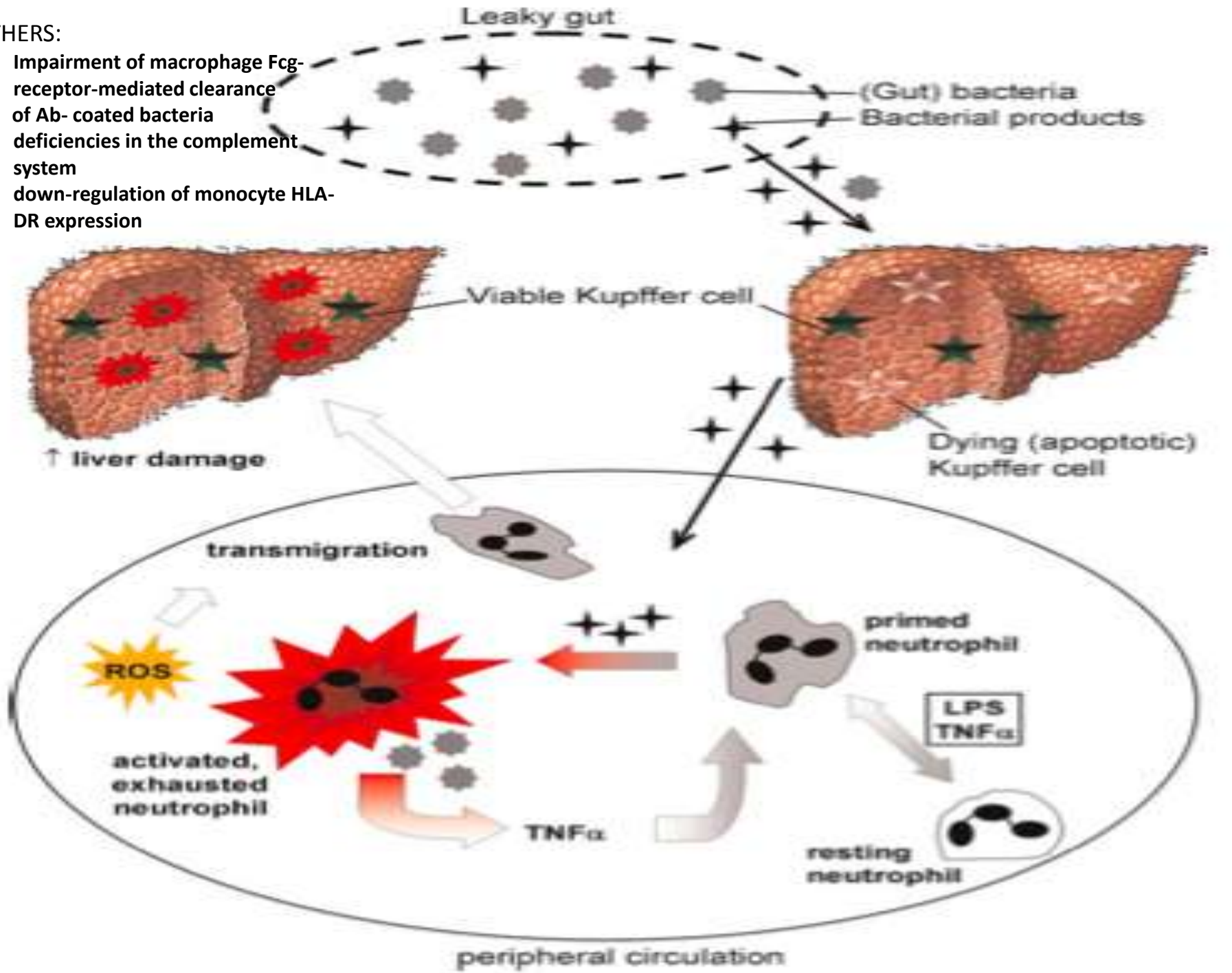
PATHOGENESIS OF SEPSIS IN CIRRHOSIS

Pathophysiological Mechanisms of Increased Susceptibility to Infections

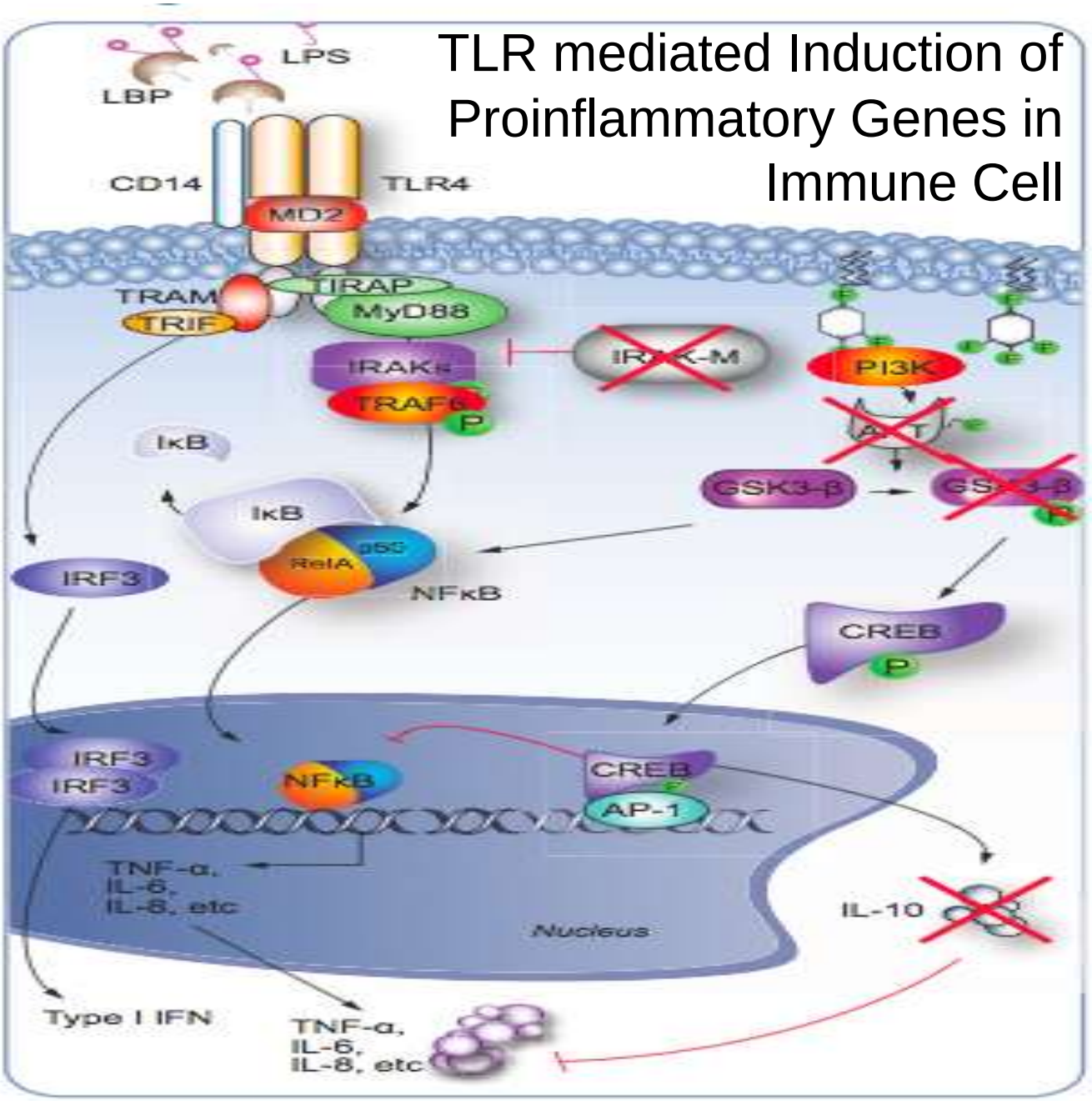
- Immune Dysfunction
- Kupffer Cells
- Neutrophils
- Monocyte
  - Cytokine STORM
- Genetic predisposition
  - NOD2 (nucleotide-binding oligomerization domain containing 2)
  - Mannose-binding lectin deficiency
- Intrinsic cellular defect
- GUT permeability
- Endotoxin
- Lipoprotein
- Albumin dysfunction
- Toll Like receptors
  - Toll-like receptor (TLR)2 polymorphisms

OTHERS:

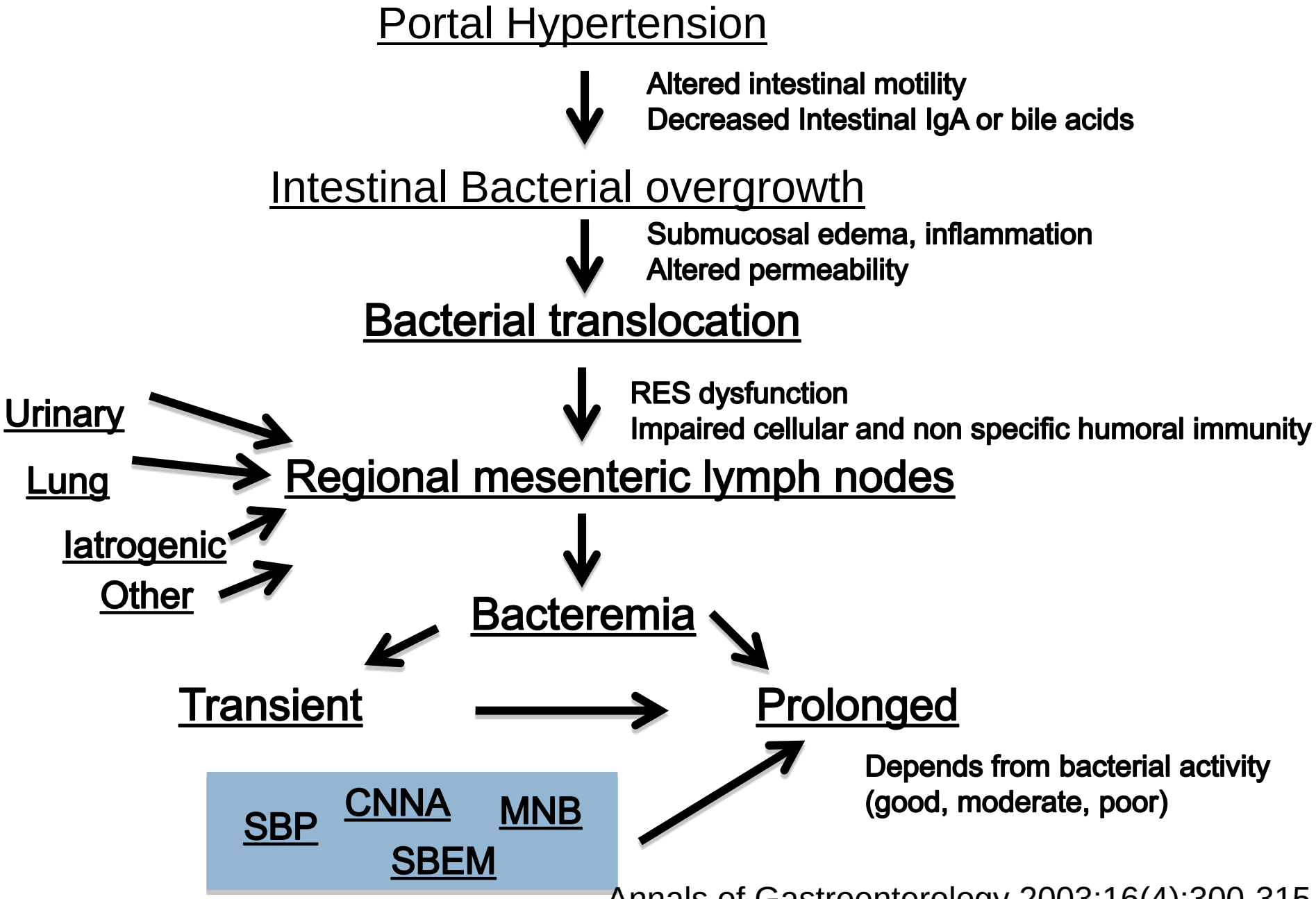
- **Impairment of macrophage Fcg-receptor-mediated clearance of Ab- coated bacteria**
- **deficiencies in the complement system**
- **down-regulation of monocyte HLA-DR expression**



TLR mediated Induction of Proinflammatory Genes in Immune Cell



Mechanisms involved in the pathogenesis of infections in cirrhosis



Annals of Gastroenterology 2003:16(4):300-315

Type of infection in CLD	Common Causes
Spontaneous bacterial peritonitis	Escherichia coli, Klebsiella species, Streptococcus species Enterococcus species. Infrequently anaerobic organisms
Spontaneous bacterial empyema	E. coli
Urinary tract	Gram-negatives
Community acquired pneumonia	Streptococcus pneumonia, Hemophilus influenzae, Klebsiella, Mycoplasma pneumoniae, Legionella species, Peptostreptococcus, Bacteroides melaninogenicus, Fusobacterium nucleatum

Type of infection in CLD	Common Causes
Hospital acquired pneumonia	Gram negatives and staphylococci
Bacteremia	Escherichia coli, Klebsiella pneumoniae, Aeromonas hydrophila, Staphylococcus aureus, Streptococcus group
Pulmonary or peritoneal tuberculosis	Mycobacterium tuberculosis
Lymphangitis of lower extremities or cellulites	Gram-positives and Gram-negatives
Endocarditis	Streptococcus pneumonia, Escherichia coli, Staphylococcus aureus
Meningitis	Streptococcus pneumonia, Escherichia coli, Listeria monocytogenes

Limitations of common clinical and analytical markers of infection

GENERAL POPULATION: SIRS Diagnosis

- 2 or more of the ff:

1) a core T ≥38 ° C or ≤36 ° C
2) a HR≥90 beats/min
3) tachypnea ≥20 breaths/min or partial carbon monoxide pressure (PaCO2) ≤32mmHg or the need of mechanical ventilation
4) WBC ≥12 × 10^9/L or ≤4 × 10^9/L or >10% of immature neutrophils

Limitations of common CLINICAL and analytical markers in cirrhosis

- SIRS diagnostic criteria
  - more difficult to use ; less diagnostic accuracy in cirrhosis

HEART RATE:

- hyperdynamic circulation leads to tachycardia in the absence of infection
- beta-blockers: reduces heart rate
- hepatic encephalopathy: presents w tachypnea

WHITE BLOOD COUNT

- hypersplenism decreases white blood cell count

Management of bacterial infections in cirrhosis Javier Fernandez and Thierry Gustot

Journal of Hepatology 2012

Limitations of common clinical and ANALYTICAL markers of infection

- C-reactive protein (CRP) and procalcitonin (PCT)
  - conflicting results exist regarding threshold values and diagnostic accuracy in cirrhosis
  - CRP: produced predominantly by hepatocytes
  - PCT: produced ubiquitously by thyroidal and extra-thyroidal tissues including the liver in septic patients

J Clin Endocrinol Metab 2001;86:396–404

Limitations of common clinical and ANALYTICAL markers of infection

Patients with liver failure – attenuated response

- CRP (AUC: 0.64 to 0.91)
  - LOW CRP:
    - interpret with caution in Child–Pugh C patients
- PCT (AUC: 0.68–0.89)
- Cut off: 0.5ng/ml

- some studies showing a superiority of PCT over CRP and others showing similar results

Liver Int 2009;29:1538–1542 Hepatology 2010;52:905A.

Factors predisposing to infection in cirrhosis

- Severity of the underling liver disease (Childs Pugh C)
- Ascitic fluid total protein concentration <1gr/dl
- Ascitic fluid C3 level <13mg/dl
- Total bilirubin level of >3.2 mg/dl
- Gastrointestinal bleeding
- Previous spontaneous bacterial peritonitis episodes
- Urinary, respiratory tract or other source of infection
- Iatrogenic factors (e.g. urinary bladder, intravascular catheters)
- Low platelet count (<98,000/mm3)

Annals of Gastroenterology 2003

SPONTANEOUS BACTERIAL PERITONITIS

Spontaneous Bacterial Peritonitis

ETIOLOGY:

- 60 to 72% - aerobic Grm (-) enteric bacteria
  - Escherichia coli : majority
  - Grm (+) Cocci - 29%
  - Streptococcus species - 19%
  - Klebsiella species - 13%
  - Enterococcus species - 5% Isolation of an
  - anaerobic organism – 5%
    - *ascites has too high an oxygen tension to permit anaerobic growth*

Spontaneous Bacterial Peritonitis

- 87% - asymptomatic at the time of diagnosis
  - Fever (62-69%)
  - Abdominal pain (59-64%) - diffuse
    - Rigid abdomen - infrequent even if bowel perforation occurs
  - Other clinical features:
  - hepatic encephalopathy (44- 54%)
  - abdominal tenderness (49%)
  - diarrhea (7-32%)
  - ileus (5-30%)
  - shock (8-21%)
  - hypothermia (17%)

Spontaneous Bacterial Peritonitis

- Mortality rates at 1 and 2 yrs: 50-70% and 70-75%
- Predictors:
  - Higher MELD score (25+/-8 vs 19+/-7)
  - Hepatic encephalopathy
  - Hepatorenal syndrome
  - Mechanical ventilation
  - ICU stay during hospitalization

Bajaj GUT 2012 August; 61(8): 1219-1225

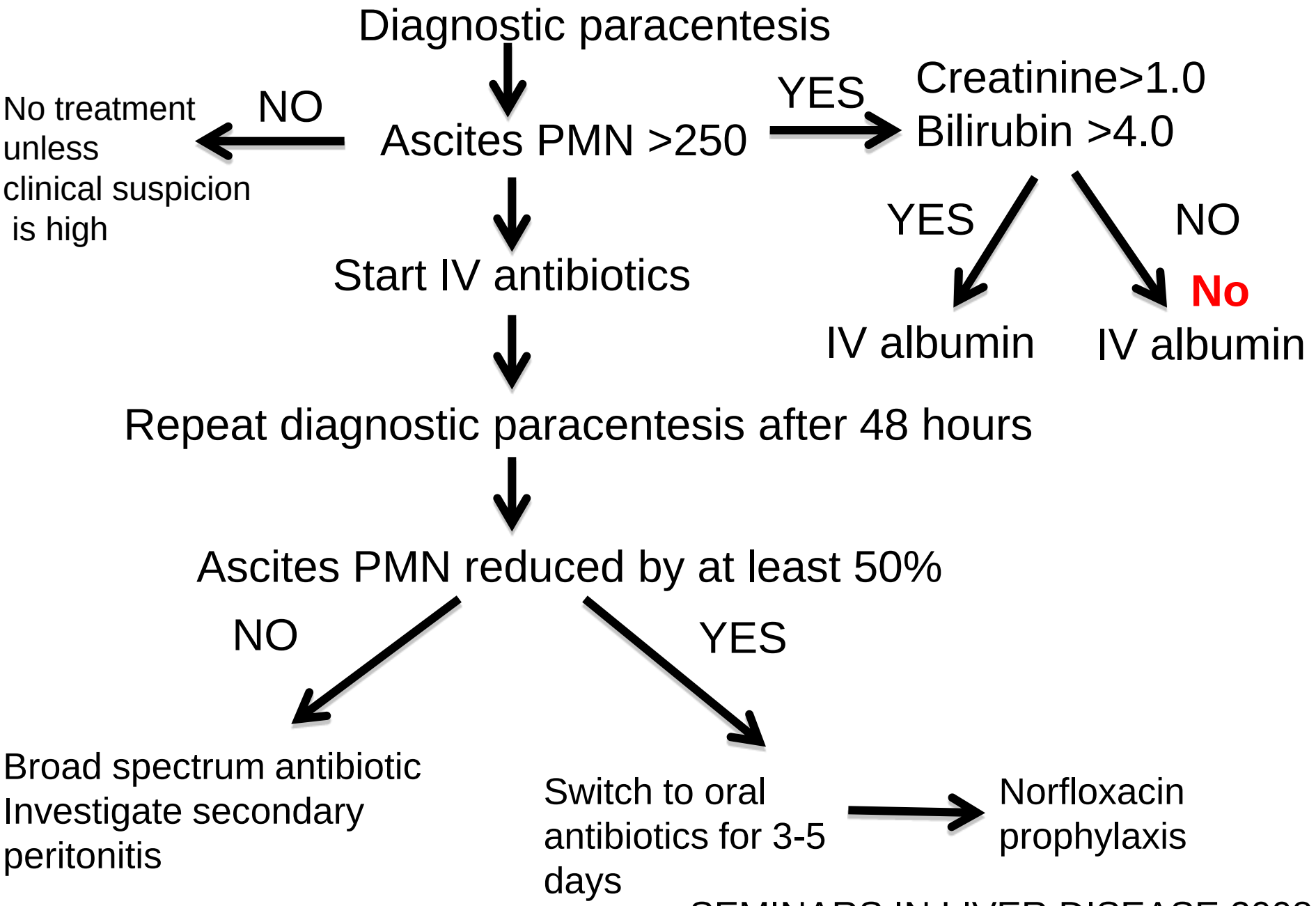
Types	PMN ascitic fluid	Culture	Comments
Culture negative neutrocytic ascites (CNNA)	≥250 cells /mm3	(-)	Should exclude: >Previous antibiotic treatment >hemorrhage >HCC >peritoneal carcinomatosis >TB & pancreatitis
Monomicrobial nonneutrocytic bacterascites (MNB)	<250 cells/mm3	single	underling liver disease is usually less
Polymicrobial bacterascites	<250 cells/mm3	multiple	Consequence of needle perforation of the gut during a diagnostic or therapeutic paracentesis

Other diagnostics:
Ascitic lactoferrin concentration: >242ng/ml Sensi: 96%/speci:97%

Spontaneous Bacterial Peritonitis

- Secondary bacterial peritonitis SHOULD be differentiated!
  - represents less than 10% of ascitic fluid infections in cirrhotic patients
  - usually polymicrobial and PMN≥250mm3 due to surgically treatable intraabdominal source of infection (e.g. perforated gut, perinephric abscess)
  - ascitic fluid analysis shows two or more of the following criteria:
    - total protein >1gr/dL and glucose <50mg/dL
    - LDH >225 U/mL (or higher than ULN of serum)

Integrated treatment of bacterial infections in cirrhotic patients



SEMINARS IN LIVER DISEASE 2008

Treatment of infection

Early empirical IV antibiotics considering:

*Type and severity of infection

*Origin of infection (nosocomial vs. healthcare-associated *vs acquired)*

*History of recent colonization or infection by multiresistant bacteria

Surgical or radiological interventions if needed

Prevention of renal failure in SBP

*IV administration of 20% albumin:

-In patients at risk for renal failure (serum creatinine >1 mg/dl and/or bilirubin >4 mg/dl)

-Dose: 1.5g/k at diagnosis and 1g/kg on Day3

*Diuretic withdrawal

*Avoidance of large volume Paracentesis

Prevention of renal failure in non-SBP infections

a. Diuretic withdrawal
b. Adequate IV and oral hydration
c. IV albumin?

Treatment or prevention of other complications

*Nonabsorbable disaccharides(lactulose or lactitol) to prevent or treat encephalopathy

*Maintenance of B blockers for EV bleeding prophylaxis

*Coagulation factors if bleeding?

Journal of Hepatology 2012

Treatment of SBP

- CEFOTAXIME
  - a 3rd generation cephalosporin
  - can achieve resolution of infection in 85% of patients with SBP
- **Dose**: 2.0 gr cefotaxime IV q8 or 12 hours
- **Duration**: 5 days of therapy has been shown to be as effective as a long course (10 days)

Annals of Gastroenterology 2003

Spontaneous Bacterial Peritonitis

- Risk factors for Recurrent episode of SBP
  - low (<1 g/dl) ascitic fluid protein levels
  - survived from a previous episode of SBP
  - gastrointestinal bleeding are at high risk to develop

- Prophylaxis
  - reduce the risk of recurrence
  - Improve the survival of this group of patients
  - mean % of patients free of infection is increased

Current indications of antibiotic prophylaxis in cirrhosis

Indication	Antibiotic and dose	Duration
GI bleeding	Norfloxacin 400 mg/12 h PO IV ceftriaxone 1 g/d in patients with advanced cirrhosis (at least 2 of the following: ascites, jaundice, hepatic encephalopathy, and malnutrition)	7 days
Primary prophylaxis in patients with low protein ascites (<15g/L)	Norfloxacin 400 mg/d PO in patients with advanced cirrhosis: CPT>9points with Bili>3mg/dl and/or Imapired renal function (Crea>1.2mg/dl; BUN>25mg/dl or Na<130meq/L	Until OLT or death
Secondary prophylaxis	Norfloxacin 400 mg/d PO	Until OLT or death

Javier Fernandez Journal of Hepatology 2012

Emergence of MDR

- Prevalence rate: 23%
  - higher incidence of treatment failure, septic shock and hospital mortality.
  - lack of efficacy of the currently recommended empirical antibiotic therapy
  - clearly ineffective in nosocomial infections (60% of treatment failure)
- CULPRIT:
- ESBL producing Enterobacteriaceae – 14%
- Enterococcus faecium – 12%
- P. aeruginosa – 6%
- MRSA – 6%

HEPATOLOGY 2012;55:1551-1561

Risk factor for infection caused by MDR

	HR
Nosocomial infection	4.43
Long term Norfloxacin prophylaxis	2.69
Infection by MDR bacteria (last 6 months)	2.45
Use of B lactam (past 3 months)	2.39

HEPATOLOGY 2012;55:1551-1561

Proposed Empiric Treatment Strategy for Nosocomial Infection

- Nosocomial SBP and SB:
  - carbapenems or with tigecycline to cover ESBL-E
- Uncomplicated UTI:
  - oral nitrofurantoin or fosfomycin
- UTI associated with SIRS:
  - carbapenem plus a glycopeptide (to cover ESBL-E and E. faecium)
- Cellulitis:
  - ceftazidime plus a glycopeptide (to cover MRSA and P. aeruginosa)
- HCA and nosocomial pneumonia:
  - carbapenems or ceftazidime plus levofloxacin plus a glycopeptide

HEPATOLOGY 2012;55:1551-1561

Long term prophylaxis of SBP and other infections in cirrhosis

Antibiotic prophylaxis is not recommended in patients with ascites who are not hospitalized with an episode of GI hemorrhage and who do not have a history of SBP

Garcia-Tsao Journal of Hepatology 2005

Initial resuscitation, early diagnosis, and antibiotic treatment

GOLDEN PERIOD: first 6 hours

- Treat sepsis-induced tissue hypoperfusion
  - mean arterial pressure ≥65 mmHg
  - CVP between 8 and 12 mmHg
  - central venous oxygen saturation ≥70%
  - urine output ≥0.5 ml/k/h

Crit Care Med 2008;36:296–327

Initial resuscitation, early diagnosis, and antibiotic treatment

- Broad-spectrum antibiotics within the FIRST hour of recognizing severe sepsis or septic shock
- De-escalation
  - should be done once the susceptibility profile of the responsible bacteria is known
- Prompt admission of the patient to the ICU

Fluid and Vasoactive Agents

- FLUIDS
  - ***Crystalloids***
    - Requires >fluid to achieve the same goals
    - > edema
  - ***Albumin***
    - associated with a decrease in mortality compared to other solutions in non-cirrhotic patients with sepsis

Norepinephrine and dopamine

- FIRST LINE

Vasopressin: second-line therapy

N Engl J Med 2008;358:877–887

Intravenous Albumin

- reduces the incidence of renal impairment (from 33% to 10%)
- improves hospital survival (from 71% to 90%) in patients with SBP

Mechanism of Action:

- plasma expander increasing cardiac preload
- attenuates endothelial dysfunction increasing peripheral vascular resistance.
- Dose: 1.5 g/kBW D1 →1g/kBW on day 3

- High risk patients that will benefit with IV albumin:
  - bilirubin >4mg/dl
  - creatinine >1.0mg/dl
    - high risk for the development of HRS (incidence between 33% and 57%)

STRESS Dose Steroids

- improves shock reversal
  - Relative adrenal insufficiency (RAI) - an inappropriate adrenal response to stress
  - frequent in non-cirrhotic patients with septic shock and is associated with refractory shock and mortality

- Current guidelines only recommend stress dose steroids in patients with vasopressor-unresponsive septic shock
- The clinical impact of stress dose steroids on the outcome of cirrhotic patients with septic shock is unclear

Hepatology 2006;44:1288–1295

Glucose Control

- Tight blood glucose control (80-110 mg/dL) with insulin therapy did not reduce mortality rates, but induced more hypoglycemic events compared to conventional strategy (180-200 mg/dL)

- intensive insulin therapy increased the 90-day mortality rate compared to targeting 144-180 mg/dL.

Vaccination

- Pneumococal Vaccination
  - influenza virus
    - the risk of direct damage or allograft reinfection is substantial
  - Adequate protection: 92% to 95% of liver transplant recipients
- Vaccination in Chronic Liver Disease
  - Hepatitis A and B superinfection
    - higher morbidity and fatality rates than in healthy persons
  - advocated in patients with chronic liver disease, including those waiting for transplantation

Semin Crit Care Med 2012;33:80–95

Nutrition

- Nutrition
- branched-chain amino acids
  - effective in restoring neutrophil phagocytosis
- mixture of arginine, omega-3 fatty acids, and nucleic acids
  - hepatic encephalopathy

Parenter Enteral Nutr 2006;30(2):91–96

Measures to decrease bacterial translocation

ANTIBIOTIC

(1)“selective intestinal decontamination” (SID)

NON ANTIBIOTIC approach

(1)changing the composition of gut bacterial flora through the administration of pre/probiotics or bile acids

(2)by accelerating intestinal transit (thereby decreasing IBO) through the use of prokinetics or b-blockers

NON ANTIBIOTIC PROPHYLAXIS

Probiotics

- Mechanism is largely speculative
- promotes the integrity of the gut barrier by normalizing intestinal permeability
- controls intestinal inflammatory responses by modulating the release of cytokines
- Lactobacillus casei
  - improves neutrophil phagocytic capacity and modulates cytokine production and TLR expression

B blocker

- slows intestinal motility in cirrhosis
- pharmacologically induced reductions in portal pressure have been associated with reductions in the development of SBP

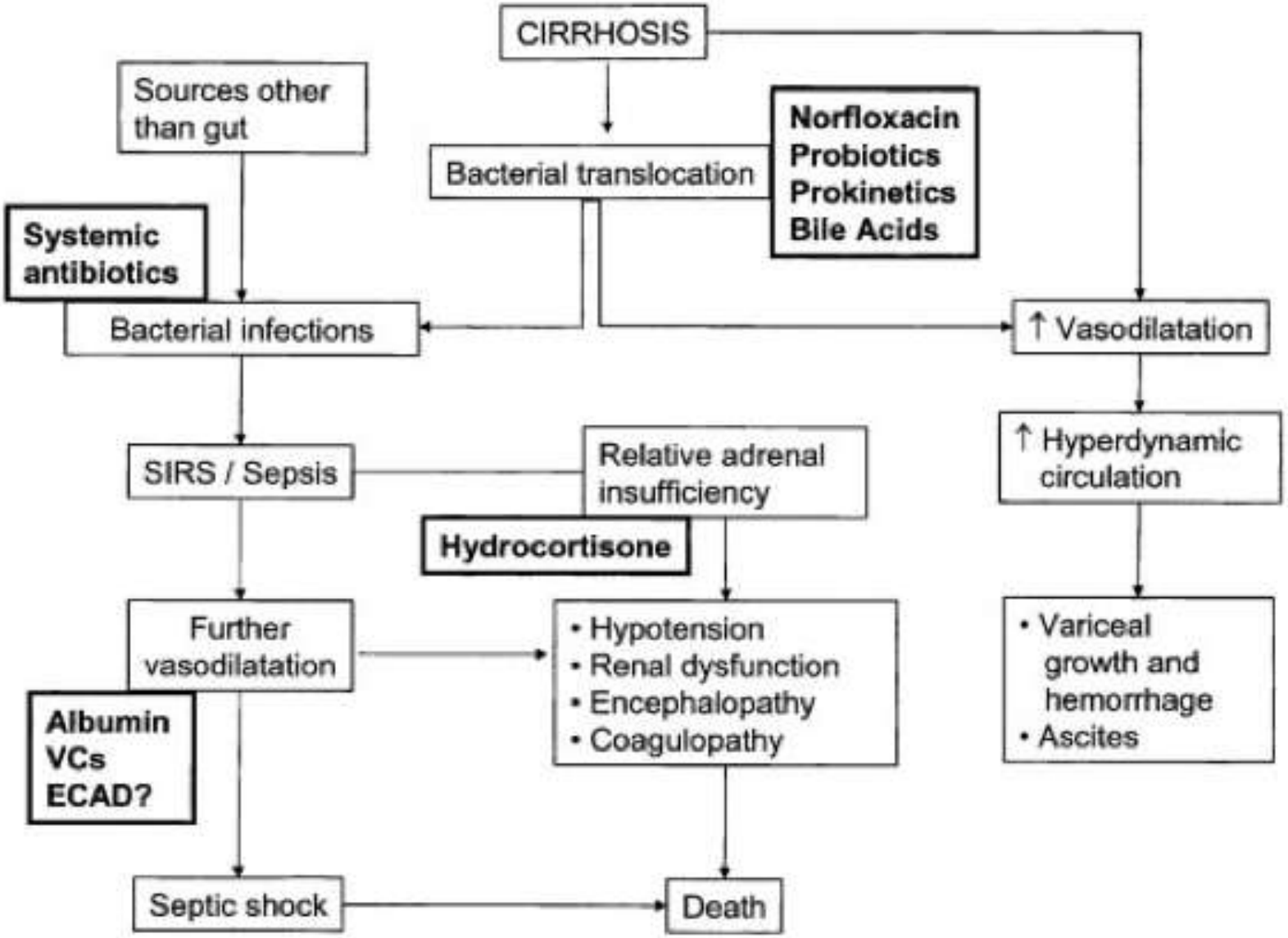
J Transplant 2005;5 (1):125–130

Bile acids

- affect the microflora and integrity of the SI

- oral administration of conjugated bile acids, such as cholylsarcosine and cholylglycine in ascitic cirrhotic rats, results in a reduction in bacterial overgrowth, BT, and endotoxemia and an increase in survival
- RCTs needed

Gut 2005;54(4):556–563



Seminars in Liver Disease/Volume 28, Number 1 - 2008

Spontaneous Bacterial Empyema

Spontaneous Bacterial empyema

- Cirrhotic hydrothorax
  - large pleural effusion (>500ml) in cirrhotic patients,

  +/- ascites, in the absence of primary pulmonary or cardiac disease
  - 4% to 6% and up to 10% in advanced liver disease
- almost half also have spontaneous bacterial peritonitis.

Annals of Gastroenterology 2003

Spontaneous Bacterial empyema

- MECHANISM:
  - transfer of peritoneal fluid directly via defects in the tedious portion of diaphragm from the abdominal cavity to the pleural space.
  - The unidirectional flow of fluid from the abdomen to the chest and the evidence of pressure gradient between the two cavities

Annals of Gastroenterology 2003

Spontaneous Bacterial empyema

- most frequent causative organisms:
  - Gram (-) bacilli particularly E. coli.
  - same pathogensesis as that of SBP
  - infection of the fluid in the thoracic cavity as an effect of spontaneous bacteremia or the passage of infected ascites from the abdomen through the diaphragm
- should be suspected when fever and dyspnea

Spontaneous Bacterial empyema

- Diagnosis :
  - (+) pleural fluid culture and PMN >250 cells /mm3
  - (-) culture with PMN > 500 cells/mm3

EXCLUDE:

- HIV infection
- parapneumonic infections with CXR and CT
- Patients who underwent variceal sclerotherapy during the previous week

Spontaneous bacterial empyema

- Treatment:
  - cefotaxime 2 g/12 h IV or ceftriaxone 1 g/12-24 h IV or amoxicillin-clavulanic acid 1-0.2 g/6-8 h IV

- Intestinal decontamination with norfloxacin appears to be effective in preventing the recurrence of infection
  - may decrease with time because of emergence of MDR

Spontaneous bacterial empyema

- Criteria for chest tube insertion:
  - frank pus
  - ph<7.1
  - glucose levels <40 mg/dl

Pneumonia

7% to 23% - aspiration of oropharyngeal contents

Organisms:

- Streptococcus pneumonia
- Hemophilus influenzae
- Klebsiella
- Mycoplasma and Legionella species
- anaerobes (mostly Peptostreptococcus, Bacteroides melaninogenicus and Fusobacterium nucleatum)

TREATMENT:

Macrolide or a quinolone (levofloxacin), along with cephalosporin

- HAP: gram negative organisms and staphylococci

Pneumonia

- Other risk factors :
  - Gastrointestinal bleeding
  - upper GI endoscopy
  - ascites

- Empiric treatment with cefipime is a reasonable first choice with the addition of clindamycin if aspiration pneumonia is possible

Dis Clin North Am 2001; 15:363-71

Soft Tissue Infection

- Lymphangitis of lower extremities
- Cellulitis of lower extremities or abdominal wall
- Organisms:
  - Gram (+) cocci; Gram (-) bacilli
    - frequent in cirrhotic patients with ascites and generalized edema
- DOC: amoxicillin-clavulanic acid 1-0.2 g/6-8 h IV or ceftriaxone 1 g/12-24 h IV + cloxacillin (2 g/6 h IV)

Annals of Gastroenterology 2003

Endocarditis

- prior invasive procedures that increase the risk of bacteriemia
- Incidence : 0.34% cirrhosis vs 0.1% without cirrhosis
- ? aortic or mitral valve (unclear)
- Pathogens: S. pneumonia, E. coli and S. aureus

Potential sources:

- upper gastrointestinal bleeding
- pneumonia
- SBP
- heart catheterization
- abdominal abscess
- TIPS placement and hip replacement

Other infections in patients With Cirrhosis

Infectious Complication	Incidence, Characteristics, and Risk Factors in Cirrhosis
RTI	• Bacterial decontamination may significantly influence incidence, but not mortality, of septicaemia * Incidence ranging from 13.6% to 48.1% of all infections
UTI	• Incidence: 7% to 74.1% of all infections * *Enterococcus faecalis* - 20% of cases • Possible relationship with hepatic encephalopathy • Recurrent UTIs implicated in PBC as AMA inducers Tx: cefotaxime 2 g/12 h IV or ceftriaxone 1 g/12-24 h IV or amoxicillin-clavulanic acid 1-0.2 g/6-8 h IV in patients with sepsis. Ciprofloxacin 500 mg/12 h PO or cotrimoxazole (160-800 mg/12 h PO) in uncomplicated infections*

American Journal of Gastroenterology 2005

Other infections in Patients With Cirrhosis

Specific Infectious Complication	Incidence, Characteristics, and Risk Factors in Cirrhosis
Meningitis	More commonly reported in alcoholic cirrhosis; overall one month case fatality rate may exceed 50%; *Streptococcus pneumoniae, Escherichia coli,* and *Listeria* the commonest pathogens implicated; nuchal rigidity may be a delayed or even absent clinical sign; mortality may reach 80% in Child-Pugh stage C
Hepatic abscess	• Mortality exceeding 60% for nonalcoholic cirrhotic patients

American Journal of Gastroenterology 2005

Special Population

Alcoholism

- most important predisposing factor for the development of pneumonia
- S. pneumonia
- anaerobic bacteria
- H. influenzae
- G(-)bacilli, particularly K. pneumoniae

- prone to develop pulmonary or peritoneal TB
- Dx: Laparoscopic investigation
- Symptoms:
  - low grade fever
  - high protein ascitic fluid
  - lymphocyte elevation

Esophageal Variceal Ligation

Infectious complications:

- Bacteremia
  - introduction of microorganisms via the sclerotherapy needle or contaminated water solution
- meningitis
- subdural empyema
- Perinephric abscess
- cerebral abscess
- Endocarditis
- bacterial peritonitis

Esophageal Scleotherapy

- bacteria translocate through intestinal walls
- calculated risk of developing peritonitis:
  - Elective EVS :0.5%
  - Emergency EVS: 3%

Isolates:

- Klebsiella pneumoniae
- streptococcus sanguis
- Enterococcus, Streptococcus group B, Staphylococcus aureus, Escherichia coli, Citrobacter freundii.

EVL vs EVS

- 10x LOWER after EVL than after EVS
- mechanical strangulation of varices by EVL using small elastic rings, may obliterate the submucosal venous channels and thereby diminish the entrance of bacteria to the blood stream
- Gram positive skin and oropharyngeal microorganisms (EVL):
  - Streptococcus pyogenes
  - Staphylococcus epidermidis
  - Staphylococcus aureus and Dipheroid species

Prophylaxis prior to EVL/EVS

- valvular heart disease
- prosthetic valves
- previous endocarditis
- previously undergone splenectomy
- patients with Childs C class cirrhosis
- recent history of variceal bleeding
- past history of bacterial peritonitis
- co morbid immunosuppressive condition

Key Points

- Bacterial infection is one of the most frequent complications and the first cause of death in cirrhosis.

- Immune defects, mainly acquired but also genetic, and bacterial translocation are the main mechanisms involved in its pathogenesis

Key Points

- Early diagnosis of infection is pivotal. CRP, prolactin and SIRS criteria have less diagnostic accuracy in cirrhosis. New diagnostic tools are clearly needed

- Whole third generation cephalosporins continue to be the gold standard antibiotic treatment of many of the infections acquired in the community.

Key points

- IV albumin reduces the incidence of renal impairment and improves hospital survival in paients with SBP and poor liver or renal fucntions.

- Restriction of prophylactic antibiotics to the high risk populations will reduce the spread of multidrug resistant bacteria in cirrhosis.