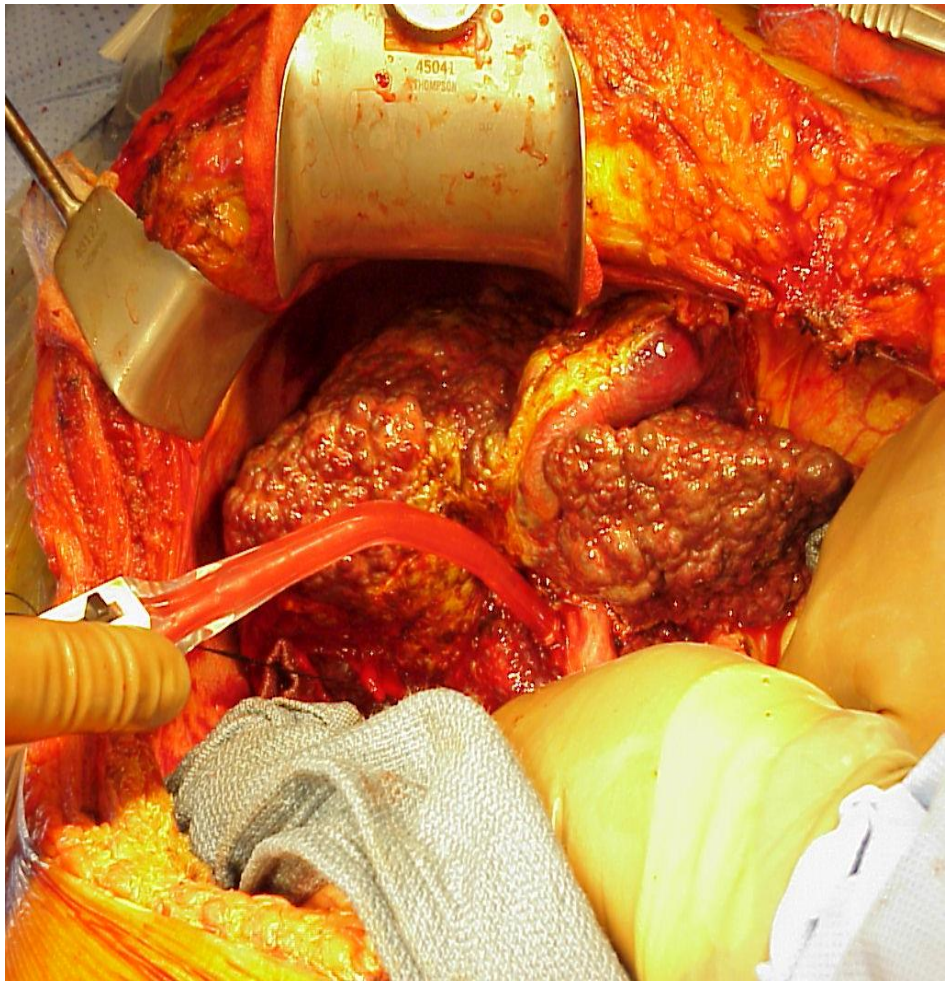
Cirrhosis Update

CIRRHOSIS
Definition



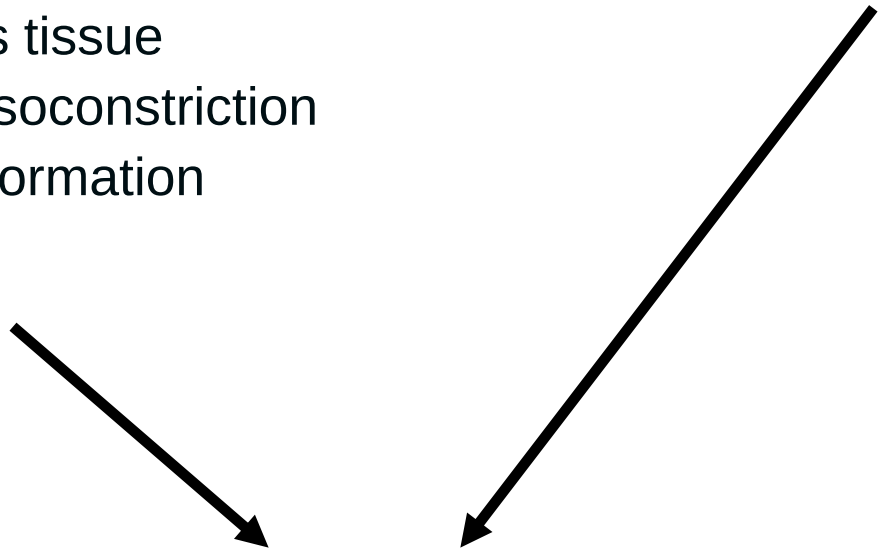
- “Irreversible” fibrous scarring within the liver which has lead to the development of regenerative nodules
- Estimated 3-4 million people in the U.S. have CLD and cirrhosis!
- CLD 15-20 million

Portal Hypertension

↑Resistance x ↑Flow = Portal Hypertension

Increased Resistance
(Architectural changes secondary to fibrous tissue formation; active vasoconstriction due to decrease in formation of endogenous NO)

Increased Blood Flow
(Splanchnic arteriolar vasodilation)



Increased Portal Pressure

Adapted from Garcia-Tsao G et al. *Hepatology.* 2007;46:922-938.

Portal Hypertension

- Consequences of portal hypertension produce symptoms:
  - Gastroesophageal varices
  - Ascites
  - Enlarged spleen
  - Hepatic encephalopathy

From: http://www.merck.com/mmhe/sec10/ch135/ch135d.html. Accessed 02/15/11.

Gastroesophageal Varices

Gastroesophageal Varices

- Gastroesophageal varices present in ~50% of patients with cirrhosis
  - Presence correlates with severity of liver disease
  - 40% of Child A patients have varices
  - 85% of Child C patients have varices
- Cirrhotic patients without varices develop them at a rate of 8% per year
  - Patients with small varices develop large varices at a rate of 8% per year

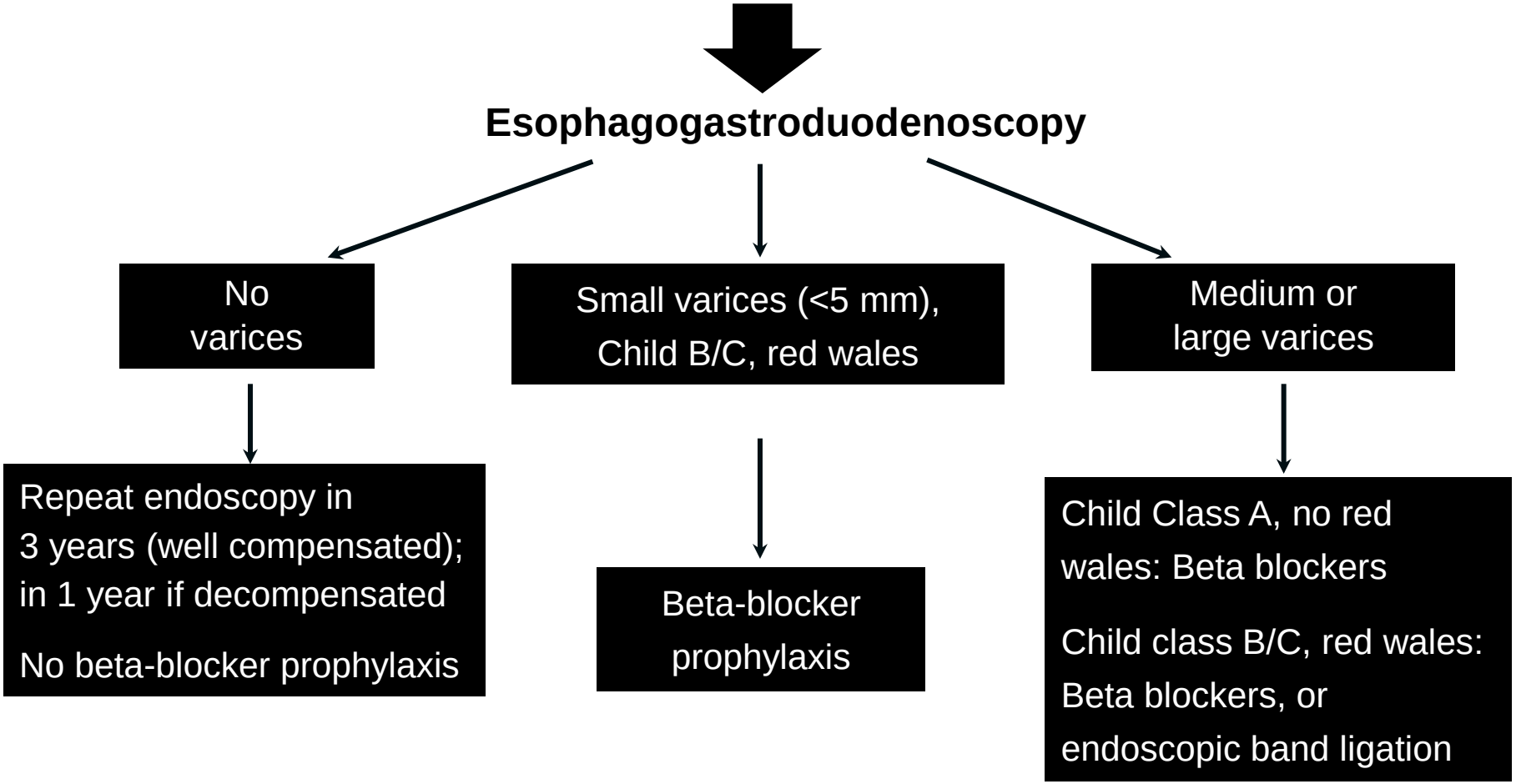
Garcia-Tsao G et al. *Hepatology.* 2007;46:922-938.

Gastroesophageal Variceal Hemorrhage

- Occurs at a yearly rate of 5% to 15%
- Most important predictor of hemorrhage is size of varices
- Other predictors of hemorrhage are:
  - Decompensated cirrhosis (Child B/C)
  - Endoscopic presence of red wale marks
- Associated with a mortality of ≥20% at 6 weeks
- Bleeding ceases spontaneously in ≤40% of patients

Garcia-Tsao G et al. *Hepatology.* 2007;46:922-938.

Cirrhosis Screening and Surveillance Management



Adapted from Garcia-Tsao G et al. *Hepatology.* 2007;46:922-938.

Management of Acute Hemorrhage

- Patients with suspected acute variceal hemorrhage require intensive-care unit setting for resuscitation and management
- Acute GI hemorrhage requires:
  - Intravascular volume support
  - Blood transfusions
  - Maintaining hemoglobin of ~8 g/dL
- Institute short-term (7-day) antibiotic prophylaxis
- Initiate therapy with somatostatin (or its analogs)
- Perform esophagogastroduodenoscopy within 12 hours; treat with endoscopic band ligation or sclerotherapy

Garcia-Tsao G et al. *Hepatology.* 2007;46:922-938.

Management of Acute Hemorrhage (Cont.)

- TIPS (transjugular intrahepatic portosystemic shunt) indicated if hemorrhage uncontrolled or recurrent bleeding despite pharmacologic and endoscopic therapy

- Balloon tamponade should be temporary measure used prior to more definitive therapy

Garcia-Tsao G et al. *Hepatology.* 2007;46:922-938.

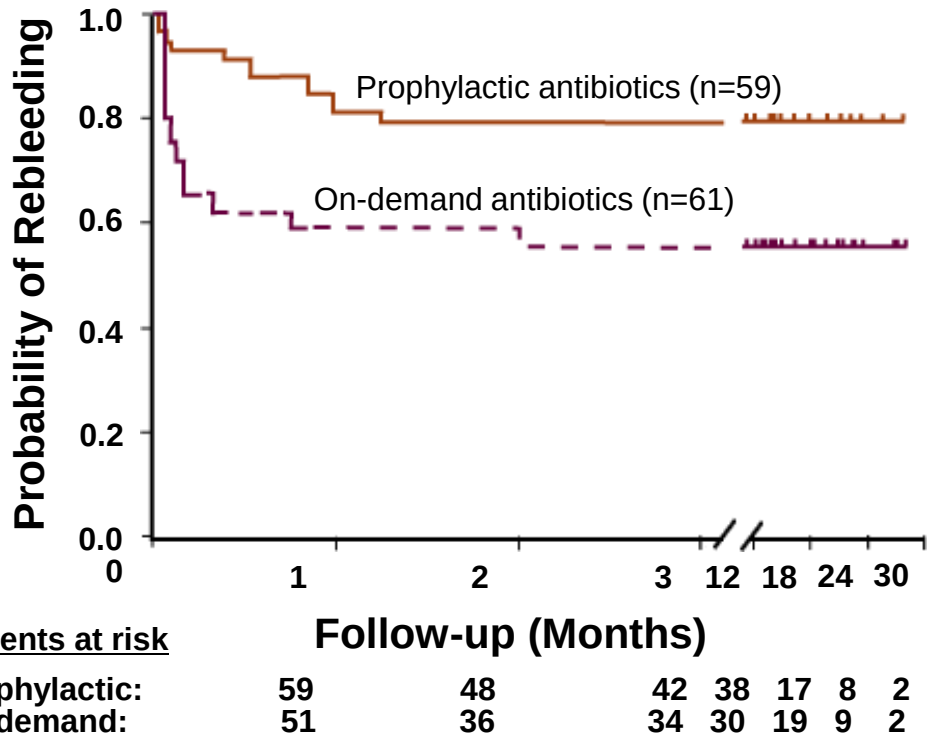
Bacterial Infection and Variceal Bleeding

- Variceal bleeding associated with increased risk of bacterial infection
  - SBP (spontaneous bacterial peritonitis), urinary tract infection, pneumonia or bacteremia
- Develops in 20% of patients within 48 hours and in 35% to 66% of patients within 2 weeks
- Compared to patients without infection, presence of infection is associated with
  - Failure to control bleeding (65% vs 15%)
  - Early rebleeding
  - Mortality (40% vs 3%)

Vivas S et al., *Dig Dis Sci.* 2001;46:2752-2757.

Antibiotic Prophylaxis During/After Acute Variceal Bleeding

- Prophylatic ofloxacin vs antibiotics only at diagnosis of infection
- ↓ infections (2/59 vs 16/61)
- Less rebleeding within 7 days
- ↓ blood transfusions for rebleeding
- Prophylactic antibiotics recommended in management of acute variceal hemorrhage



Hou M-C et al. *Hepatology.* 2004;39:746-753.

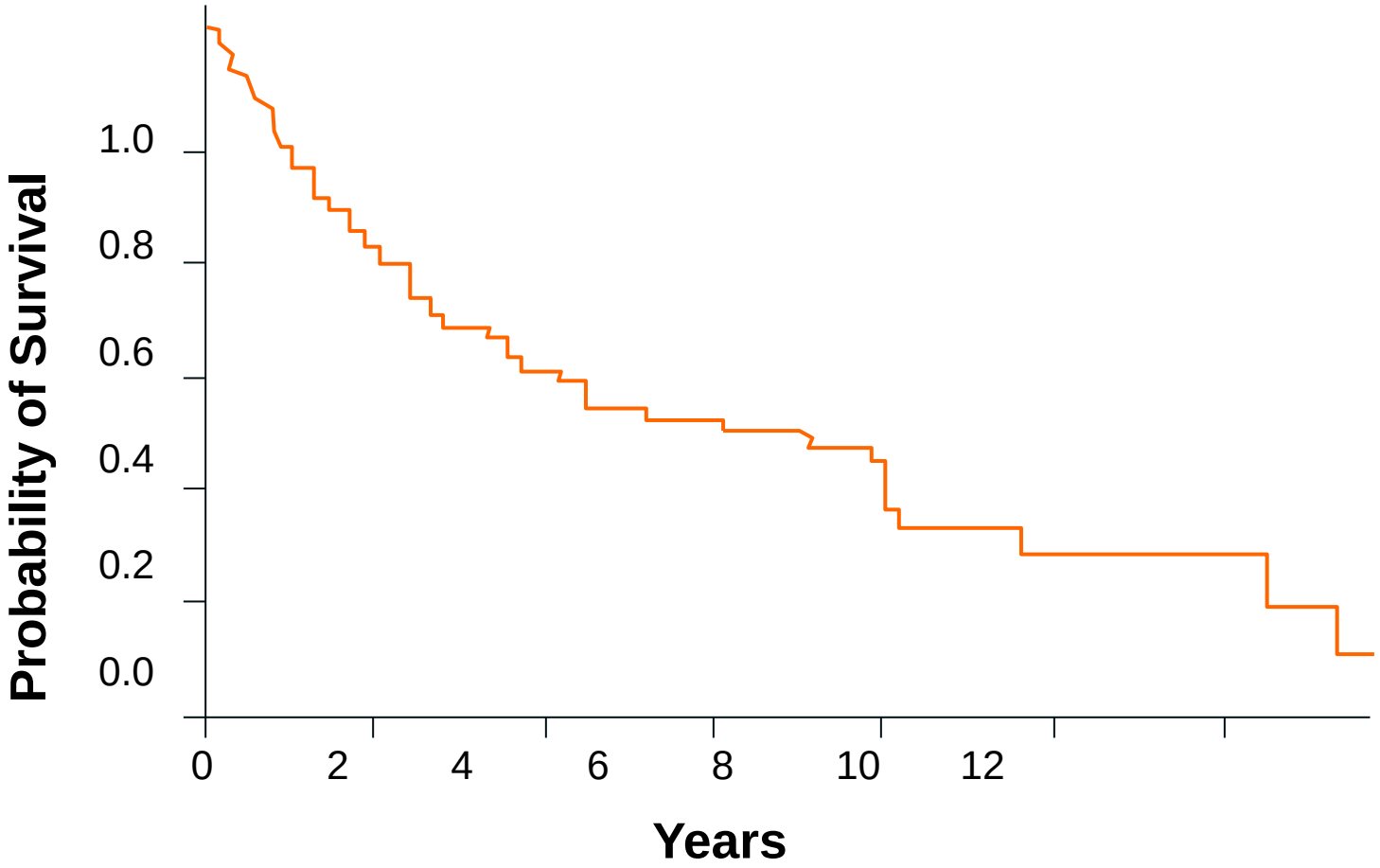
Ascites

Ascites

- Most common complication of cirrhosis
- Only occurs when portal hypertension has developed
- ~60% of patients with compensated cirrhosis develop ascites within 10 years
- 50% mortality rate within 3 years
- Patients should generally be considered for liver transplantation referral

Arroyo V, Colmenero J. *J Hepatol.* 2003;38:S69-S89.
European Association for the Study of the Liver. *J Hepatol.* 2010;53:397-417.

Prognosis of Patients with Cirrhosis at Onset of Ascites



Arroyo V, Colmenero J. *J Hepatol.* 2003;38:S69-S89.

AASLD Practice Guidelines: Ascitic Fluid Analysis

Routine	Optional	Unusual	Unhelpful
Cell count and differential	Culture in blood culture bottles	Acid-fast bacteria smear and culture	pH
Albumin	Glucose	Cytology	Lactate
Total protein	Lactose dehydrogenase	Trigylceride	Cholesterol
	Amylase	Bilirubin	Fibronectin
	Gram's stain		Glycosamino-glycans

Runyon BA. *Hepatology.* 2009; 49:2087-2107.

Management of Ascites

First-Line Therapy

Tense ascites

↘

Paracentesis

↘

Sodium restriction (<2 Gm/24 Hrs) and diuretics*

→

Refractory Ascites 10 %

→

Non-tense ascites ↗

Second-Line Therapy

- Repeated large volume paracentesis (LVP)†
- TIPS
- Liver Transplantation

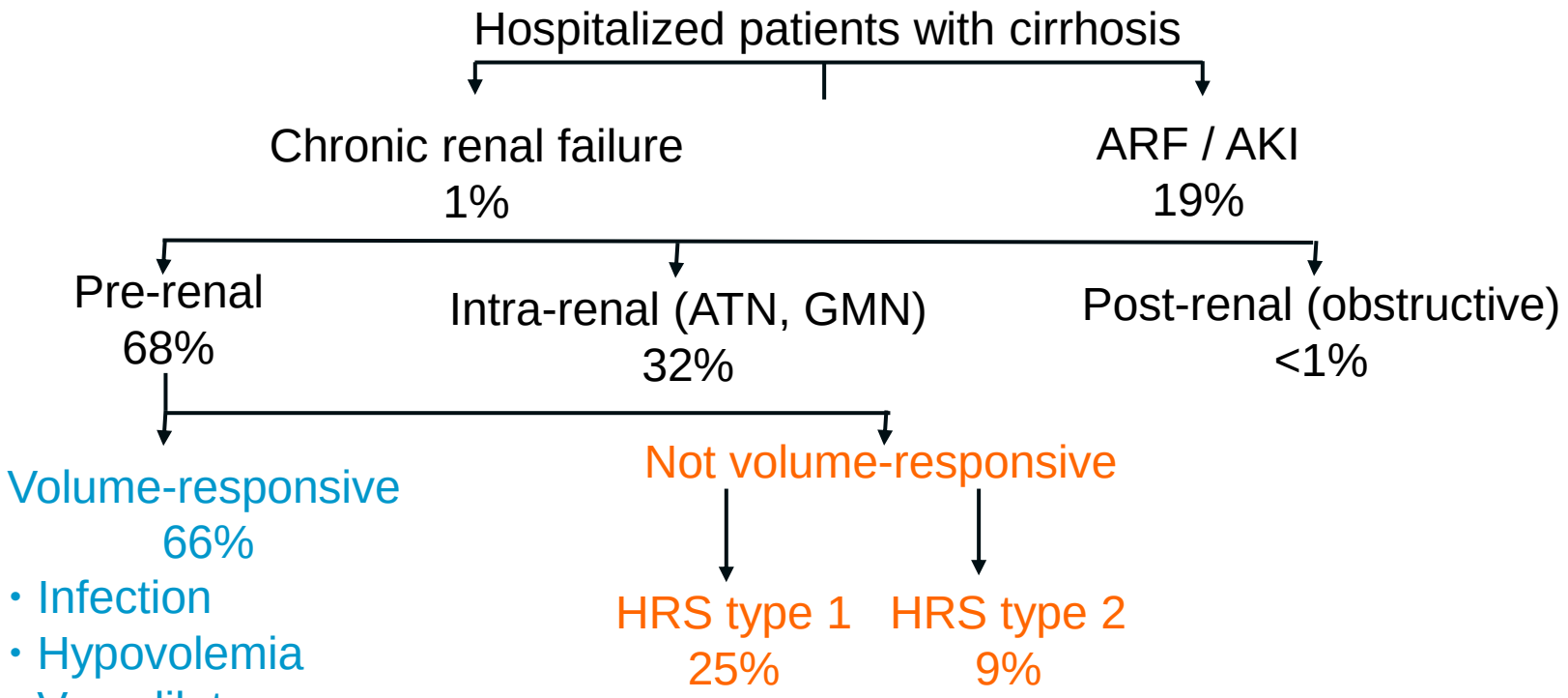
***Diuretics: Spironolactone 100 mg/day, furosemide 40 mg/day or bumetanide 1 mg/day; uptitrate stepwise to spironolactone 400 mg/day, furosemide 160 mg/day or bumetanide 4 mg/day as tolerated**

†Albumin infusion of 12 gm/liter of fluid removed is a consideration for repeated LVP; post-paracentesis albumin infusion may not be necessary for < 5 liters removed

Adapted from Runyon BA. *Hepatology.* 2009; 49:2087-2107.

Renal Dysfunction

Renal Injury in Cirrhosis

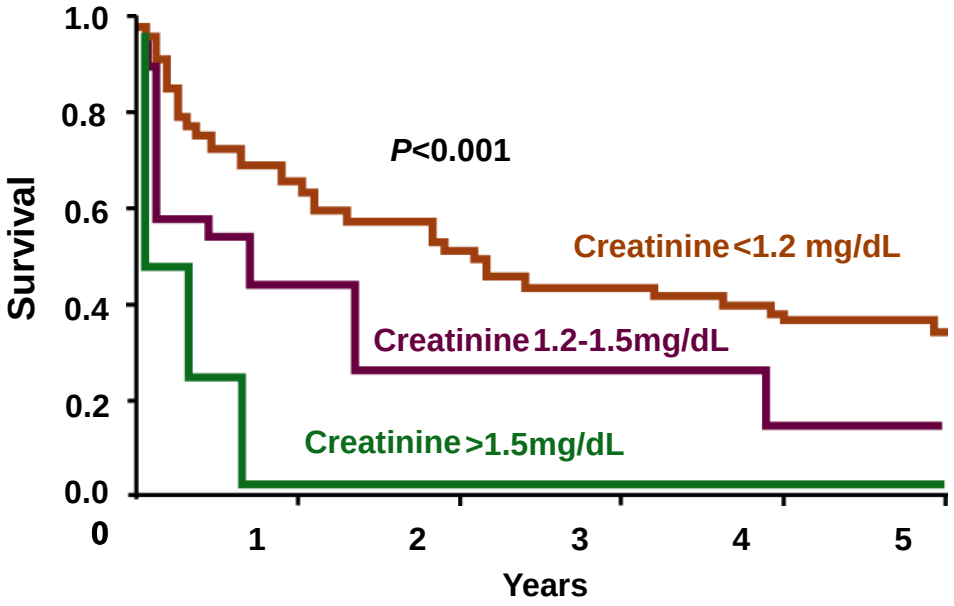


ARF: Acute renal failure	GMN: Glomerulonephritis
ATN: Acute tubular necrosis	AKI: Acute kidney injury
HRS: Hepatorenal syndrome	

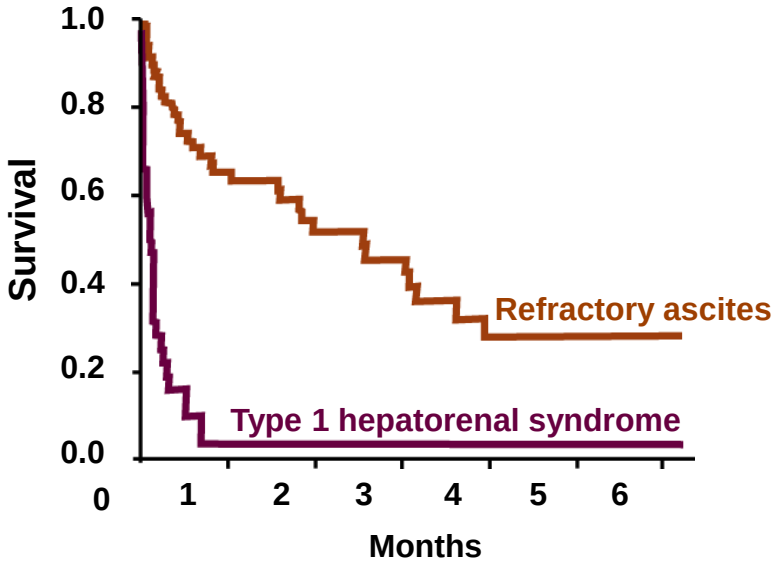
Garcia-Tsao G et al. *Hepatology.* 2008;48:2064-2077.

Survival is Decreased with Renal Dysfunction

Survival in Cirrhosis Based on Level of Renal Dysfunction



Survival Among Patients With Cirrhosis and Hepatorenal Syndrome



Blackwell: *Science*, Oxford, UK.
Gines et al. *N Engl J Med.* 2004;350:1646-1654.

Prevention of Acute Renal Injury in Cirrhotics

- Prevent/treat volume depletion or vasodilatation
  - Careful use of diuretics
  - Avoidance of diarrhea with use of lactulose
  - Use of albumin after large-volume paracentesis
- Avoid use of aminoglycosides and NSAIDs
- Aggressively treat hypovolemia/hypotension occurrence

Garcia-Tsao G et al. *Hepatology.* 2008;48:2064-2077.

Hepatorenal Syndrome

Hepatorenal Syndrome: Risk Factors

- Development of bacterial infections, particularly SBP, is the most important risk factor
  - Hepatorenal syndrome develops in ~30% of patients with spontaneous bacterial peritonitis
  - Treatment with albumin infusion/antibiotics reduces the risk of developing hepatorenal syndrome and improves survival

European Association for the Study of the Liver. *J Hepatol.* 2010;53:397-417.

Hepatorenal Syndrome: Prognosis

- The prognosis of hepatorenal syndrome is poor
  - Average median survival ~ 3 months
  - High MELD score and type 1 hepatorenal syndrome are associated with very poor prognosis
    - Median survival of patients with untreated type 1 hepatorenal syndrome is ~ 1 month

European Association for the Study of the Liver. *J Hepatol.* 2010;53:397-417.

Hepatic Encephalopathy (HE)

Treatment Goals for OHE

- Provision for supportive care
- Identification and removal of precipitating factors
  - Infection, GI bleed, dehydration
- Reduction of nitrogenous load from gut
- Correction of electrolyte abnormalities
- Long-term therapy assessment
  - Control of potential precipitating factors
  - Higher likelihood of recurrent encephalopathy
  - Assessment of need for liver transplantation

Adapted from Blei AT et al. *Am J Gastroenterol.* 2001;96(7):1968-1976.

Current Therapy Options for HE

Drug Name	Drug Class	Indication
Lactulose	Poorly absorbed disaccharide	• Decrease blood ammonia concentration • Prevention and treatment of portal-systemic encephalopathy
Rifaximin	Non-aminoglycoside semi-synthetic, nonsystemic antibiotic	Reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients ≥ 18 years of age.
Neomycin	Aminoglycoside antibiotic	Not to be used, renal and ototoxic risk
Metronidazole	Synthetic antiprotozoal and antibacterial agent	Not approved for HE
Vancomycin	Aminoglycoside antibiotic	Not approved for HE

Adapted from http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/UCM203247.pdf, accessed 02/17/11 and http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022554lbl.pdf, accessed 02/17/11.

Lactulose

- Currently the mainstay of therapy of HE; ~70% to 80% of patients with acute and chronic HE improve with lactulose treatment
- Mechanism of action:
  - A non-absorbable dissacharide that is fermented in the colon
  - Metabolism by the bacterial flora in the colon to lactic acid lowers the colonic pH
  - Cathartic effect can increase fecal nitrogen excretion with up to a 4-fold increase in stool volume

Mullen KD et al. *Semin Liver Dis*. 2007;27(Suppl 2):32-47.
Ferenci P. *Semin Liver Dis*. 2007;27(suppl 2):10-17.
Bajaj JS. *Aliment Pharmacol Ther* 2010;31:537-547.

Lactulose (Cont.)

- Administered orally, by mouth or through a nasogastric tube or via retention enemas
- Dose: 45 to 90 g/day, titrated to achieve 2 to 3 soft stools per day with a pH below 6
- Principal side effects include abdominal distension, cramping, diarrhea, electrolyte changes, and flatulence
- Systematic review of clinical studies found insufficient evidence to support or refute the use of lactulose for HE

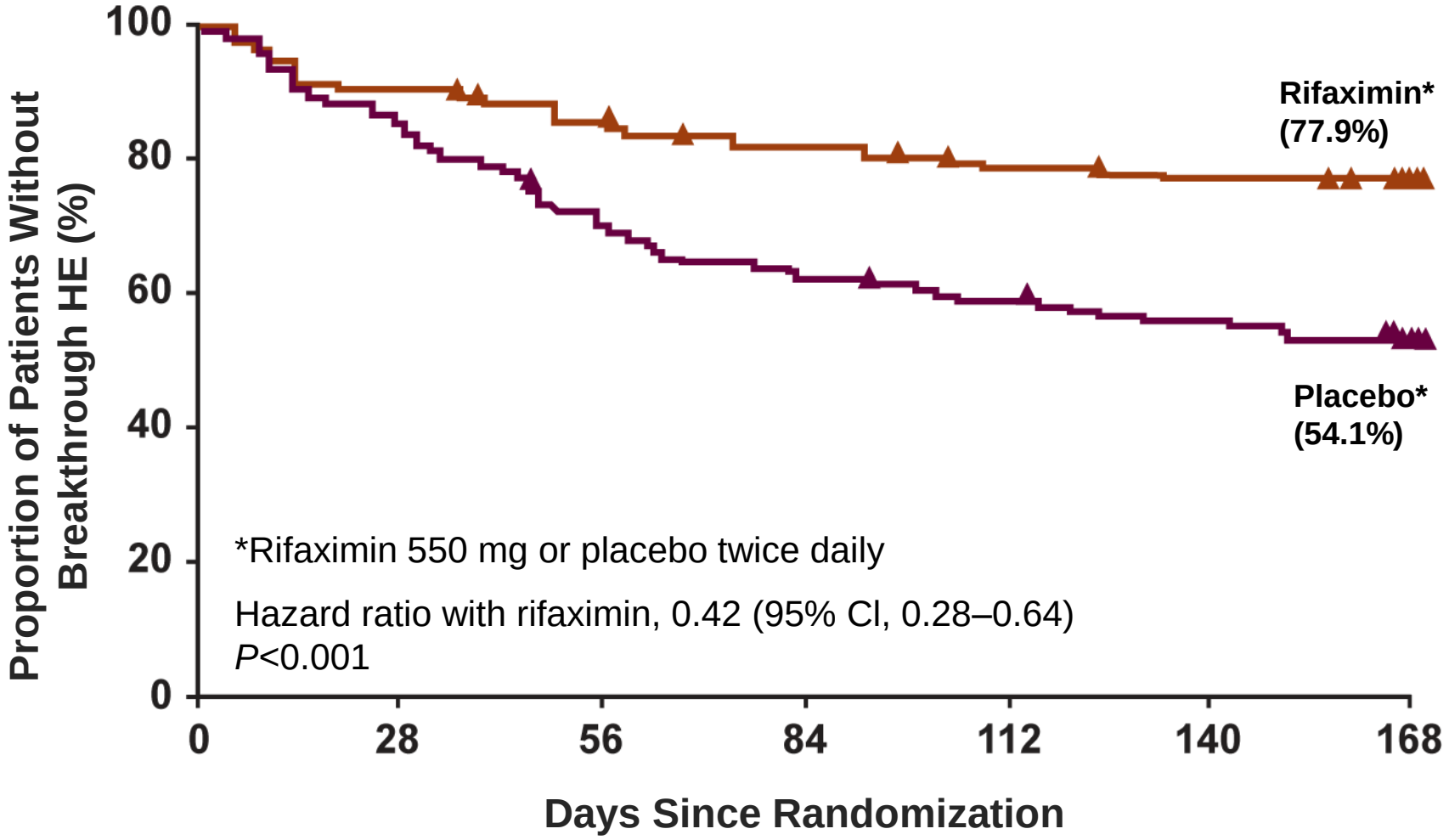
Ferenci P. *Semin Liver Dis*. 2007;27(suppl 2):10-17.
Als-Nielsen et al. *BMJ* 2004;328:1046-1051.
Bajaj JS. *Aliment Pharmacol Ther* 2010;31:537-547.

Rifaximin

- Minimally absorbed (<0.4%) oral antibiotic
- Broad-spectrum in vitro activity against aerobic and anaerobic enteric bacteria
- No clinical drug interactions reported
- No dosing adjustment required in patients with liver disease or renal insufficiency
- Approved for overt recurrent HE risk reduction in patients ≥18 years of age
- In registration trials, 91% of patients were given lactulose concomitantly

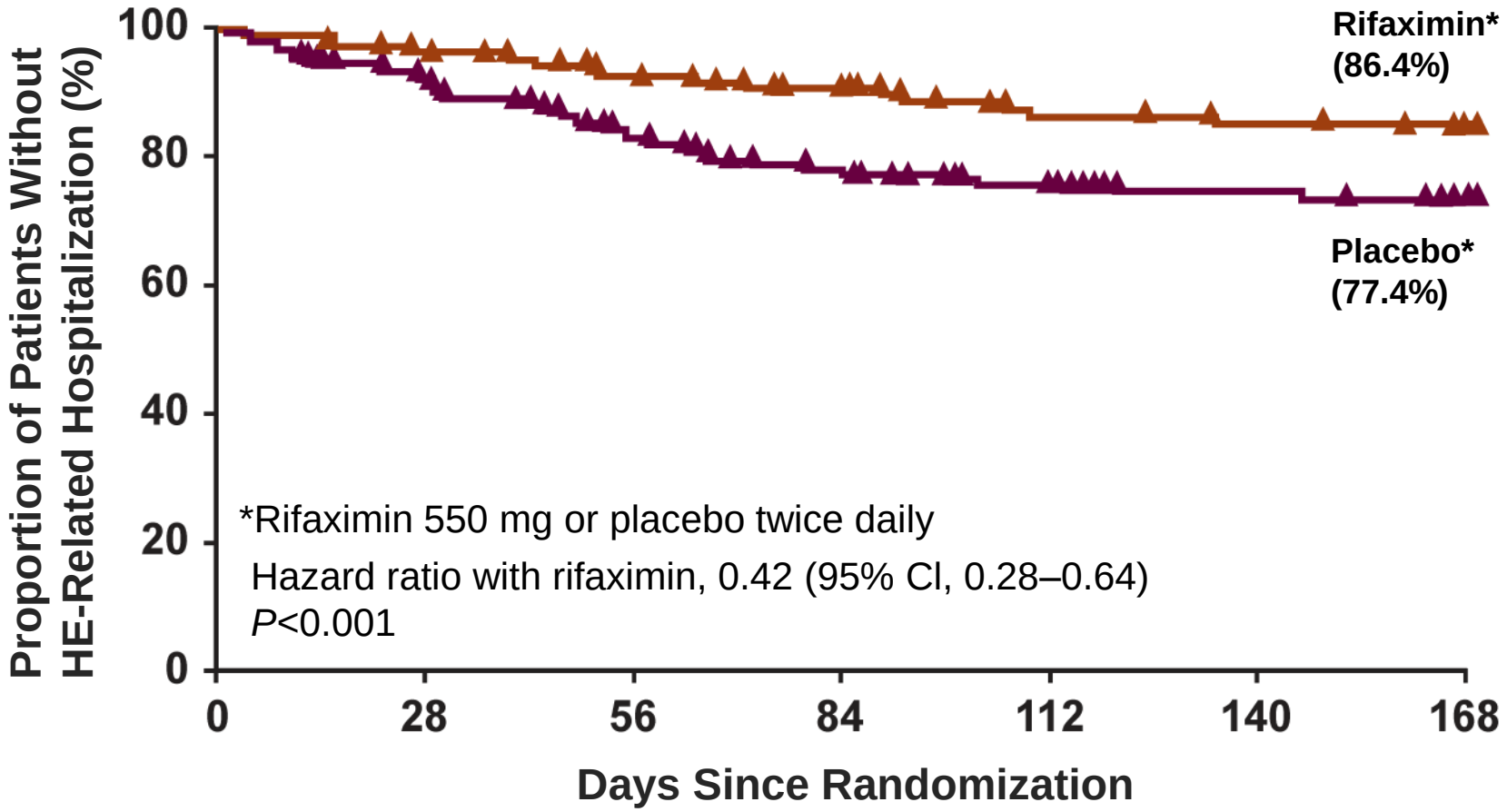
Bass NM. *Semin Liver Dis*. 2007;27(suppl 2):18-25.
Mullen KD et al. *Semin Liver Dis*. 2007;27(suppl 2):32-47.

Rifaximin Trial: Time to First Breakthrough HE Episode Primary End Point



Bass NM et al. *N Engl J Med.* 2010;362:1071-1081.

Rifaximin Trial: Time to First HE- Related Hospitalization Key Secondary End Point

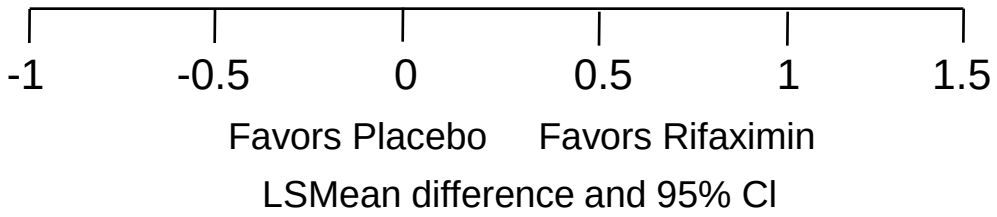


Bass NM et al. *N Engl J Med.* 2010;362:1071-1081.

Rifaximin Trial: Rifaximin Improves Health-Related Quality of Life

CLD,Questionnaire Domain Scores: Differences in least square means of time-weighted average values and 95% CI intervals, rifaximin (n=101) vs. placebo (n=118) groups

Domain	*P*-value
Fatigue	0.0087
Abdominal symptoms	0.0090
Systemic symptoms	0.0160
Activity	0.0022
Emotional function	0.0065
Worry	0.0436
Overall	0.0093



Sanyal A et al. Aliment Pharmacol Ther 2011;34:853-861.

Rifaximin Trial: Side Effects Similar to Placebo

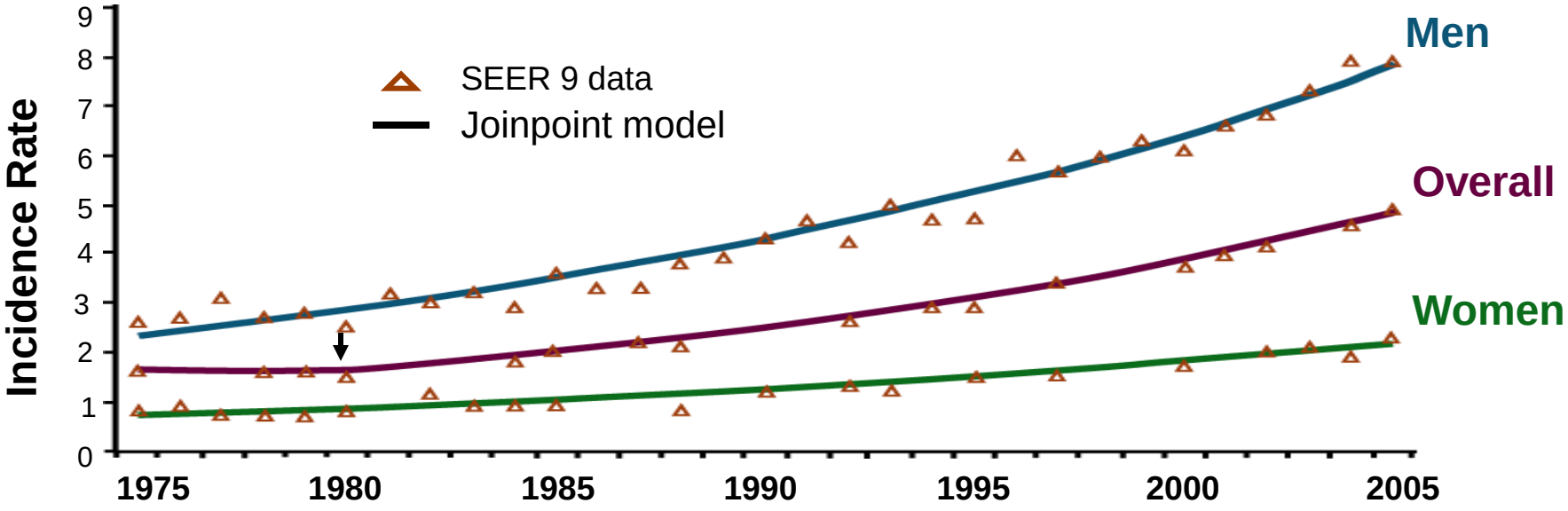
- Incidence of adverse events did not differ significantly between 2 study groups (*P*>0.05 for all comparisons)

	Adverse Events Reported in ≥10% of Patients in Either Study Group	
Event	**Rifaximin (n=140)**	**Placebo (n=159)**
Any event, n (%)	112 (80.0)	127 (79.9)
Nausea	20 (14.3)	21 (13.2)
Diarrhea	15 (10.7)	21 (13.2)
Fatigue	17 (12.1)	18 (11.3)
Peripheral edema	21 (15.0)	13 (8.2)
Ascites	16 (11.4)	15 (9.4)
Dizziness	18 (12.9)	13 (8.2)
Headache	14 (10.0)	17 (10.7)

Bass NM et al. *N Engl J Med.* 2010;362:1071-1081.

Hepatocellular Carcinoma (HCC)

HCC Incidence Tripled Over the Last Three Decades



Altekruse SF, JClin Oncol. 2009 Mar 20;27(9):1485-9.

AASLD Practice Guidelines on Screening & Surveillance for HCC

- AASLD recommends surveillance using AFP + US every 6-12 months for at-risk patient groups:
  - Hepatitis B carriers
    - Asian males >40 years
    - Asian females >50 years
    - All cirrhotic hepatitis B carriers
    - Family history of HCC
    - Africans >20 years
    - Non-cirrhotic hepatitis B carriers with high HBV DNA levels or more severe current/past levels of inflammatory activity
  - Cirrhosis due to hepatitis C, alcohol, or other causes

Bruix & Sherman. AASLD Practice Guideline: Management of Hepatocellular Carcinoma, *Hepatology* 2005; 42(5):1208.

Imaging Studies

- AASLD Criteria - HCC
  - Nodules > 1 cm (previously ≥ 2 cm) both early arterial enhancement and rapid venous/late phase wash out with on dynamic contrast CT/MRI
  - Any other findings require biopsy or interval growth for HCC diagnosis

Liver Biopsies of HCC Are Rarely Needed!

Risks

Pain

Bleeding

Needle Tract Seeding

Mis-diagnosis

Health Maintenance of the Cirrhotic Patient

- Vaccinations
- Bone disease screening, surveillance and management
- HCC Screening and Surveillance
- Varices Screening and Surveillance
- Nutritional Support
  - Vitamin assessment for Vit A and D deficiency
  - Mineral assesment: Zinc and Mg++
- Review Medication List