ACLF: Where are we now?

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Outline

• Burden of ACLF
• Specific definitions and their validation
• Impact of infections
• Effect of ACLF on mortality
• Effect of ACLF on transplant suitability
Burden of ACLF
Interim Consensus Definition 2014

Acute on chronic liver failure is a syndrome in patients with

- **Chronic liver disease**
- **With or without previously diagnosed cirrhosis which is**
- **Characterized by acute hepatic decompensation resulting**
  - in liver failure (jaundice and prolongation of the INR) and
  - one or more extra-hepatic organ failures
- **That is associated with increased risk for mortality within a period of 28 days and up to 3 months from onset**

WGO consensus statement Jalan et al. Gastroenterology 2014;147(1):4-10
Simplified Definition of ACLF

ACLF is a condition in patients with underlying chronic liver disease with or without cirrhosis that is associated with mortality within 3 months in the absence of treatment of the underlying liver disease, liver support, or liver transplantation.

Bajaj JS et al : Hepatology. 2018
Acute On Chronic Liver Failure: Sub Types

Chronic liver disease → Compensated cirrhosis → Decompensated cirrhosis

Type A ACLF
Type B ACLF
Type C ACLF

Precipitants:
- Viruses
- Drugs
- Alcohol
- Ischemic
- Surgery
- Sepsis
- Idiopathic

Jaundice
Ascites
Variceal bleeding
Hepatic encephalopathy

Hepatic and extrahepatic organ failures
The diagram illustrates the NACSELD-ACLF score, showing the percentage of 1-month mortality based on the number of organ failures. The mortality rates are as follows:

- 0 organ failures: 4%
- 1 organ failure: 13%
- 2 organ failures: 64%
- 3 organ failures: 72%

The graph indicates a significant increase in mortality with an increase in the number of organ failures, highlighting the importance of monitoring and managing organ failures in patients with liver disease.
NACSELD-ACLF as an independent predictor of Patient Survival in all patients.

<table>
<thead>
<tr>
<th>Effect</th>
<th>p-value</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NACSELD-ACLF</td>
<td>&lt;0.0001</td>
<td>0.176 (0.121, 0.254)</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.0001</td>
<td>0.954 (0.938, 0.969)</td>
</tr>
<tr>
<td>WBC</td>
<td>&lt;0.0001</td>
<td>0.574 (0.488, 0.676)</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.0096</td>
<td>1.357 (1.077, 1.710)</td>
</tr>
<tr>
<td>MELD</td>
<td>&lt;0.0001</td>
<td>0.918 (0.900, 0.938)</td>
</tr>
<tr>
<td>Had Infection</td>
<td>0.0156</td>
<td>0.669 (0.483, 0.927)</td>
</tr>
</tbody>
</table>

O’Leary et al NACSELD Hepatology 2018
Increasing number of hospitalizations for ACLF and cirrhosis


The Hong Kong Association for the Study of Liver Diseases
The Economic Burden of ACLF is Immense

<table>
<thead>
<tr>
<th></th>
<th>Total cost per year</th>
<th>Mean cost per hospitalization</th>
<th># Hospitalizations/year</th>
<th>LOS</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>10 bill</td>
<td>14,894</td>
<td>658,884</td>
<td>7</td>
<td>7%</td>
</tr>
<tr>
<td>ACLF</td>
<td>1.8 bill</td>
<td>51,841</td>
<td>32,335</td>
<td>16</td>
<td>50%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>$17 billion (all costs, including outpatient)</td>
<td>7,206 or $4913</td>
<td>1.1 million</td>
<td>5.2</td>
<td>4.1%</td>
</tr>
<tr>
<td>CHF</td>
<td>$32 bill? (all costs, including outpatient)</td>
<td>10,775</td>
<td>1 million</td>
<td>5</td>
<td>5.3%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>$24.3 billion</td>
<td>$19,330</td>
<td>808,000</td>
<td>8.8</td>
<td></td>
</tr>
</tbody>
</table>

ACLF: Approach to Management

- Determine Prognosis
  - Reverse precipitating event
  - Treat Infection
  - Support organ dysfunction
  - Consider liver transplantation
- Future directions
## Comparison of the Definitions for Acute-on-Chronic Liver Failure (ACLF)

<table>
<thead>
<tr>
<th></th>
<th>Asian Pacific Association for the Study of Liver (APASL)</th>
<th>European Association for the Study of Liver-Chronic Failure (EASL-CLIF)</th>
<th>North American Consortium for Study of End-stage Liver Disease (NACSELD)</th>
<th>(WGO Proposal)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Derivation</strong></td>
<td>Consensus and observational study</td>
<td>Prospective, observational study</td>
<td>Prospective study in patients with Cirrhosis</td>
<td>Consensus</td>
</tr>
<tr>
<td><strong>Patient Population</strong></td>
<td><strong>Inclusion</strong></td>
<td><strong>Compensated cirrhosis</strong></td>
<td>** Decompensated cirrhosis by implication**</td>
<td>Non-cirrhotic chronic liver disease to decompensated cirrhosis</td>
</tr>
<tr>
<td></td>
<td>Chronic liver disease</td>
<td>Compensated and decompensated cirrhosis</td>
<td>HIV infection</td>
<td>Not stated</td>
</tr>
<tr>
<td></td>
<td>Compensated cirrhosis</td>
<td></td>
<td>HIV infection</td>
<td>Not stated</td>
</tr>
<tr>
<td></td>
<td>Inclusion</td>
<td></td>
<td>Prior organ transplantation</td>
<td>Not stated</td>
</tr>
<tr>
<td></td>
<td>Exclusion</td>
<td></td>
<td>Significant comorbidity</td>
<td>Not stated</td>
</tr>
<tr>
<td></td>
<td>Infection, prior hepatic decompensation</td>
<td>HCC outside Milan criteria</td>
<td>Untreated malignancies</td>
<td>Not stated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HIV infection</td>
<td></td>
<td>Not stated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prior organ transplantation</td>
<td></td>
<td>Not stated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Significant comorbidity</td>
<td></td>
<td>Not stated</td>
</tr>
<tr>
<td><strong>Severity Score</strong></td>
<td>Liver failure defined as jaundice (serum bilirubin ≥5 mg/dL) and coagulopathy (INR of ≥1.5 or prothrombin activity of ≤40%). Ascites or encephalopathy develops within 4 weeks.</td>
<td>Hepatic and extrahepatic organ failure.</td>
<td>Extrahepatic organ failure.</td>
<td>Not Stated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not stated</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td>Diagnosis can be made early enough for intervention to alter disease course. Diagnosis is sensitive but not specific for early mortality</td>
<td>Diagnosis of ACLF may be made too late to impact disease outcome.</td>
<td>Diagnosis of ACLF may be made too late to impact disease outcome.</td>
<td>Working definition for data collection to ultimately arrive at a validated definition</td>
</tr>
<tr>
<td>Type</td>
<td>APASL</td>
<td>EASL-CLIF</td>
<td>NACSELD</td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>----------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>Total bilirubin ≥5 mg/dL and INR ≥1.5</td>
<td>Bilirubin level &gt;12 mg/dL</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>Acute Kidney Injury Network criteria</td>
<td>Creatinine level of ≥2.0 mg/dL or renal replacement therapy</td>
<td>Need for dialysis or other forms of renal replacement therapy</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>West-Haven hepatic encephalopathy grade 3-4</td>
<td>West-Haven hepatic encephalopathy grade 3-4</td>
<td>West-Haven hepatic encephalopathy grade 3-4</td>
<td></td>
</tr>
<tr>
<td>Coagulation</td>
<td>INR ≥ 1.5</td>
<td>INR ≥ 2.5</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Circulation</td>
<td>Use of vasopressor (terlipressin and/or catecholamines)</td>
<td>Presence of shock defined by mean arterial pressure &lt;60 mm Hg or a reduction of 40 mm Hg in SBP despite fluid resuscitation and cardiac output</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiration</td>
<td>PaO₂/FiO₂ of ≤200 or SpO₂/FiO₂ of ≤214 or need for mechanical ventilation [Note: Accepted ratio is ≤300 for ALI or ≤200 for ARDS]</td>
<td>Need for mechanical ventilation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Definitions of ACLF: APASL, CLIF, NACSELD

a. No universal agreement
b. Variability in underlying etiology/precipitants
c. Variable time of presentation from onset
d. Limited expert follow-up
e. Have not impacted management in any way
Acute on Chronic Liver Failure

Prognostic Models

Prognosis (art of foretelling disease course):

Criteria for selection of prognostic factors:

a. Should be sensitive, specific, widely available
b. Should allow early recognition to facilitate specific therapies

Note: ● Scores of multi-organ dysfunction
(SOFA, APACHE, NACSELD, CLIF) reflective not predictive

● Specific for mortality within 4-14 days
● Not sensitive for mortality 14-90 days
● May not allow early intervention to reverse disease course

May be used to exclude patients from studies
Prognostication of ACLF using Admission Biomarkers
Predictors of Acute-on-Chronic Liver Failure development

After removing patients who already had ACLF on admission

<table>
<thead>
<tr>
<th>PREDICTORS OF ACLF</th>
<th>p-value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission MELD</td>
<td>&lt;0.0001</td>
<td>1.14 (1.10, 1.18)</td>
</tr>
<tr>
<td>Admission SIRS criteria</td>
<td>&lt;0.0001</td>
<td>2.25 (1.31, 3.88)</td>
</tr>
<tr>
<td>Admission 6 months</td>
<td>0.0169</td>
<td>2.58 (1.19, 5.60)</td>
</tr>
<tr>
<td>prior to this one</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission Rifaximin</td>
<td>0.0680</td>
<td>1.64 (0.96, 2.76)</td>
</tr>
</tbody>
</table>

Sicker admitted cirrhotic patients with a previous hospitalization in the past 6 months are more like to develop ACLF 48 hours after admission, especially when inflammation is present, likely related to infections.
Despite similar MELD score, stool microbiota in infected patients are different from uninfected cirrhotic patients on admission in single-center studies.

Bajaj JS et al. J Hepatol 2014
Stool microbiota in infected patients are different from uninfected cirrhotic patients on admission in multi-center studies

Bajaj JS et al NACSELD Clin Gastro Hep 2018
Stool microbiota at baseline can predict organ failures, and 30-day mortality in single-center studies

- Significantly higher endotoxin
- Lower dysbiosis ratio
- Lower Lachnospiraceae & Veillonellaceae

- Lower Lachnospiraceae in ACLF and HE
- Independent prediction of mortality with relative abundance of Pasteurellaceae

Bajaj JS et al J Hepatol 2014, Chen et al J Gastroenterol Hepatol 2015
In Multi-Center Studies, Microbiota on Admission Predicted Inpatient Outcomes

Bajaj JS et al NACSELD Clin Gastro Hep 2018
ACLF: Approach to Management

- Determine Prognosis
  - Reverse precipitating event
  - Treat Infection
    - Support organ dysfunction
    - Consider liver transplantation
    - Future directions
Role of infections in ACLF
Spectrum and causative organisms are evolving

Bajaj JS et al (NACSELD) Hepatology 2014
Clues that can indicate infections in cirrhosis

• Usual signs of infection may be absent due to impaired immune response

• Other signs and symptoms could be relevant
  – Altered mental status or hepatic encephalopathy
  – Acute kidney injury
  – Asymptomatic patients with ascites can have “silent” SBP
  – Increase in WBC count may not be dramatic since cirrhotic patients have a lower baseline
Judicious use of albumin prevents mortality and AKI in SBP but not in other infections

Inappropriate antibiotics increase mortality almost 10-fold

- Risk factor: Multidrug resistance organism

Arabi YM et al. Hepatology, 2012
Drug resistant organisms and fungi are associated with mortality in cirrhosis

De-escalating Antibiotics: Spanish Stewardship Program

Re-evaluation of antibiotic treatment at 48-72 h

Positive cultures
- Adjust antibiotic treatment to the susceptibility pattern of the isolated strains (monotherapy if possible)

Negative or no cultures

Good clinical outcome
- Switch carbapenem and anti-pseudomonal antibiotics to third-generation cephalosporins if no isolation of ESBL-producing enterobacteria or *Pseudomonas aeruginosa*
- Stop daptomycin, linezolid or glycopeptide if no isolation of MRSA, VSE, VRE or MRCNS,
- Consider switching echinocandins to fluconazole or withdraw them if *Candida spp.* are not isolated

Bad course
- Perform new cultures, consider changing catheters and performing imaging studies
- New antibiotic schedules if clinical deterioration

Maintain treatment for 5 days if no source of infection and for 7 days in the rest of infections*
Second infections independently decrease survival in patients with I-ACLF

<table>
<thead>
<tr>
<th>Effect</th>
<th>p-value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-ACLF</td>
<td>&lt; 0.0001</td>
<td>0.16 (0.08, 0.30)</td>
</tr>
<tr>
<td>Second Infection</td>
<td>0.0045</td>
<td>0.41 (0.22, 0.76)</td>
</tr>
<tr>
<td>Admission MELD</td>
<td>0.0078</td>
<td>0.94 (0.90, 0.98)</td>
</tr>
<tr>
<td>Admission WBC</td>
<td>0.0160</td>
<td>0.62 (0.42, 0.91)</td>
</tr>
<tr>
<td>Admission Albumin</td>
<td>0.0054</td>
<td>1.85 (1.20, 2.85)</td>
</tr>
</tbody>
</table>

Bajaj JS NACSELD Hepatology 2012
Second infections are potentially preventable

• Type:
  – Respiratory (28%): 42% associated with aspiration, 28% with ventilation
  – Urinary (26%): 50% associated with urinary catheterization
  – *C. difficile* (12%): all were on antibiotics

• Organisms:
  – Gram Positive (39%): VRE > MRSA > VSE > Others
  – Gram negative (20%): *E. coli* > *Klebsiella* > Others
  – Fungal (14%): all Candida
  – No organisms were isolated in the remaining 28%
Infections after discharge (subsequent infections) are often unrelated to the original infection.

**Determinants**
- Age
- PPI Use
- SBP
- Prophylaxis

After discharge for an index infection

Within 6 months

45% Subsequent infection

55% No infection

26% Infection in the same location

74% Infection in a different location

O’Leary NACSELD et al. Clinical Gastro Hep 2015
Evolving Role of Primary and Secondary SBP Prophylaxis

Bajaj et al
Am J Gastro
2018
ACLF: Approach to Management

• Determine Prognosis
• Reverse precipitating event
• Treat Infection
  • Support organ dysfunction
  • Consider liver transplantation
• Future directions
Hepatic Regeneration with G-CSF

Change in MELD and CTP Scores

Kedarisetty CK et al Gastro 2015;148:1362-70
Artificial Liver Support: Current Status 2018

- HELIOS study (Prometheus): 145 patients “ACLF”. Survival benefit only if MELD >30 or HRS. No overall survival benefit
- RELIEF study (MARS) 189 patients with ACLF. No survival benefit
- MARS survival benefit at 14 days selected sub-group

Mortality Profile at 90-days in ACLF is higher than on the Waiting List.
Risk for Delisting Following Infection-associated ACLF

Cirrhosis With Infection
n = 413

Not Listed for Liver Transplantation
n = 277

Listed for Liver Transplantation
n = 136

Delisted/Dead Within 6 Months of Infection
n = 57

Transplanted Within 6 Months of Infection
n = 47

Alive at 6 Months After Infection
n = 32

42%

Reddy KR et al., Liver Transpl 2015
### ACLF

**Medical management in ICU for organ support**

<table>
<thead>
<tr>
<th>Day 3-7</th>
<th>No ACLF</th>
<th>ACLF-1</th>
<th>ACLF-2</th>
<th>ACLF-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality rate according to our data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 28</td>
<td>10%</td>
<td>21%</td>
<td>57%</td>
<td>87%</td>
</tr>
<tr>
<td>Day 90</td>
<td>24%</td>
<td>42%</td>
<td>74%</td>
<td>95%</td>
</tr>
<tr>
<td>Day 180</td>
<td>38%</td>
<td>50%</td>
<td>79%</td>
<td>96%</td>
</tr>
</tbody>
</table>

- **Assessment for regular LT**
  - No
  - Yes: Continue treatment

- **Assessment for early 28-day LT**
  - No
  - Yes: Continue treatment, Futility

**Contraindication for LT?**

- Regular LT:
  - No: Continue treatment
  - Yes: Continue treatment, Futility

- Early 28-day LT:
  - No: Continue treatment
  - Yes: Continue treatment, Futility

**Survival rate according to our data**

- Day 180:
  - Regular LT: 85%
  - Early 28-day LT: 58%
  - Continue treatment: 80%
  - Futility: 0%

*Gustot et al. Hepatology 2015*
Acute-on-Chronic Liver Failure:

4 OF can affect Tx Listing/Transplantation

Wong et al NACSELD AASLD 2016
Liver Transplantation for ACLF

• ACLF patients have higher mortality than Status 1 patients after 1-2 weeks.
• Patients with ACLF should receive high priority for transplant
• “Futility Scores” to exclude patients from transplantation should be validated in this group
ACLF: Approach to Management

• Determine Prognosis
• Reverse precipitating event
• Treat Infection
• Support organ dysfunction
• Consider liver transplantation
• Future directions
# Future Directions

<table>
<thead>
<tr>
<th>Areas of Need in ACLF</th>
<th>Specific Steps Needed to Address the Gaps</th>
</tr>
</thead>
</table>
| Burden of ACLF       | 1. Consortia that include centers that are not transplant centers  
                        2. Education about ACLF beyond academic centers |
| Definition           | 1. Focus on narrowing the differences  
                        2. Simplifying definitions to increase generalizability  
                        3. Focus on separate diagnostic and prognostic markers  
                        4. Could conventional prognostic scoring systems in ACLF patients perform better if markers of systemic inflammation and circulatory dysfunction are included? |
| Pathogenesis         | 1. Research to identify PAMPs and DAMPs as diagnostic biomarkers of the mechanism of ACLF  
                        2. Excessive responses to DAMP(s) might also be under control of genetic factors, and appropriate genome-wide association studies are required  
                        3. No comprehensive description of the landscape of circulating immune-suppressed cells is available in patients with ACLF  
                        4. Cytokine/chemokine signatures for identification and grading of systemic inflammation are required  
                        5. Changes in microbiota in differing stages of ACLF |
| Organ failure management | 1. Biomarkers should be developed to identify early tissue dysfunction before failure sets in  
                                2. Should the type of precipitating event (extrahepatic versus intrahepatic) be included in these prognostic scores?  
                                3. Prevention of organ failures is critical  
                                4. Changes in bacteriology and increasing importance of infections as modulators of ACLF are needed  
                                5. Organ-specific therapies are required  
                                6. Bridging therapies with liver-assist devices and elucidating the role of LT  
                                7. What is the most appropriate time to decide prognosis in ACLF patients (given the dynamic course of ACLF)? |
| Nonmedical approaches for ACLF | 1. Greater multidisciplinary coordination between palliative care, transplant, and inpatient hepatology services  
                                2. Improved education of trainees, professionals involved in ICU, Infectious disease, LT care as well as palliative care professionals |

Bajaj Wong STC et al Hepatology 2017
Pro-Active not Reactive Definitions
Summary and Take-Home Messages

• ACLF represents an increasingly large healthcare and economic burden with a high mortality
• Infections are one of the major reasons for ACLF, and their bacteriology of infections is changing radically.
• Fungal infections and second infections can profoundly impact survival as well as readmissions with infections
• A simple score, NACSELD-ACLF can predict 30-day mortality in patients with and without infections
• A select group of patients with ACLF perform well after liver transplant but criteria need to be standardized
Acknowledgements: NACSELD PIs and coordinators
Acknowledgements: NACSELD PIs and coordinators, Grifols, NIH

- VCU: JS Bajaj, Melanie White, Nicole Noble, Ariel Unser
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- U Toronto: Florence Wong, M Khokar
- Mayo Rochester: Patrick Kamath, Siddharth Singh
- U Texas Houston: Michael Fallon, Sachin Batra
- Yale: Guadalupe Garcia-Tsao
- U California San Francisco: Jennifer Lai
- U Rochester: Benedict Maliakkal, K Doyle
- Mercy Medical Center, Baltimore: Paul Thuluvath, A Poonia
- Emory University: Ram Subramanian
- MUSC: David Koch
- U California San Diego: Heather Patton
- Beth Israel Deaconess: Raza Malik
- U Alberta, Edmonton: Puneeta Tandon
HCA infections in Cirrhosis require Broad spectrum antibiotics

<table>
<thead>
<tr>
<th>Sites</th>
<th>Standard Treatment</th>
<th>Broad Spectrum Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous bacterial peritonitis, Cholangitis</td>
<td>Cefotaxime (2 g/8 h IV)</td>
<td>Imipenem/cilastatin (500 mg/6 h IV) + vancomycin (1 g/12 h IV)</td>
</tr>
<tr>
<td>Spontaneous bacteremia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UTI</td>
<td>Amoxicillin/clavulanic acid (2.2 g/8 h IV) or ciprofloxacin (500 mg/12 h PO) (if no quinolone prophylaxis)</td>
<td>Imipenem/cilastatin (500 mg/6 h IV)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Amoxicillin/clavulanic acid (2.2 g/8 h IV) + azithromycin (500 mg/24 h PO)</td>
<td>Imipenem/cilastatin (500 mg IV/6 h) + vancomycin (1 g/12 h IV) + azithromycin (500 mg/24 h PO)</td>
</tr>
<tr>
<td>Soft tissue infections</td>
<td>Amoxicillin/clavulanic acid (2.2 g/8 h IV)</td>
<td>Imipenem/cilastatin (500 mg/6 h IV) or tigecycline (50 mg/12 h IV after a load dose of 100 mg)</td>
</tr>
</tbody>
</table>

In patients randomized to broad spectrum antibiotics:
• Lower treatment failure, 18% vs 51%, p=0.001
• Lower LOS, 12 vs 18 days, p=0.03
• MDR prevalence and second infections were similar between groups

Empiric Antibiotics: Spanish Stewardship Program

Severe sepsis or shock? or APACHE II ≥ 15 or SOFA score ≥ 8?

NO

Risk factors for MDR bacteria?

NO

High-risk source of infection or high CRP?

NO

Ceftriaxone

YES

YES

Meropenem + glycopeptide + ciprofloxacin, amikacin and/or colistin + echinocandin

ETAPENEM + glycopeptide
Nosocomial infections in cirrhosis.
Prevalence of multi-resistant bacteria

<table>
<thead>
<tr>
<th></th>
<th>Italy</th>
<th>Korea</th>
<th>France</th>
<th>Spain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community-acquired</td>
<td>16%</td>
<td>10%*</td>
<td>13%*</td>
<td>9%</td>
</tr>
<tr>
<td>infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nosocomial infections</td>
<td>33%</td>
<td>41%*</td>
<td>33%*</td>
<td>35%</td>
</tr>
</tbody>
</table>

* Gram-negative bacteria resistant to cefotaxime

Predictors of antibiotic resistance

- Systemic antibiotic exposure within 30 days
- High MELD score
- Nosocomial infections
- Low serum albumin

Nosocomial SBP needs broad-spectrum antibiotics

The combination of meropenem plus daptomycin was significantly more effective than ceftazidime in the treatment of nosocomial SBP (86.7 vs. 25%; $P < 0.001$).

Catheter-associated UTI: Appropriate indications

All Other Indications For Catheter Placement Should Be Carefully Considered!

CDC recommendations 2009 Gould et al
C. difficile worsens outcomes in cirrhosis

![Graph showing mortality and length of stay (LOS) for cirrhosis (Cirr) only, C. difficile (C diff) only, and cirrhosis plus C. difficile (Cirr+Cd) with p-values of <0.0001 for both mortality and LOS.]

Bajaj JS et al Am J Gastroenterol 2010
Modifiable Risk Factors for C. Difficile

- Antimicrobial exposure
- Acquisition of *C. difficile*
- Advanced age
- Underlying illness
- Immunosuppression
- Tube feeds
- ? Gastric acid suppression

CDC, ACG Guidelines for C. Difficile 2013
Central Line Bundle to prevent blood stream infections

- Hand Hygiene
- Maximal barrier precautions
- Chlorhexidine skin antisepsis
- Optimal catheter site selection
- Daily review of line necessity

Mermel et al 2000 Ann Int Med, Furuva et al PLOS one 2011
FDA-Approved Indications for PPIs

- Healing of erosive esophagitis (EE);
- Maintenance of healed EE;
- Treatment of gastroesophageal reflux disease (GERD);
- Risk reduction for gastric ulcer (GU) associated with nonsteroidal anti-inflammatory drugs (NSAIDs);
- Helicobacter pylori (H. pylori) eradication to reduce the risk of duodenal ulcer (DU) recurrence, in combination with antibiotics;
- Pathological hypersecretory conditions, including Zollinger-Ellison (ZE) syndrome; and
- Short-term treatment and maintenance of DUs.

What is not FDA-approved

- Healing of banding ulcers
- Abdominal pain of unknown origin
- Hospitalized for any reason
- Variceal bleeding treatment
- Just because someone walks into your office and has a pulse
## Association of PPIs with infections exists in most reports

<table>
<thead>
<tr>
<th>Association</th>
<th>Study type</th>
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</tr>
</thead>
</table>
| YES         | Bajaj, et al  
Choi, et al  
Northup, et al  
Bulcewicz, et al  
Goel, et al  
Waidmann et al  
Bajaj et al  
O’leary et al (NACSELD)  
Merli et al  
Sargenti et al | Case-control (SBP/C.diff)  
Case-control  
Retro cohort  
Case-control  
Retro cohort  
Case-control  
Retro cohort  
Propensity-matched cohort  
Prosp cohort  
Prosp cohort | NO          | Campbell et al  
Mandorfer et al  
Terg et al | Case control  
Retro Cohort  
Prosp Cohort |

The Hong Kong Association for the Study of Liver Diseases
## Beta-blockers and infections in cirrhosis: jury is still out

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Sample size</th>
<th>BB Risk association</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bajaj et al</td>
<td>Propensity matched database study</td>
<td>1836 1:1 early and 1462 1:1 advanced pts</td>
<td>HR for infections crossed 1</td>
<td>No association</td>
</tr>
<tr>
<td>Merli et al</td>
<td>Case-control</td>
<td>400 hospitalized cirrhotics</td>
<td>Hazard Ratio 0.46</td>
<td>Protective</td>
</tr>
<tr>
<td>Manderfer et al</td>
<td>Retrospective analysis</td>
<td>607 patients requiring paracentesis</td>
<td>In SBP BB reduced survival and HRS</td>
<td>Harmful</td>
</tr>
</tbody>
</table>
**Statin and infections/decompensation in cirrhosis: optimism**

<table>
<thead>
<tr>
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<th>Sample size</th>
<th>Statin Risk association</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motzkus-Feagans et al</td>
<td>Propensity matched database study</td>
<td>1006 vs 3520 pts</td>
<td>Hazard ratio 0.67 for infections</td>
<td>Protective</td>
</tr>
<tr>
<td>Kumar et al</td>
<td>Retrospective analysis</td>
<td>81 vs 162 controls</td>
<td>Hazard Ratio 0.58 for decompensation</td>
<td>Protective</td>
</tr>
<tr>
<td>Mohanty et al</td>
<td>Propensity matched database study</td>
<td>685 vs 2062 controls</td>
<td>Hazard Ratio 0.55 for decompensation</td>
<td>Protective</td>
</tr>
</tbody>
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