News You Can Use: Hot Topics in Internal Medicine

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Disclosure

I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

Objectives

- Identify and evaluate recent primary literature pertinent to the practice of Internal Medicine
- Compare and contrast latest literature recommendations with present standards of care
- Incorporate current evidence-based recommendations into clinical practice

News You Can Use

Liver – Alcoholic Hepatitis

- Controversial management
  - 30-50% mortality
- Maddrey’s discriminant function (MDF)
  - 4.6 x (PT-control PT) + bilirubin
- Score ≥ 32 believed to merit drug therapy

Liver – Alcoholic Hepatitis

- Prednisolone
  - 40 mg Qday*
  - Maddrey (1978): Reduced mortality
  - Meta-analysis did not favor use
  - Reduced early mortality if MDF ≥ 32
- Pentoxifylline
  - 400 mg TID*
  - Akriviadis (2000): Reduced mortality
  - Reduced hepatorenal syndrome as cause of death (50% vs. 92%)
- Combination
  - COPE (2012): No survival benefit
  - Mathurin (2013): No survival benefit

*Given for 28 days
Liver – Alcoholic Hepatitis

Prednisolone or Pentoxifylline for Alcoholic Hepatitis - STOPAH

1103 patients

Placebo (n=276) 35/268 (13%)
Prednisolone (n=277) 38/265 (14%)
Pentoxifylline (n=276) 30/238 (19%)
Combination (n=274) 35/260 (13%

Endpoints Pentoxifylline No Pentoxifylline p-value
28-day mortality 85/518 (16%) 83/535 (16%) NS
90-day mortality or transplant 139/478 (29%) 146/490 (30%) NS
1-year mortality or transplant 205/365 (56%) 216/382 (57%) NS


Liver – Alcoholic Hepatitis

Considerations:
- Statistical evaluation
- Incidence of infection and mortality
- Exclusion criteria

Potential short-term benefit
No mortality benefit

Prednisolone
Pentoxifylline

Liver – Beta-blocker therapy

1. Reduced blood flow through liver
2. Portal vein hypertension
3. Mesenteric splanchnic vasodilation

Compensatory Responses:
- Increase sympathetic response
- Increase renin-angiotensin-aldosterone system
- May form collaterals

Liver – Beta-blocker therapy

Role of non-selective beta blocker (NSBB) in cirrhosis

Hemodynamic
- Reduce sympathetic response
- Decreases cardiac output
- Splanchnic vasoconstriction
- Prevent esophageal varices

Non-hemodynamic
- Reduce bacterial translocation


Secondary prevention of esophageal varices
- Lebrec (1981): 90% in propranolol arm vs. 50% on placebo free of GIB at 1 year
- Targeted a 25% reduction in heart rate

Primary prevention of esophageal varices
- Pascal (1987): 74% in propranolol arm free of GIB at 1 year vs. 39% in placebo
- Targeted a 20-25% reduction in heart rate

Evolving role of beta-blockers
- Varying literature of beneficial or detrimental effect in the following:
  - Hepatorenal syndrome (HRS)
  - Spontaneous bacterial peritonitis (SBP)
  - Window hypothesis

Liver – Beta-blocker therapy

**Non Selective Beta-Blocker in Spontaneous Bacterial Peritonitis**

**Inclusion**
- 607 patients with cirrhosis, undergoing first paracentesis
  - 362 no NSBB, 245 NSBB

**Primary outcome**
- Impact of NSBB on transplant-free survival
  - Development of HRS

**Secondary outcomes**
- Rates of HRS, Rates of AKI, Hemodynamic parameters

**Hypothesis**
- Development of SBP closes the window of opportunity for NSBB treatment

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Liver – Beta-blocker therapy

**Transplant Free Survival**
- 1 mortality after SBP diagnosis in NSBB group
  - HR 1.644 (p=0.007)

**Acute Kidney Injury**
- Incidence of AKI in NSBB group
  - (17/86, 20% vs. 7/90, 8%; p=0.021)

**Hepatorenal Syndrome**
- Incidence of HRS in NSBB group
  - (20/83, 24% vs. 9/82, 11%; p=0.027)

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Liver – Beta-blocker therapy

**Conclusions**
- NSBB provides benefit up to development of SBP
- Worsened transplant-free survival in pts with SBP
- SBP may close the therapeutic window of benefit

**Considerations**
- Limitations of study
- Management after SBP resolves

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News You Can Use

**Liver**
- Renal
- Infectious Disease
- Cardiology
- Anticoagulation

**Renal**
- Progression to ESRD
  - Bone/Mineral disorders
  - Anemia
  - Acidosis
  - Phosphate binders
  - Vitamin D products
  - Calcimetic
  - Erythropoietin stimulating agents (ESA)
  - Iron supplementation
  - Bicarbonate supplementation
  - Resolves with dialysis

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News You Can Use

**Liver**
- Renal
- Infectious Disease
- Cardiology
- Anticoagulation
Renal - Ferric Citrate

- Well tolerated, minimal side effects
- Comparable to standard phosphorus binders
- Increased iron stores, reduced IV iron and ESA dosing

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ferric citrate</th>
<th>Active control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin (ng/mL)</td>
<td>858 (568-1105)</td>
<td>576 (333-883)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>36.0 (27.5-47.0)</td>
<td>28.0 (21.0-34.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IV Iron (mg/wk)</td>
<td>12.9 (1.0-28.9)</td>
<td>26.8 (13.4-47.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESA dose (units/wk)</td>
<td>5303 (2023-9695)</td>
<td>6934 (2665-12,375)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Renal - Ferric Citrate

- FDA approved Fall 2014
- Cost comparison
- Considerations of iron supplementation

Renal - Vitamin D

- Benefits of Vitamin D
  - Maintain skeletal health
  - Pleiotropic effects
  - Immunomodulating, antitumor, renal protective, CV

<table>
<thead>
<tr>
<th>25-hydroxyvitamin D levels (ng/mL)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>Deficiency</td>
</tr>
<tr>
<td>20-29</td>
<td>Insufficiency</td>
</tr>
<tr>
<td>≥30</td>
<td>Sufficiency</td>
</tr>
</tbody>
</table>
Renal – Vitamin D

**Vitamin D3 vs. doxercalciferol**
- First randomized controlled trial in 2010, CKD stages 3-4
- Vitamin D3 had greater impact on PTH levels in CKD stage 3

**25-OH supplementation in dialysis**
- Inconsistent effects of 25(OH)D supplementation
- 25(OH)D levels ≥30 associated with maximal PTH suppression

**Recommendations**
- No consensus from guidelines, clinical judgement
- DIVINE and VITAL studies ongoing

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**Dialysis Infection and Vitamin D in New England**
- 105 dialysis patients with 25(OH)D ≤ 32 ng/mL
- 25(OH)D levels >32 ng/mL in 90.9%, 64.5%, 35.3%
- Similar rate of hospitalization, infection, CV events

All-cause mortality lower in ergocalciferol arms (p=0.02)

News You Can Use

**Liver**
- 524 patients with cellulitis or abscess
- Clindamycin 300 mg TID (n=254)
- TMP/SMX 1 DS BID (n=260)

Outcomes: Cure rates at 1-month follow-up, adverse events

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**Infectious Disease (ID)**
- 850,000 hospital admissions
- 14.2 million outpatient visits
- Most common pathogens:
  - Staphylococcus aureus
  - Streptococcus pyogenes
- 2014 IDSA updated guidelines

**ID – Skin/Soft tissue**
- Conclusions
  - Similar cure rates
  - Similar adverse events
- Considerations
  - Dosing strategies
  - Limitations to study
  - Exclusion criteria
  - Choosing an agent
Antibiotic associated diarrhea (AAD) common occurrence
- 15-39% caused by *Clostridium difficile* (CD)
- Mechanism not fully elucidated
  - High-risk antibiotics
  - Cumulative antibiotic exposure
  - Prolonged hospital stay, previous hospitalization
  - Age ≥ 65 years
  - Proton pump inhibitor, nasogastric tube

ID – Probiotics

Inpatient adults ≥ 65 years randomized
Lactobacillus/bifidobacterium vs. placebo
Incidence of AAD within 8 wks, CD within 12 wks

<table>
<thead>
<tr>
<th>Probiotic (n=1493)</th>
<th>Placebo (n=1488)</th>
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</thead>
<tbody>
<tr>
<td>Incidence of AAD</td>
<td>159 (10.8%)</td>
</tr>
<tr>
<td>Incidence of CD</td>
<td>12 (0.8%)</td>
</tr>
</tbody>
</table>

No difference in side effects
Insufficient evidence to support use of probiotic

PLACIDE (2013)

Considerations of PLACIDE in clinical practice
- Complexity of lactobacillus preparations
  - 170 species, 17 subspecies
- Safety of probiotics
  - Serious infections rare in literature, associated with severe comorbidities (malignancy, GI conditions)

Update in Clinical Infectious Diseases journal

Liver
Renal
Infectious Disease
Cardiology
Anticoagulation

Liver

Cardiovascular (CV)

Dual antiplatelet therapy (DAPT) recommendations

2004
- Bare metal: Continue for 1 month, ideally 1 year
- Drug eluting: Continue for 3-6 months depending on type, up to 1 year if low risk of bleed

2007
- Bare metal: Continue for 1 month, ideally 1 year
- Drug eluting: Continue for at least 12 months

2009
- Bare metal: Continue for at least 12 months
- Drug eluting: Continue for at least 12 months


CV – DAPT

Benefit of dual antiplatelet therapy beyond 1 year
Randomization after drug eluting stent placed

Aspirin
Aspirin + thienopyridine
Aspirin + placebo vs. Aspirin + thienopyridine
Aspirin alone

Primary outcomes:
- Stent thrombosis
- Major cardiovascular or cerebrovascular events

Increased bleeding in 30-month group
- 1.6% vs. 2.5%, p=0.001

Higher all cause mortality in 30-month group
- 1.5% vs. 2.0%, p=0.05

Results 12-month (n=4941) 30-month (n=5020) p-value
Stent thrombosis 65 (1.4%) 19 (0.4%) p<0.001
Major events 285 (5.9%) 211 (4.3%) p<0.001

Increased events in 3-month observational group

Conclusions/Considerations
- Study population selected
- Duration of DAPT still in question
- Choice of thienopyridine

CV - PEGASUS

Primary outcome: composite of cardiovascular death, myocardial infarction (MI), stroke

Ticagrelor 90 mg BID
Ticagrelor 60 mg BID
Placebo

All patients received low-dose aspirin


CV - PEGASUS

Median time since MI – 1.7 years
- Age >50 years, at least 1 major risk factor
- Median follow-up duration – 33 months

Ticagrelor 90 mg (n=7050) Ticagrelor 60 mg (n=7045) Placebo (n=7067)
Composite endpoint 493 (7.85%) 487 (7.77%) 578 (9.04%)
Major bleeding 127 (2.60%) 115 (2.30%) 54 (1.06%)
Fatal bleeding 32 (0.63%) 33 (0.71%) 30 (0.60%)


Cardiovascular

Aspirin
Thienopyridine
Anticoagulant

WOEST
- Aspirin/ clopidogrel/ warfarin vs. clopidogrel/ warfarin
- Less bleeding, no increased stent thrombosis

PIONEER-AF PCI
- DAPT vs. triple therapy with rivaroxaban
- In progress - evaluating incidence of bleeding and CV events

Anticoagulation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran (Pradaxa)</td>
<td>150 mg PO BID</td>
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<tr>
<td></td>
<td>CVT/PE: Heparin x 5-10 days, 150 mg PO BID</td>
</tr>
<tr>
<td></td>
<td>CrCl &lt;30: Do not use</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td>20 mg PO Qday</td>
</tr>
<tr>
<td></td>
<td>1.5 mg PO BID x 3 wk, 20 mg PO Qday</td>
</tr>
<tr>
<td></td>
<td>CCl &lt;30: Do not use</td>
</tr>
<tr>
<td>Apixaban (Eliquis)</td>
<td>5 mg PO BID</td>
</tr>
<tr>
<td></td>
<td>10 mg PO BID x 1 wk, 5 mg PO BID</td>
</tr>
<tr>
<td></td>
<td>CCl &lt;30: Do not use</td>
</tr>
</tbody>
</table>

*Indicates if two of these criteria are met

Anticoagulation - Apixaban

Apixaban dosing in hemodialysis (HD)

- 8 patients with ESRD, 8 healthy individuals
- Levels obtained up to 72 hours after each dose

- 5 mg dose HD 7-day washout HD 5 mg dose
- 9% Drug recovery
  - ESRD: 7% of dose
  - Healthy: 18% of dose
- FDA approved dosing regimen for hemodialysis for AF

Anticoagulation

- New developments/Future uses
- Design of the rivaroxaban for heparin-induced thrombocytopenia study
  - Gulick RM, et al. Dept of Health and Human Services 2015; 216

Headlines

- Liver
  - In AH, no mortality benefit with pentoxifylline, possible short-term mortality benefit with prednisolone
  - Beta-blocker in SBP could lead to increased development of HRS and increased mortality
- Renal
  - Newly approved ferric citrate is comparable phosphate binder while reducing iron and ESA requirements
  - Inactive vitamin D should be utilized in ESRD patients for its nutritional efficacy benefit and mortality benefit

Infectious Disease

- No difference between TMP/SMX or clindamycin for skin and soft tissue infections (SSTI)
- Questionable benefit of probiotics in preventing Clostridium difficile infections

Cardiovascular

- Continuing DAPT beyond 12 months associated with reduced CV events, increased bleeding
- Literature surrounding triple therapy in the pipeline

Anticoagulation

- Apixaban has FDA approved dosing for atrial fibrillation in ESRD patients based on small study population
- Potential role of new anticoagulants in HIT
- Rivaroxaban and apixaban are contraindicated with protease inhibitors per HIV guidelines

News You Can Use
References