Disclosures

- None
Objectives

► Highlight impact of antimicrobial resistance and implications on healthcare today

► Discuss new antimicrobials, when to use them and what challenges remain

► What’s in the pipeline
The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism.
Background

► 1928 Discovery of Penicillin revolutionized modern medicine
► 1930s-1960s golden era of antibiotics
► Overuse of antibiotics in the healthcare and agricultural industry
► Rapid emergence of resistant pathogens
  ► Antimicrobial resistance poses a serious global threat
► 2 million infections and 23,000 deaths per year due to antibiotic resistant bacteria in the US
  ► $55 billion dollar cost

New Wave of Resistant Infections

Figure 1

Deaths caused by select bacteria in the United States.

Fair RJ, Tor Y. Antibiotics and Bacterial Resistance in the 21st Century. Perspectives in Medicinal Chemistry. 214:6
Antibiotic threats in the United States

**Urgent Threats**
- Clostridium difficile
- Carbapenem resistant Enterobacteriaceae (CRE)
- Drug resistant Neisseria gonorrhoea

**Concerning Threats**
- Multidrug resistant Acinetobacter
- Multi-drug resistant Pseudomonas
- Extended spectrum beta lactamase producing Enterobacteriaceae
- Drug resistant Tuberculosis
- Drug resistant Streptococcus pneumoniae
- MRSA
- Drug resistant Salmonella
- Drug resistant Shigella

**Serious Threats**
- Vancomycin resistance Staphylococcus aureus (VRSA)
- Erythromycin resistant Group A Streptococcus
- Clindamycin resistant Group B Streptococcus
WHO list of bacteria for which new antibiotics are urgently needed

**Priority 1: CRITICAL**
- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing

**Priority 2: HIGH**
- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter* spp., fluoroquinolone-resistant
- *Salmonellae*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant

**Priority 3: MEDIUM**
- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella* spp., fluoroquinolone-resistant
GLOBAL

A failure to address the problem of antibiotic resistance could result in:

10m deaths by 2050

Costing £66 trillion
Global Response Action Plan

- WHO priority list of antibiotic resistant bacteria
- Increasing global awareness to the health crisis
- Global commitment to create an antibiotic R&D enterprise powerful enough to produce 10 new systemic antibiotics by the year 2020.
- Prioritize funding
<table>
<thead>
<tr>
<th>Gram Positive agents</th>
<th>Gram negative agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linezolid</td>
<td>Ceftolazane/Tazobactam</td>
</tr>
<tr>
<td>Tidezolid</td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td></td>
</tr>
<tr>
<td>Ceftaroline</td>
<td></td>
</tr>
<tr>
<td>Dalbavancin</td>
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</tr>
<tr>
<td>Oritavancin</td>
<td></td>
</tr>
</tbody>
</table>
## New Antibiotics 2015-2019

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime-Avibactam</td>
<td>cUTI, cIAI</td>
<td>Feb 2015</td>
</tr>
<tr>
<td>Delafloxacin</td>
<td>ABSSSI</td>
<td>June 2017</td>
</tr>
<tr>
<td>Meropenem-Vaborbactam</td>
<td>cUTI</td>
<td>August 2017</td>
</tr>
<tr>
<td>Plazomycin</td>
<td>cUTI</td>
<td>June 2018</td>
</tr>
<tr>
<td>Eravacycline</td>
<td>cIAI</td>
<td>August 2018</td>
</tr>
<tr>
<td>Omadacycline</td>
<td>CABP, ABSSSI</td>
<td>October 2018</td>
</tr>
<tr>
<td>Imipenem-Cilastatin-Relebactam</td>
<td>cIAI, UTI</td>
<td>July 2019</td>
</tr>
<tr>
<td>Lefamulin</td>
<td>CABP</td>
<td>August 2019</td>
</tr>
</tbody>
</table>
Delafloxacin
(Bexdela-Melinta Therapeutics- June 2017)

► Novel Quinolone , concentration dependent killing.
► FDA approval
  ► ABSSSTI in adult patients.
► Targets DNA gyrase and topoisomerase
► Spectrum
  ► Gram positive pathogens (MRSA/MSSA), *S.pneumoniae* other gram positives except *Enterococci*
  ► gram negative rods
    ► Activity against *P.aeruginosa* is weaker than Ciprofloxacin
► Greater in vitro potency than Levaquin against most gram positive organisms including 32 fold greater activity against MRSA. Only Quinolone with MRSA indication
► 300 mg IV Q12 H or 450 mg PO BID (bioequivalent)
► Dose adjustment in renal insufficiency, not recommended in ESRD / dialysis patients
► Side effects –GI , headaches, no QT prolongation in initial studies

Analysis of Pooled Phase III Efficacy Data for Delafloxacin in Acute Bacterial Skin and Skin Structure Infections

2 multicenter, randomized, double blind, double dummy non-inferiority trials N=1510 adults with ABSSSI, pooled for analysis (PROCEED TRIAL)

- Delafloxacin 300 mg IV Q 12H vs Vancomycin/Aztreonam (Trial 1)
- Delafloxacin 300 mg IV Q12H X 6 doses, then switch to 450 mg BID vs Vancomycin/Aztreonam (Trial 2)

- End point >20% improved erythema at 48-72 hours
- ITT 81.3% Delafloxacin vs 80.7% Comparator (95% CI -3.2% to 4.7)
- IV/oral Delafloxacin fixed-dose monotherapy was non-inferior to IV vancomycin/Aztreonam combination
- Well tolerated in each Phase III study, as well as in the pooled analysis
Delafloxacin Summary

- Broad spectrum gram positive/gram negative, including MRSA & pseudomonas, also has atypical and anaerobic coverage
  - Does not cover Enterococci
  - Pseudomonal coverage weaker than Ciprofloxacin
- Available in oral formulation, bioavailable
- Quinolone class with increased risk of side effects
  - Tendinitis, tendon rupture, CNS side effects, neuropathy
- QT prolongation not seen in studies, may serve as an alternative agent in select situations
- Further data are needed for other indications
- Approved for ABSSSI for which several treatment options already exist
  - Could be used in special situations – allergy, oral option
Question

► Initial studies have not shown cases of QT prolongation, seizures or tendon rupture with Delafloxacin

a. True
b. False
Omadacycline
(Nuzyra-Paratek Pharmaceuticals- October 2018)

- Aminomethycycline antibiotic (Tetracycline) ; IV/PO formulation
- Spectrum of activity
  - Gram positive agents including MRSA
  - PCN resistant and MDR S.pneumoniae
  - Vancomycin resistant Enterococcus spp
  - Gram negative bacteria NOT Pseudomonas
  - Atypicals
- Mechanism of action
  - Binds to 30S ribosomal subunit and inhibits protein synthesis
- Active against certain antibiotic resistance mechanisms
  - Tetracycline efflux
  - Ribosomal protection
- FDA indication
  - Community-acquired bacterial pneumonia (CABP)
  - Acute bacterial skin and skin structure infections (ABSSSI).

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Treatment Group</th>
<th>Primary End Point</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>OASIS I (Phase 3)</td>
<td>Omadacycline 100mg IV Q12H X 2 doses then 100 mg IV Q24H Vs Linezolid 600 mg IV Q12H</td>
<td>Survival with reduction in skin lesion &gt;20% at 48-72H 84.8% vs 85.5% 95% CI -6.3-4.9</td>
<td>Any adverse events 48.3% vs 45.7% Nausea 12.4% vs 9.9%</td>
</tr>
<tr>
<td>ABSSSI</td>
<td>N=645</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OASIS II (Phase 3)</td>
<td>Omadacycline 450mg PO daily X2 doses, then 300 mg PO daily Vs Linezolid 600 mg PO Q12H</td>
<td>Reduction in skin lesion &gt;20% at 48-72H 88% vs 83% 95% CI -0.2-10.3</td>
<td>Nausea 30% vs 8%</td>
</tr>
<tr>
<td>ABSSSI</td>
<td>N=735</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Omadacycline for CABP

► Phase 3 multicenter, RCT
► N=774 with CABP
► Treatment Group
  ► Omadacycline 100 mg Q12H X 2 doses then 100 mg IV daily vs Moxifloxacin 400 mg IV daily
  ► Oral transition allowed after 3 days (300mg daily or 400 mg daily). Total duration 7-14 days
► Primary end point
  ► Early clinical response in 3-5 days in ITT
► Secondary end point
  ► Clinical response post treatment 5-10 days after last dose
► Omadacycline non Inferior to Moxifloxacin for early clinical response
  ► (81.1% vs 82.7% 95% CI -7.1 to 3.8)
  ► post treatment response (87.6% vs 85.1% 95% CI, −2.4 to 7.4)
► Adverse events 41.1% vs 48.5% (GI side effects most common)

Omadacycline Summary

- Broad spectrum-Gram positive, gram negative, MRSA, VRE, NOT pseudomonas, atypicals
- IV and PO formulations
  - Oral formulation advantageous in certain situations
- Increased microbial potency
- Indicated for ABSSSI and CABP for which reasonable alternatives already exist
  - Single agent alternative instead of Beta lactam-macrolide combination
  - Could be useful in select situations with allergies
- Low C.diff risk
- Role in treatment of infections with MDR gram negative pathogens is not defined
Lefamulin
(Xenleta-Nabriva Therapeutics- Aug 2019)

► First-in-class, semi-synthetic pleuromutilin antibiotic for the treatment of community-acquired bacterial pneumonia (CABP)
► Spectrum -gram positive and atypical organisms associated with CABP
  ► S.pneumoniae, H.influenza, M.pneumoniae, Legionella pneumophila, Chlamydophila pneumoniae
  ► S.aureus –MRSA, VRE, also active against MDR N.gonorrhoea and M.genitalium
  ► No activity against pseudomonas, Acinetobacter and Enterobacteriaces
► Inhibition of protein synthesis by binding to the peptidyl transferase center of the 50S bacterial ribosome, thus preventing the binding of transfer RNA for peptide transfer
► Cross resistance with other drug classes is unlikely
► IV 150 mg BID and PO 600 mg BID formulations

## Lefamulin Clinical Trials - CABP

<table>
<thead>
<tr>
<th>Study population</th>
<th>Treatment group</th>
<th>End point</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEAP 1 trial</td>
<td>Lefamulin 150 mg IV q12H n=276 Vs Moxifloxacin 400 mg IV q24H (n=275)</td>
<td>Early clinical response at 96 hours 87.3% vs 90.2%, (-2.9% 95% CI−8.5 to 2.8) Clinical response at test of cure visit 86.9% vs 89.4%, (-2.5%, 95% CI −8.4 to 3.4).</td>
<td>Treatment related side effects 2.9% vs 4.4%</td>
</tr>
<tr>
<td>LEAP 2 trial</td>
<td>Lefamulin 600 mg PO q12H X 5 days n=370 Vs Moxifloxacin 400 mg PO q24 H X 7 days n=368</td>
<td>Early clinical response at 96 hours 90.8% vs 90.8% (97.5% CI, -4.4%, ∞) Clincial response at test of cure 87.5% vs 89.1% (97% CI -6.3%,∞)</td>
<td>Diarrhea 12.2% vs 1.1%</td>
</tr>
</tbody>
</table>

Lefamulin Summary

- Strengths
  - Very potent against S.aureus (MRSA), S.pneumoniae, & VRE
  - IV/PO formulation
  - May be an option for drug resistant N.gonorrhea
- Quinolone sparing agent for pneumonia treatment
- Limited gram negative activity
- Safety data limited
- More studies are needed

Ceftolozane/Tazobactam vs Ceftazidime/Avibactam

|---|---|
| • Novel Cephalosporin  
• Gram negative activity expanded by the addition of Tazobactam  
• Gram negative bacilli –ESBL, Pseudomonas including CR-pseudomonas  
• No gram positive, staph aureus/Enterococcal coverage  
• Not active against Carbapenem resistant organisms | • Avibactam is a broad spectrum beta lactamase inhibitor  
• Addition to Ceftazidime extends spectrum  
• ESBL, Amp C beta lactamse, KPC, OXA-48 carbapenemase  
• Pseudomonas with high MIC to Ceftazidime alone  
• No activity against Acinetobacter sp, metallo beta lactamses  
• Approved for cIAI + Metronidazole, cUTI including pyelonephritis, and |

Zhanel GG et al. Drugs 2013; 73: 159
Meropenem – Vaborbactam
(Vabomere – The Medicines Company Aug 2017)

► Novel boronic acid beta-lactamase inhibitor
  ► Inhibit class A carbapenemases  KPCs
  ► Vaborbactam reduces Meropenem MIC in the presence of KPC production
  ► Not active against class B/D carbapenemases -metallo-beta-lactamases, not useful against MDR Acinetobacter or Stenotrophomonas
  ► Vaborbactam does not improve activity of Meropenem against Carbapenem resistant pseudomonas
  ► Active against MDR Enterobacteriaceae ESBLs, AmpC

► Indication cUTI in adults
  ► Escherichia coli, K. pneumoniae, and Enterobacter cloacae species complex

► Dosing 4 grams (2g Meropenem & 2g Vaborbactam) q8H
► Extended infusion over 3 hours
► Serum levels are above MIC for a longer period of time
► Drug drug interactions with Valproic acid
► Drug of choice for Enterobacteriaceae with KPC
A 32 year old female quadriplegic patient with a tracheostomy and chronic Vent dependence is admitted with a right lower lobe pneumonia. She has had prior colonization with pseudomonas. Current tracheal aspirate shows growth of pseudomonas aeruginosa with the following sensitivity pattern.

Her temperature is 39 degrees, RR 32, WBC 20, Cr 2.3.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefepime</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Resistant</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Resistant</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Resistant</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Meropenem</td>
<td>Resistant</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>Resistant</td>
</tr>
</tbody>
</table>
Question

- Which of the following would be the most appropriate antibiotic choice.
  
a. Ceftazidime  
b. Colistin  
c. Meropenem-vaborbactam  
d. Ceftolazane-Tazobactam
a. Ceftazidime is intermediate in sensitivity and would not be a good choice given how sick this patient is

b. Colistin can be used for MDR pseudomonas, however treatment is frequently limited by toxicity. Patient has renal insufficiency and this may not be the best choice

c. Meropenem-Vaborbactam is not effective against Carbapenem resistant strains of pseudomonas.

d. Ceftolazane-Tazobactam has high intrinsic activity against pseudomonas aeruginosa. Sensitivity will need to be requested and treatment could be empirically initiated.
Plazomicin
(Zemdri™ – Achaogen June 2018)

► Aminoglycoside – engineered to evade modifications by aminoglycoside modifying enzymes.

► MOA
  ► Binds to bacterial 30S ribosomal subunit, inhibits protein synthesis in a concentration-dependent manner.

► Spectrum
  ► gram-negative bacteria including ESBL, CRE, and organisms with aminoglycoside-modifying enzymes

► Efflux pump upregulation may not have coverage of Pseudomonas or Acinetobacter species

► Indicated for the treatment of cUTIs in adults with limited treatment options.

► Dose of 15 mg/kg intravenously every 24 hours for 4-7 days

► Nephrotoxicity, ototoxicity, NM blockade

Non inferiority trial

N=609 cUTI including pyelonephritis

- Plazomycin (15mg/kg daily) vs Meropenem 1g Q8H.

Optional step down therapy after at least 4 days of IV therapy, total duration 7-10 days.

End points - composite cure (clinical and microbiological eradication) at day 5, and at test of cure visit (TOC).

Composite cure 88% vs 91.4% (95%CI -10.0-3.1).

- TOC visit, composite cure 81.7% Plazomycin, 70.1% Meropenem (CI 2.7-20.3)

Once daily Plazomycin was non inferior to Meropenem for treatment of cUTI and acute pyelonephritis caused by Enterobacteriaceae including MDR strains

Eravacycline
(Xerava-Tetraphase Pharmaceuticals Aug 2018)

► Novel fully synthetic fluorocycline antibiotic – Tetracycline class
► Spectrum - aerobic and anaerobic gram positive and gram negative bacteria, most anaerobes and MDR bacteria
  ▶ CRE, ESBL, MRSA, VRE, CRAB
► MOA
  ▶ Disrupts bacterial protein synthesis by binding to 30s ribosomal subunit, prevents peptide chain elongation
  ▶ Bacteriostatic
► Retains activity against bacteria with two acquired tetracycline specific resistance mechanisms – Efflux pumps, target site modification -16s rRNA, 30s ribosomal protein
► FDA approval Complicated intra-abdominal infections adults > 18 years of age - 2018

Eravacycline clinical Trial

- Phase 3, multicenter, randomized clinical trial
- N=541, cIAI, ITT
- Treatment Group
  - Eravacycline 1.0mg/kg Q12H vs Ertapenem 1 gram Q24H
- Primary end point
  - Complete resolution or significant improvement of infection
  - TOC 28-31 days after first dose, Follow up 38-50 days after first dose
- ITT clinical cure at TOC 86.8%in vs 87.6%i (95%CI, −7.1%to 5.5%)
- Eravacycline demonstrated noninferiority to ertapenem for the treatment of patients with cIAI
- More adverse events in Eravacycline vs Ertapenem
  - Nausea 8.1% vs 0.7%
  - Phlebitis 3% vs 0.4%
  - Life threatening or fatal events similar in both groups

Eravacycline summary

- Intra abdominal infection with beta-lactam allergy, fluoroquinolone resistance
- Low C.diff risk
- ? Ceftriaxone resistant gonorrhea
- ? NTM- M.abscesses
Relebactam

- Novel non B-lactam beta lactamase inhibitor

Inhibits

- Class A carbapenemases –KPC
- Class C cephalosporinases –Amp C

Inhibiting Amp C restores Pseudomonas aeruginosa susceptibility to Imipenem but not to other Carbapenems

Combining Relebactam with Imipenem can restore Imipenem activity against Imipenem non susceptible gram negatives

- ESBLs, Amp C and KPC , MDR/CR pseudomonas
- Not metallo beta lactamses or class D beta lactamses
  - does not improve imipenem sensitivity in Acinetobacter baumanii or Stenotrophomonas
- Found to be safe for cIAI and cUTI

## Imipenem/Relebactam clinical trial

<table>
<thead>
<tr>
<th>Study population</th>
<th>Treatment group</th>
<th>Primary end point</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESTORE-IMI 1 Phase 3 Randomized, double blind , multicenter N=47</td>
<td>HAP/VAP, cIAI, cUTI Imipenem/Relebactam 500mg/250mg IV q6H + Colistimethate sodium placebo (n=31) Vs Imipenem 500mg q6H + Colistin 300mg load, then 150mg q12H (n=16)</td>
<td>mMITT (n=21 vs n=10) Favorable overall response 71% vs 70% (90% CI -27.5, 21.4) Favorable 28 day clinical response 71% vs 40% (90% CI 1.3, 51.5) 28 day mortality 10% vs 30% (90% CI -46.4, 6.7)</td>
<td>Serious adverse events 10% vs 31% Drug related AE 16% vs 31% Treatment related Nephrotoxicity 10% vs 52% (p=0.002)</td>
</tr>
</tbody>
</table>

Imipenem/Relebactam Summary

- Promising agent for treatment of certain Carbapenemase producing Enterobacteriaceae (KPC/ESBL) and MDR / CR pseudomonas
  - Colistin resistance within CRE is increasingly being reported
  - Though Ceftazidime/Avibactam has shown to be effective for CRE, resistance has emerged
- Not effective for Imipenem resistant Acinetobacter baumanii and Stenotrophomonas strains
- Less toxicity compared to alternative treatment options
### Which drug for which bug?

<table>
<thead>
<tr>
<th>Infection</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDR Pseudomonas</td>
<td>Ceftolozane-Tazobactam</td>
</tr>
<tr>
<td></td>
<td>Ceftazidime-Avibactam</td>
</tr>
<tr>
<td></td>
<td>Meropenem-Vaborbactam</td>
</tr>
<tr>
<td></td>
<td>Imipenem-Relebactam</td>
</tr>
<tr>
<td>CR Pseudomonas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Imipenem-Relebactam</td>
</tr>
<tr>
<td></td>
<td>Ceftolozane-Tazobactam</td>
</tr>
<tr>
<td>ESBL producing Enterobacteriaceae</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ceftolozane/Tazobactam</td>
</tr>
<tr>
<td></td>
<td>Ceftazidime/Avibactam</td>
</tr>
<tr>
<td></td>
<td>Carbapenems</td>
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<tr>
<td></td>
<td>Plazomycin, Eravacycline</td>
</tr>
<tr>
<td>Carbapenem resistant Enterobacteriaceae</td>
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<td></td>
<td>Ceftazidime-Avibactam</td>
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<td>Meropenem-Vaborbactam</td>
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<td></td>
<td>Plazomycin</td>
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<td></td>
<td>Imipenem-Relebactam</td>
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<tr>
<td></td>
<td>Eravacycline</td>
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</table>
# Drugs in the pipeline

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class</th>
<th>Company</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iclaprim</td>
<td>2,4-diaminopyrimidine</td>
<td>Motif Bio PLC</td>
<td>S. aureus</td>
</tr>
<tr>
<td>Ceftobiprole</td>
<td>β-lactam cephalosporin</td>
<td>Basilea Pharmaceutica International Ltd.</td>
<td>S. aureus, K. pneumoniae, Enterobacter spp.</td>
</tr>
<tr>
<td>Cefiderocol</td>
<td>Siderophore Cephalosporin</td>
<td>Shionogi</td>
<td>K. pneumoniae, A. baumannii, P. aeruginosa, Enterobacter spp.</td>
</tr>
<tr>
<td>IV Fosfomycin</td>
<td>Epoxide</td>
<td>Nabriva</td>
<td>MDR Gram negatives</td>
</tr>
<tr>
<td>Aztreonam-Avibactam</td>
<td>Monobactam Inhibitor</td>
<td>Pfizer</td>
<td>MDR Gram negatives</td>
</tr>
</tbody>
</table>

[http://pewtrusts.org/antibiotic-pipeline](http://pewtrusts.org/antibiotic-pipeline)
Future Challenges

► Despite recent advances, treatment of MDR bacterial infections remains challenging, specifically MDR Enterobacteriaceae
► Antimicrobial stewardship efforts need to be intensified
► Though new antibiotics are being developed, they generally belong to existing classes, and there is ongoing need to develop novel new classes of antibiotics.
► Challenges in treatment remain for
  ► blood stream infections, endocarditis, bone and joint infection
  ► Cidal agents, oral agents, long acting agents
► Need for agents with CNS penetration
► Oral options – antipseudomonal agents
References


Thank You
Complications of immune checkpoint inhibitors

Manish R. Patel, D.O.
October 11, 2019
Disclosures

• I will not discuss experimental or off-label uses of investigative products or devices.

• Research funding: Merck, Astra-Zeneca, and Fate Therapeutics

• Advisory Board: Nektar Therapeutics
Overview

• Brief review of immune checkpoint inhibitor and why we use them
• Discuss mechanism of immune checkpoint inhibitors
• Review relevant cases of immune checkpoint toxicity
• Discuss management of immune-related toxicity
THE BREAKTHROUGH

Immunotherapy and the Race to Cure Cancer

CHARLES GRAEBER

New York Times Bestselling Author of The Good Nurse
What are immune checkpoints?

Adaptive Immune Resistance

Pardoll, Nature 2012
Nobel Laureates!

Tasuku Honjo

James Allison
## FDA approvals

### Anti-PD-1 antibodies

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab (Keytruda)</td>
<td>Lung, melanoma, RCC, head and neck, cervical, HCC, GE jxn tumors, Merkel Cell, Lymphoma, bladder</td>
</tr>
<tr>
<td>Nivolumab (Opdivo)</td>
<td>Lung, melanoma, RCC, head and neck, cervical, HCC, Lymphoma, bladder</td>
</tr>
</tbody>
</table>

### Anti-PD-L1 antibodies

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab (Tecentriq)</td>
<td>Lung, melanoma, RCC, head and neck, cervical, HCC, GE jxn tumors, Merkel Cell, Lymphoma, bladder</td>
</tr>
<tr>
<td>Durvalumab (Imfinzi)</td>
<td>Lung, melanoma, RCC, head and neck, cervical, HCC, Lymphoma, bladder</td>
</tr>
<tr>
<td>Cemiplimab (Libtayo)</td>
<td>Cutaneous squamous cell ca</td>
</tr>
<tr>
<td>Avelumab (Bevencio)</td>
<td>Merkel Cell, bladder</td>
</tr>
</tbody>
</table>

### Anti-CTLA4 antibodies

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab (Yervoy)</td>
<td>Melanoma, RCC (with opdivo),</td>
</tr>
</tbody>
</table>
Tolerable

• Not chemotherapy
  – No alopecia
  – No neutropenia
  – No nausea/vomiting

• Most patients can tolerate this treatment
  – Even poor performance patients
But....

There’s a downside
Adaptive Immune Resistance

Autoimmunity

Hepatocyte
Pneumocyte
Colonic epithelium
Rheumatologist’s Treasure Trove

• Immune checkpoint blockade can lead to almost ANY autoimmune manifestation
• Also can occur ANY time after starting
• Not cumulative like with chemotherapy
Discussion with the patient

• Common, not severe (about 15-20% of pts)
  – Skin rash
  – Thyroid disease
  – Arthralgias/arthritis

• Not so common, more severe
  – Colitis (up to 5-15%)
  – Pneumonitis (3-5%)

• Rare, severe
  – Encephalitis
  – Myocarditis
  – Hepatitis
Timing of irAEs

- Typical time course for development:
  - Cutaneous side effects earlier around 3-4 weeks
  - GI and liver side effects after about 6-7 weeks
  - Endocrine side effects around 9 weeks
Toxicity

Distribution of grade 1-2 IRAEs

Distribution of grade 3-5 IRAEs
Diagnosis of IrAE

- No blood test for diagnosis (no circulating autoantibodies)
- Most are going to be clinical diagnosis
- Almost anything could be immune-related
  - Need to keep a high index of suspicion
  - Pt is on immune checkpoint inhibitor and has a new symptom – need to consider whether or not it is related.
  - But also rule out other causes
General Principles

• Grade Severity
  – Asymptomatic – lab or imaging only (Grade 1)
    • Usually can monitor
    • Can continue immune therapy (but consider holding)
    • Monitor closely for progression to symptomatic disease
  – Mild (Grade 2)
    • Possibly symptomatic treatment (e.g. loperamide for diarrhea, topical steroids for rash)
    • Consider holding dose
  – Severe (Grade 3/4)
    • Debilitating or requiring hospitalization
    • Hold immunotherapy
    • Systemic STEROIDS – 1mg/kg prednisone, if life threatening 2mg/kg IV solumedrol. Taper over 4-6 weeks
    • If life-threatening, maybe not rechallenge
Patient case #1

- 77 yo man with recurrent head and neck cancer.
- Failed standard chemotherapy
- Started Nivolumab 480mg IV q28 days
- 1 month later, he presents to ED
  - Worsening shortness of breath over past several weeks
  - Off and on fevers and chills
  - Was treated for a UTI
  - Hypoxic to 80% on RA – 95% on 2L NC
Case #1 continued

• CT report
  – No PE
  – Peribronchovascular nodular infiltrate bilaterally
  – Could be infection vs autoimmune pneumonitis
What is the next step in management of this patient?

a) Draw blood cultures, sputum culture, start antibiotics, await response

b) Start empiric steroids for presumed immune pneumonitis

c) Empiric antibiotics and steroids, blood and sputum cultures
Case #1 Follow up

- Empiric antibiotics – Vancomycin/Piperacillin-tazobactam
- Empiric 1mg/kg prednisone
- SOB resolved next day on room air
- Cultures all negative
- Continued prednisone taper for 4 weeks
- Retreated with Nivolumab
  - So far, no return of toxicity
Pneumonitis

• Pneumonitis can be severe and life threatening
• Workup with chest CT, spirometry, TTE with EF
  – Can consider bronchoscopy
• CT findings range from ground glass opacities to disseminated nodular infiltrates to organizing pneumonia
• Clinical diagnosis
  – Typical imaging pattern without obvious other cause.
## Grading of pulmonary toxicity

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>Ground glass changes on CT, confined to one lobe</td>
</tr>
<tr>
<td>2</td>
<td>Dyspnea, cough, fever, increasing O2 requirements</td>
<td>&lt;50% lung parenchyma</td>
</tr>
<tr>
<td>3</td>
<td>Severe symptoms</td>
<td>&gt;50% lung parenchyma, both lobes involved</td>
</tr>
<tr>
<td>4</td>
<td>Life threatening respiratory compromise</td>
<td>&gt;50% lung parenchyma</td>
</tr>
</tbody>
</table>
Guidelines

PULMONARY ADVERSE EVENT(S)  GRADING  MANAGEMENT

Mild (G1)  Moderate (G2)  See ICI_PULM-2

Pneumonitis

Mild (G1)  Moderate (G2)  Severe (G3–4)

• Consider holding immunotherapy
• Reassess in 1–2 weeks
  ➤ H&P
  ➤ Pulse oximetry (resting and with ambulation)
  ➤ Consider chest CT with contrast
    ➤ Consider repeat chest CT in 4 weeks or as clinically indicated for worsening symptoms

• Hold immunotherapy
• Pulmonary consultation
• Consider infectious workup:
  ➤ Nasal swab for potential viral pathogens
  ➤ Sputum culture, blood culture, and urine culture
  ➤ Consider bronchoscopy with bronchoalveolar lavage (BAL) to rule out infection and malignant lung infiltration
  ➤ Consider chest CT with contrast
  ➤ Repeat chest CT in 3–4 weeks
  ➤ Recommend infectious evaluation with institutional immunocompromised panel
  ➤ Consider empiric antibiotics if infection has not yet been fully excluded
  ➤ Prednisone/methylprednisolone 1–2 mg/kg/day
  ➤ Monitor every 3–7 days with:
    ➤ H&P
    ➤ Pulse oximetry (resting and with ambulation)
  ➤ If no improvement after 48–72 hours of corticosteroids, treat as grade 3
Guidelines

Severe (G3–4)\textsuperscript{d} pneumonitis\textsuperscript{a}

- Permanently discontinue immunotherapy\textsuperscript{f}
- Inpatient care
- Infectious workup:
  - Consider that patient may be immunocompromised
  - Nasal swab for potential viral pathogens
  - Sputum culture, blood culture, and urine culture
- Pulmonary and infectious disease consultation, consider PFTs
- Bronchoscopy with BAL to rule out infection and malignant lung infiltration
- Consider empiric antibiotics if infection has not yet been fully excluded
- Methylprednisolone 1–2 mg/kg/day. Assess response within 48 hours and plan taper over ≥6 weeks
- Consider adding any of the following if no improvement after 48 hours:
  - Infliximab 5 mg/kg IV, a second dose may be repeated 14 days later at the discretion of the treating provider
  - Mycophenolate mofetil 1–1.5g BID then taper in consultation with pulmonary service
  - Intravenous immunoglobulin (IVIG)\textsuperscript{i}
Case #2

• 53 yo man with uveal melanoma with metastasis to lungs.
• Began nivolumab 3mg/kg q2 wks – added ipilimumab after 2 months – CT shows disease is responding in the lungs
• 2 months later – develops fever, watery non-bloody diarrhea and nausea/vomiting over 2 days – 6-8 watery stools in past 2 days.
• CT abd – shows no evidence of colitis, some mild enhancement in the small bowel
What is next best step in management?

a) Send stool for C. difficile, enteric pathogens
b) GI consult for colonoscopy
c) 1mg/kg prednisone
d) All of the above
Case #2 continued

- C. diff is negative, enteric pathogens is negative
- Vanc/Cefepime started empirically due to fever
- Pt started on 1mg/kg prednisone
- Hosp. day #2
  - No improvement
  - 3L diarrhea on Prednisone increased to 2mg/kg
  - Given diphenoxylate/atropine
- Hosp day #3
  - Bl cultures negative- abx d/c,
  - 7L diarrhea, worsening abd pain, hypokalemic
  - Infliximab started 5mg/kg
- Hosp day 6
  - Diarrhea almost resolved
  - Patient discharged with steroid taper over the next 6 weeks
- Immune therapy permanently discontinued
- Of note, he did not require additional systemic therapy for his melanoma for 2 years
## Grading of GI toxicity

<table>
<thead>
<tr>
<th>Grade</th>
<th>Bowel movements</th>
<th>Other symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;4 a day</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>4-6 a day</td>
<td>Abd pain, mucus or blood in stool</td>
</tr>
<tr>
<td>3</td>
<td>&gt;7 a day</td>
<td>Severe abdominal pain, interfering with ADLs, hospitalization</td>
</tr>
<tr>
<td>4</td>
<td>&gt;7 a day</td>
<td>Life threatening consequences</td>
</tr>
</tbody>
</table>
# Guidelines

**Gastrointestinal Adverse Event(s)**

- Mild (G1)
  - Diarrhea
  - Colitis

- Moderate (G2) or Severe (G3–4)

**Assessment/Grading**

- Stool evaluation to rule out infectious etiology
  - Nucleic acid amplification tests (NAATs) for GI pathogens/bacterial culture
  - C. difficile
  - Ova & parasites; molecular testing for *Giardia* and *Cryptosporidium* spp and *E. histolytica*; consider microsporidia, *Cyclospora/isospora* spp
  - Viral pathogens testing when available
  - Based on institutional availability, consider lactoferrin/calprotectin
  - Consider abdominal/pelvic CT with contrast
  - Consider GI consultation
  - Colonoscopy or flexible sigmoidoscopy ± esophagogastroduodenoscopy (EGD) with biopsy

**Management**

- Consider holding immunotherapy
- Loperamide or diphenoxylate/atropine
- Hydration
- Close monitoring

- Hold immunotherapy
- Prednisone/methylprednisolone 1 mg/kg/day
  - No response in 2–3 days:
    - Increase dose to 2 mg/kg/day
    - Consider adding infliximab

- G3: Discontinue anti-CTLA-4; consider resuming anti-PD-1/PD-L1 after resolution of toxicity
- G4: Permanently discontinue immunotherapy agent responsible for toxicity

- Consider inpatient care for provision of supportive care
- Intravenous (IV) methylprednisolone (2 mg/kg/day)
  - No response in 2 days:
    - Continue steroids, consider adding infliximab
    - If infliximab-refractory, consider vedolizumab
Endocrinopathies

- Most common is acquired hypothyroidism
  - TSH checked prior to each infusion
  - Treatment: Synthroid
- Adrenal Insufficiency
  - AM cortisol, ACTH
  - Hydrocortisone replacement
- Panhypopituitarism
  - Subtle presentation
  - Difficult to diagnose
  - Requires hormone replacement
- Type I DM
Endocrinopathy

• PERMANENT
  – Does not return to normal even after discontinuation of treatment
  – Requires lifelong replacement therapy
• Does not require holding therapy
  – Typically can safely continue with therapy
Conclusions

• IrAE are common but most are mild
  – Usually manageable with steroids if identified early
  – Can add other immune suppression if no response to steroids (or consider other cause)
  – Steroid taper over 4-6 weeks
    • Typically not associated with loss of efficacy
    • Typically can safely rechallenge patients
  – Often IrAE can be associated with good prognosis

Pease, et al, SITC 2018 Annual meeting – Abs 10703
Take Aways

- Immune checkpoint inhibitors are effective and usually not toxic
- There is no diagnostic test for determining immune related toxicity
  - Need to keep it in the differential
  - ANY Autoimmune phenomena can be seen on ICB
- If a patient is sick, do not hesitate to start empiric steroids while you consider other causes
  - Call your friendly oncologist for help!
Thank you!
Update in Cirrhosis

Nicholas Lim, MD
Assistant Professor of Medicine
Division of Gastroenterology, Hepatology and Nutrition
ACP Minnesota Chapter Meeting
October 11th 2019
Disclosures

Disclosure of Relevant Financial Relationships
• I have no financial relationships to disclose

Disclosure of Off-Label and/or Investigative Uses
• I will be discussing off-label and/or investigational drug use in this presentation
  –Terlipressin
Learning Objectives

Upon completion of the activity, participants should be better able to:

1. Discuss the potential positive impact of statins on outcomes in cirrhotic patients
2. Discuss the approach for the diagnosis of hepatorenal syndrome and the current state of treatment
3. Discuss emerging data on liver transplantation for severe alcoholic hepatitis in the US
Overview

• Statins in cirrhosis
• Hepato-renal syndrome
• Liver transplantation for alcoholic hepatitis
Statin Use in Cirrhosis
Statins

• HMG co-reductase A inhibitors approved by FDA in 1987
• Primary and secondary prevention of CAD, CVA & PVD
• Other benefits of statins unproven\(^1\)
• 0.5-3% patients develop abnormal LFTs on statins
  – Usually within first 3-months and dose-dependent
  – 0.1% develop ALT>10X ULN\(^2\)
  – Pravastatin (hydrophilic)- no risk\(^3\)
  – Fluvastatin (lipophilic)- increased risk\(^4\)

1. He et al. Annals Int Med 2018
2. Charles et al. AJM 2005
NAFLD

• NAFLD is the fasting growing indication for liver transplantation in the US\textsuperscript{1}
  – Obesity epidemic, HCV clearance

• Significant proportion of NAFLD patients have CAD
  – CVS disease carries highest mortality risk in NAFLD

• Need for statin use in cirrhotic patients increasing

• Statins underutilized in NAFLD patients\textsuperscript{2}
  – 59.6\% patients treated appropriately
  – Patients with recognized NAFLD less likely to get statins compared to those with unrecognized NAFLD

Benefits of Statins in Cirrhosis

• Statins have been shown to:
  – ↓Hepatic decompensation\(^1\)
    • HR 0.55, 95% CI 0.39-0.77
  – ↑Overall survival\(^1\)
    • HR 0.56, 95% CI 0.46-0.69
  – ↓HCC risk\(^2\)
    • OR 0.44, 95% CI 0.46-0.69
  – ↑Overall survival after variceal bleed\(^3\)
    • HR 0.39, 95% CI 0.15-0.99

2. Kim et al. J Hepatol 2018
Effects of Hypercholesterolemia and Statin Exposure on Survival in a Large National Cohort of Patients with Cirrhosis

• VA retrospective cohort study on newly diagnosed patients with cirrhosis

• Total 74,894 patients
  – 21,921 statin users
  – 51,023 non-statin users
  – 8794 new statin users

• Outcomes
  – Death
  – Hepatic decompensation
  – HCC
  – MACEs

• Statin exposure
  – Converted into equivalent doses of simvastatin

Kaplan et al. Gastro 2019
New Statin Use Improves Survival in Cirrhosis

A

Survival probability

Strata
 Existing user HR 1.06 (95% CI 1.05-1.10)

P < .0001

Existing user HR 1.06 (95% CI 1.03-1.08)

New initiator HR 0.49 (95% CI 0.47-0.51)

B

Survival probability

Strata
 Existing user
 Non-initiator
 New initiator

P < .0001

Kaplan et al.
Gastro 2019
Total Cholesterol As A Surrogate for Liver Function

Kaplan et al. Gastro 2019
Secondary Outcomes

- **HCC**
  - Existing users: **HR 0.94**, 95%CI 0.88-1.00, p= 0.06
  - Statin-naïve, Child-B: **HR 0.9**, 95%CI 0.83-0.98, p= 0.01

- ** Decompensation**
  - Statin-naïve: **HR 0.95**, 95%CI 0.95, 95%CI 0.9-0.99, p= 0.01

- **MACEs**
  - Statin-naïve: **HR 1.04**, 95%CI 1.01-1.07, p= 0.008

Kaplan et al. Gastro 2019
Hepato-renal Syndrome
Hepato-renal Syndrome

- Hepato-renal syndrome (HRS) is a rare, life-threatening condition that affects ~11% of patients admitted to hospital with cirrhosis and ascites.
- It is (almost) a *diagnosis of exclusion* and is *over-diagnosed* in patients with both cirrhosis and acute kidney injury.
- Traditionally, divided into Type-1 (acute) & Type-2 (subacute/chronic).
Pathophysiology of HRS

Cirrhosis → Portal (sinusoidal) hypertension

Splanchnic/systemic vasodilatation → ↓ Effective arterial blood volume

Activation of neurohumoral systems → Renal vasoconstriction

HRS
Etiologies of Renal Dysfunction in Cirrhosis

Adapted from Martín-Llahí et al. Gastroenterology. 2011
## Diagnosis of HRS

- No specific tests to diagnose HRS
- **Rule out** other causes of AKI

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rule out Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doubling of serum creatinine (&gt; 2.25mg/dl within 2 weeks)</td>
<td>No current or recent treatment with nephrotoxic drugs</td>
</tr>
<tr>
<td>No improvement of serum creatinine after at least 2 days with diuretic withdrawal and volume expansion with albumin</td>
<td>Absence of parenchymal kidney disease as indicated by proteinuria &gt; 500mg/day, microhematuria (&gt; 50 red blood cells per high power field) and/or abnormal renal ultrasonography</td>
</tr>
<tr>
<td>Absence of any type of shock</td>
<td>Presence of ascites</td>
</tr>
<tr>
<td>Absence of infection</td>
<td>Urine Na&lt;5</td>
</tr>
</tbody>
</table>
Probability of Survival in HRS

Treatment of HRS

- Liver transplantation
- Albumin
- Midodrine/octreotide/albumin
MOA “Cocktail” for HRS

Angeli et al. Hepatology 1999

Treatment of HRS

- Liver transplantation
- Albumin
- Midodrine/octreotide/albumin
- Vasopressin
- Terlipressin
REVERSE trial: Significant improvement in renal function

Serum Cr

GFR (4-variable MDRD)

Boyer et al. Gastroenterology 2016
Treatment of HRS

• Liver transplantation
• Albumin
• Midodrine/octreotid/albumin
• Vasopressin
• Terlipressin
  – New data coming soon
Liver Transplantation for Alcoholic Hepatitis
Alcoholic Hepatitis

• Alcoholic hepatitis (AH) is characterized by acute onset of jaundice due to excessive alcohol use
  – 4 per 100,000 US admissions each year
  – 10% of deaths related to alcohol-related liver disease

• NIAAA working definition of AH
  – Onset of jaundice within 60 days of heavy consumption (> 50 g/day) of alcohol for a minimum of 6 months
  – Serum bilirubin >3 mg/dL, elevated AST (50-400 U/L) and AST:ALT ratio >1.5
  – No other obvious cause for hepatitis
Alcoholic Hepatitis

• Severe AH
  – Maddrey’s discriminant function ≥32
  – ~70% 6-month mortality if unresponsive to steroids

• Management
  – Abstinence
  – Nutrition
  – Medical therapy
    • Steroids, pentoxifylline, NAC, G-CSF, anti-TNF
**STOP-AH Trial**

### Table 2. Mortality at 28 Days, 90 Days, and 1 Year.*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Prednisolone</th>
<th>No Prednisolone</th>
<th>Pentoxifylline</th>
<th>No Pentoxifylline</th>
<th>Prednisolone</th>
<th>Pentoxifylline</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-Day mortality — no./total no. (%)</td>
<td>73/526 (14)</td>
<td>95/527 (18)</td>
<td>85/518 (16)</td>
<td>83/535 (16)</td>
<td>0.72 (0.52–1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>90-Day mortality or liver transplantation — no./total no. (%)</td>
<td>144/484 (30)</td>
<td>141/484 (29)</td>
<td>139/478 (29)</td>
<td>146/490 (30)</td>
<td>1.02 (0.77–1.35)</td>
<td>0.87</td>
</tr>
<tr>
<td>1-Year mortality or liver transplantation — no./total no. (%)</td>
<td>210/371 (57)</td>
<td>211/376 (56)</td>
<td>205/365 (56)</td>
<td>216/382 (57)</td>
<td>1.01 (0.76–1.35)</td>
<td>0.94</td>
</tr>
</tbody>
</table>

* The interaction between interventions was investigated as a secondary analysis.

- Multivariate analysis for 28-day mortality (for use of prednisolone) OR 0.61 (95% CI, 0.41 to 0.91), p=0.02
- 28-day mortality lower than expected (in placebo group)= 17%

Thursz MR et al. NEJM 2015
Liver Transplantation for Severe AH

Mathurin P et al. NEJM 2011
## LTx for Alcoholic Hepatitis: Outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th># of Patients</th>
<th>Period of Abstinence (days)</th>
<th>MELD</th>
<th>1-yr Patient Survival</th>
<th>Return to harmful drinking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mathurin</td>
<td>France</td>
<td>26</td>
<td>&lt;90</td>
<td>34</td>
<td>77%</td>
<td>10%</td>
</tr>
<tr>
<td>Im</td>
<td>NY</td>
<td>9</td>
<td>33</td>
<td>39</td>
<td>89%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Weeks</td>
<td>MD</td>
<td>46</td>
<td>51</td>
<td>33</td>
<td>97%</td>
<td>17%</td>
</tr>
</tbody>
</table>
ACCELERATE-AH

• Retrospective study of 147 patients undergoing early liver transplant for severe alcoholic hepatitis at 12 liver transplant centers

• All patients:
  – Severe AH (MDF>32)
  – No prior diagnosis of chronic liver disease or AH
  – <6 months sobriety from alcohol

• Outcomes
  – 1-year survival
  – 3-year survival
  – Post-LT alcohol use

Lee et al. Gastro 2018
ACCELERATE-AH

• Outcomes
  – 1-year survival = 94% (95% CI 89-97%)
  – 3-year survival = 84% (95% CI 75-90%)
  – 18 deaths
    • 7 alcohol-related
  – Median follow-up = 1.6 years
    • 101 (72%) had no post-LT alcohol use
    • 25 (18%) had slips
    • 15 (11%) had sustained alcohol use
  – Risk factor for sustained post-LT alcohol use
    – >10 drinks per day at presentation

Lee et al. Gastro 2018
Caveats

• Demographics
  – 73% male
  – 83% white
  – 66% privately insured

• Variability in transplant criteria with center
  – 10/12 centers required full agreement of LT committee

• NIAAA inclusion criteria for ETOH hepatitis
  – Only 79% patients met these criteria

• Explant histology
  – Only 59% had steatohepatitis (acute changes)
  – 96% had cirrhosis
<table>
<thead>
<tr>
<th>Pro</th>
<th>Against</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life-saving treatment for patients who will otherwise die</td>
<td>Public losing trust may affect liver donation</td>
</tr>
<tr>
<td>“6-month rule” imperfect</td>
<td>Not enough long-term prospective data to support such a divergence from SOC</td>
</tr>
<tr>
<td>• 20% of patients relapse by 5 years</td>
<td></td>
</tr>
<tr>
<td>Good outcomes</td>
<td>High MELD-Na will mean that all these patients will be top of waitlist</td>
</tr>
<tr>
<td>Alcoholism separate disease to alcoholic liver disease</td>
<td>Amplify disparities in LT that pre-exist (white, male, insured)</td>
</tr>
</tbody>
</table>
Summary

• Statin use in patients with cirrhosis is safe and may provide additional benefits for liver-related outcomes
• Hepato-renal syndrome remains a condition with a poor prognosis but new data will soon provide another tool to improve survival
• Liver transplantation for alcoholic hepatitis is here to stay but better data is needed in order to select the best candidates given the potential strain on a sparse donor pool
Questions
Just stop!
Things that add no value

Minnesota ACP Scientific Meeting, October 11, 2019

David R. Hilden, MD MPH FACP

Vice President of Medical Affairs / President of Medical Staff
Hennepin Healthcare
Associate Professor of Medicine, University of Minnesota Medical School
Governor, Minnesota Chapter, American College of Physicians
FIG. 2.—THE KNEE-JERK.
Method of obtaining it when it
I have no disclosures
What’s ahead

• Difference between high- and low-value care

• Choosing Wisely

• Three steps for identifying high-value care

• Things we do that add no value
High-value care
High value care:

Health benefits outweigh the cost
Three steps to determine high value care

1. Assess harms, benefits, and costs
2. Assess downstream effects
3. Determine incremental costs needed to get the health benefit
Choosing Wisely®
<table>
<thead>
<tr>
<th></th>
<th>Don’t obtain screening ECG in asymptomatic, low risk individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Don’t obtain imaging in patients with non-specific low back pain</td>
</tr>
<tr>
<td>3</td>
<td>In simple syncope with normal neuro exam, don’t get brain imaging (CT or MRI)</td>
</tr>
<tr>
<td>4</td>
<td>In pts with low pretest probability of VTE, obtain a D-dimer before any imaging</td>
</tr>
<tr>
<td>5</td>
<td>In preoperative evaluation, don’t get a CXR in absence of clinical suspicion of thoracic pathology</td>
</tr>
</tbody>
</table>
Stop doing these things
Topic 1: Syncope and TTE

- 55 yo woman with hypothyroidism and hypertension presented after abrupt LOC at a dinner party. She denied chest pain, shortness of breath, or dizziness.

- Vitals in the ED: BP 142/80, HR 88, RR 12, Afebrile

- She is admitted to your Observation unit for syncope.

- What evaluation do you do?
Syncope

A symptom of abrupt, transient LOC with decreased postural tone, rapid recovery, probably due to decreased cerebral perfusion
Topic 1: Syncope and TTE

- Should you order an echo in syncope work-up?
- Reasons why you might get TTE:
  - Looking for structural heart disease
  - Looking for scary risk factors (VT/VF) and reduced EF
    - Aortic stenosis
    - HOCM
    - Large pericardial effusion leading to tamponade
    - Pulmonary hypertension
    - Large pulmonary embolism
- Otherwise, don’t order an echo
Diagnostic yield of TTE is low in syncope

- It is ordered often
  - 5-7% in all syncope patients
  - 30-90% in other studies

- It rarely leads to a diagnosis
  - TTE finds a dx in 0-2-4% of cases in 3 studies
  - Finds structural lesions in 2-4%

- It is expensive
  - At $1,000-$2,000 per echo (charges), costs $60,000 - $130,000 to find one case
TTE and syncope

- Downstream effects
  - Potentially increased LOS
  - Incidental findings leading to more diagnostic testing
So what should you do for syncope workup?

- **Always:**
  - History
  - Physical
  - Risk factor analysis
    - European Society of Cardiology 2018 guidelines
    - Canadian calculator

- **Often**
  - CBC (anemia)
  - Telemetry (+/- benefit)
  - Observe 24 hours
  - BNP
Do not order routine echocardiogram for unselected syncope patients
82 yo woman falls getting out of car at grocery store.

In ED, found to have femoral neck fracture which is repaired by ortho.

POD2 in the evening, she is alert only to self, making non-sensical statements, occasionally hollering out, and not able to participate in PT. Vitals are normal except BP 145/62.

Nurse is asking for a dose of haloperidol.
Topic 2: Delirium and anti-psychotics

Delirium – 5 features

- Disturbance of **attention**

- Different from baseline, fluctuating, over short time period

- Additional cognitive deficit (e.g. memory)

- Not explained by something else

- Presence of a culprit (medical condition, medication, ingestion)

Photo: Wellcome images, via Wikimedia Commons
Topic 2: Delirium and anti-psychotics

- Should you order anti-psychotics for delirium?

- Reasons why you might order anti-psychotics
  - Agitated patients at risk of harm to self or others
  - RASS = Richmond Agitation-Sedation Scale

- Otherwise, don’t routine order anti-psychotics
Delirium is common, possibly preventable and dangerous

- General hospitalized older adults: 30-50%
- Major elective surgery: 15-25%
- Hip repair surgery: up to 50%
- ICU patients: up to 82%

- Poor clinical outcomes, higher rates of physical and cognitive decline, increased institutionalization, increase mortality

- Non-pharmacologic interventions are effective
  - Family interaction, early mobilization, calm environment, sleep enhancement
Anti-psychotics and delirium

• Annals study October 1, 2019 (last week):

  • No evidence that routine use of haloperidol or second-generation anti-psychotics has benefit in patients with delirium in the hospital

  • No effect or mixed data on: LOS, severity of delirium, sedation, incidence of delirium, duration, mortality
Do not order haloperidol or second-generation anti-psychotics for delirium in hospitalized patients in the absence of agitation.
Topic 3: Docusate in the hospital

• Same patient as before: 82 yo woman falls getting out of car at grocery store.

• In ED, found to have femoral neck fracture which is repaired by ortho. We love ortho.

• POD1, no BM, you prescribe docusate. Prob on order set

• POD2, still no BM

• POD3, still waiting

• POD4, you decide to try something that actually works
Docusate: how did this stuff become so popular?

- Docusate is a detergent, supposed to soften up stool by absorbing water
- Almost no data at all, and what’s with the WHO calling it “an essential medicine”?
- McGill University
  - Docusate = 64% of laxatives given
  - Average = 10 doses / admission
  - 50% discharged on docusate
  - $60K per year

Photo: Public domain
Topic 3: Docusate in the hospital

- Harms: it doesn’t work
- 1,2,3,4 days of no relief for patients is not good.
- Constipation is common: 40% of patients in hospital
- Many contributing factors: immobility, comorbid conditions, post-operative ileus, anesthetics, medications (including opioids).
- Patients are getting older
- Um . . . stercolith, anyone?
Instead of docusate, do something that works

- **GI people like (AJG):**
  - Polyethylene glycol (Grade A)
  - Psyllium (Grade B)
  - Lactulose (Grade B)

- Sennosides work too

- Helen the HCMC nurse from a bygone era

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Photo: Public domain

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Do not use docusate for prevention or treatment of constipation
Topic 4: Malnutrition and pre-albumin

• Should you check a pre-albumin?

• Reasons why you might check pre-albumin
  • Made in liver, in circulation prior to excretion in GI and kidneys
  • Called transthyretin (transports thyroid hormones)
  • Short half-life, so potentially a good marker
Malnutrition is a big deal and we don’t see it

- No patient case, you know who we are talking about – it’s all your patients

- Acute, subacute, or chronic nutritional state (over- or under-) leading to change in body composition and diminished function

- WAY under-documented
  - 20-50% of hospitalized patients
  - Only 3% documented on discharge

- Up to 12x higher risk for mortality in one European study

Photo: Wellcome images, via Wikimedia Commons
So why is pre-albumin not so great . . .

- Not specific
  - Pre-albumin is a *negative* acute phase reactant – falsely low
- Not a good measure of protein stores
- Not sensitive
  - Should be low in malnutrition (in absence of inflammatory state), but it is not consistent low
  - People with BMI as low as 12 can have normal pre-albumin
So why is pre-albumin not so great . . .

- Doesn’t always correct with improved nutrition
  - Alzheimer study: prealbumin didn’t improve even though arm circumference, skin thickness, weight all did improve
  - CRP is correlated with pre-albumin but not nutrition measures

- Doesn’t consistently correlate with outcomes
  - 2005 analysis of 99 studies showed no correlation between pre-albumin and outcomes.
Instead of pre-albumin, do this

- Consult your registered dietician (RD)
- Other possibly more meaningful measures:
  - Anorexia
  - Non-volitional weight loss
  - Reduced lean mass
  - Co-existing inflammatory disease burden
  - Low BMI
Do not check pre-albumin to assess nutritional status

The Curbsiders podcast #165 Things We Do For No Reason™ Part 2, August 2, 2019 by Justin Berk


Mary Lacy, MD, Justin Roesch, MD, Jens Langsjoen, MD, Things We Do For No Reason: Prealbumin Testing to Diagnose Malnutrition in the Hospitalized Patient. J. Hosp. Med 2019;4;239-241. Published online first October 31, 2018.. doi:10.12788/jhm. 3088