# Infectious Diseases Odds and Ends: Focus on Developments in Hepatology and Gram-Negative Infections

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**Disclosure**  
I have no conflicts of interest to disclose.

## Objectives

By the end of the presentation, learners should be able to:

- Explain contemporary Hepatitis C Virus (HCV) antiviral treatment strategies for patients of various complexities.
- Describe and apply novel methods to expand the role of the pharmacist in treating HCV.
- Compare and contrast novel and future antibiotics, and their roles in the treatment of multi-drug resistant infections.

## Meet HS

- HS is a 55 yo WM with chronic HCV  
- Prior injection drug and alcohol use  
- Prior relapse with peginterferon + ribavirin  
- HCV Genotype 1a  
- AST 80 units/mL, ALT 110 units/mL, Child-Pugh A  
- HTN controlled on lisinopril and amlodipine

## HCV Prevalence

Centers for Disease Control and Prevention, 2017.  
U.S. Incidence

[Graph showing the incidence of Hepatitis C from 1960 to 2020.]

Natural History

- 100 patients infected with HCV
- 75-85 develop chronic infection
- 60-70 develop chronic liver disease
- 5-20 develop cirrhosis
- 1-5 die of cirrhosis or liver cancer

[Diagram showing the progression from infection to death.]

Screening

[Graph showing the prevalence of Hepatitis C over time.]

Diagnostic Testing

<table>
<thead>
<tr>
<th>HCV Antibody</th>
<th>HCV Viral Load</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Undetectable</td>
<td>Prior exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Closed acute infection or successful chronic infection treatment</td>
</tr>
<tr>
<td>Positive</td>
<td>Detectable</td>
<td>Current acute or chronic infection</td>
</tr>
<tr>
<td>Negative</td>
<td>Undetectable</td>
<td>Not exposed or infected</td>
</tr>
<tr>
<td>Negative</td>
<td>Detectable</td>
<td>?? - False negative antibody test (?)</td>
</tr>
</tbody>
</table>


Genotypes

- Genotypes 1-6
- Genotype 1b most prevalent worldwide
- 75% U.S. patients have Genotype 1

Other Baseline Tests & Counseling

- Testing
  - HIV Screening
  - HAV, HBV Screening
  - HAV and HBV Immunization if susceptible

- Counseling
  - Transmission Risks
  - Avoidance of Alcohol
  - Avoidance of Hepatotoxic Medications
  - Limit Iron Intake

Treatment Goals

- Prevent complications
- Prevent clinical progression
- Prevent death

Virological Response

<table>
<thead>
<tr>
<th>Response Name</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Null Responder</td>
<td>Fail to achieve at least 2 log drop in viral load</td>
</tr>
<tr>
<td>Partial Responder</td>
<td>Greater than 2 log drop in viral load, but failed to achieve undetectable levels</td>
</tr>
<tr>
<td>Virological Relapse</td>
<td>End of Treatment Response, but detectable viral load after treatment ends</td>
</tr>
<tr>
<td>Breakthrough</td>
<td>Reappearance of viral load during treatment</td>
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Direct-Acting Antivirals (DAAs)

- Overall well tolerated, all oral regimens
- Combination tablets

<table>
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<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Name Suffix</th>
<th>Examples</th>
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<td>NS3/4A</td>
<td>Protease Inhibitor</td>
<td>-previr</td>
<td>Voxlprevir, Glecaprevir, grazaprevir</td>
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<tr>
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<td>Replication Complex Inhibitor</td>
<td>-asvir</td>
<td>Ledipasvir, Ombitasvir, Elbasvir, Velpatasvir</td>
</tr>
<tr>
<td>NS5B Nucleotide Analog</td>
<td>Polymerase Inhibitor</td>
<td>-buvir</td>
<td>Sofosbuvir</td>
</tr>
<tr>
<td>NS5B Non-Nucleotide Analog</td>
<td>Polymerase Inhibitor</td>
<td>-buvir</td>
<td>Dasabuvir</td>
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</tbody>
</table>

HCV Life Cycle

- Overall well tolerated, all oral regimens
- Combination tablets

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### Critical Information Guiding Treatment

**Genotype**

- Genotype 1a

**Treatment naïve vs. Treatment experienced**

- If experienced, what was prior regimen(s)?

**No cirrhosis vs. Compensated cirrhosis vs. Decompensated cirrhosis**

- Decompensated cirrhosis: Specialist referral

**Post-Liver Transplant?**

- No

**Full medication regimen**

- Lisinopril and Amlodipine

### Treatment Guidelines: Treatment Naïve

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Recommended</th>
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<tr>
<td>1a or 1b</td>
<td>LDV/SOF $\times 12$ weeks</td>
<td>GLE/PIB $\times 8-12$ weeks</td>
<td>SOF/VEL $\times 12$ weeks</td>
<td>EBR/GZR $\times 12$ weeks</td>
</tr>
<tr>
<td>2</td>
<td>GLE/PIB $\times 8-12$ weeks</td>
<td>SOF/VEL $\times 12$ weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>GLE/PIB $\times 8-12$ weeks</td>
<td>SOF/VEL $\times 12$ weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>LDV/SOF $\times 12$ weeks</td>
<td>GLE/PIB $\times 8-12$ weeks</td>
<td>SOF/VEL $\times 12$ weeks</td>
<td>EBR/GZR $\times 12$ weeks</td>
</tr>
<tr>
<td>5 or 6</td>
<td>LDV/SOF $\times 12$ weeks</td>
<td>GLE/PIB $\times 8-12$ weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**LDV = Ledipasvir; SOF = Sofosbuvir; GLE = Glecaprevir; PIB = Pibrentasvir; VEL = Velpatasvir; EBR = Elbasvir; GZR = Grazoprevir**

### Treatment Guidelines: Treatment Experienced

- Similar to Treatment Naïve

- What was prior treatment?
  - DAA regimen or just PEG-RBV?
  - Prior Protease Inhibitor: can’t use another protease inhibitor
  - Compensated Cirrhosis: longer duration or add ribavirin for some regimens

- SOF/VEL/VOX niche

### HIV/HCV Co-infection

- Same treatment as non-HIV-infected
- Do NOT interrupt HIV treatment for HCV treatment
- Drug-Drug Interaction Screening CRITICAL!

#### “Safe to Use”

- SOF, LDV/SOF, VEL/SOF

#### “Caution”

- SOF/VEL/VOX, GLE/PIB, DCV, RBV

#### “Stop”

- EBR/GZR, OBV/PTV/r, SIM

### Other Special Populations

- Decompensated Cirrhosis: “Specialist referral”:
  - LDV/SOF + RBV $\times 12$ weeks OR
  - SOF/VEL + RBV $\times 12$ weeks OR
  - DCV + SOF + RBV $\times 12$ weeks

- Post-Liver Transplant
  - LDV/SOF + RBV $\times 12$ weeks OR
  - GLE/PIB $\times 12$ weeks

- Renal Impairment
  - C/Cl > 30mL/min: all regimens OK
  - C/Cl = 30mL/min: all regimens OK

### Drug-Drug Interaction Concerns with DAAs

- Acid-suppressing Drugs
- P-glycoprotein (P-gp) Inducers
- Statins
- Amiodarone

Useful reference: [https://www.hep-druginteractions.org/](https://www.hep-druginteractions.org/)
So What Can a Pharmacist Do?

Process of Getting Treated

Pharmacist Role in Screening

Federally Qualified Health Center in Florida
- Daily pharmacist review of patients born 1945-1965
- If not previously screened for HCV, alert to nurse and provider recommending screening

Pharmacist Role in Pre-Treatment Evaluation

Federally Qualified Health Center in Florida
- Clinical Pharmacist protocol to assist providers
  - Ordering/reviewing lab results
  - Selecting best treatment
  - Drug-drug interactions
  - Cost

Pharmacist Role During Treatment

Federally Qualified Health Center
- Assist with manufacturer coupons, other cost issues
- Call patient at end of week 1, week 4 (adherence)
- Call patient monthly (side effects)

Veterans Affairs Healthcare System
- Prescriptive authority
- Patient visits at least at baseline and week 4
- PRN calls and additional visits
- Patients can be seen by Clinical Video Telehealth
- Notes in chart
Pharmacist Role After Treatment

Federally Qualified Health Center
- Send letter to provider
  - Medication refill date information
  - Estimated date of completion

Veterans Affairs Health Care System
- Order SVR lab
- Call patient with results
- Document encounter/results
- Discharge from pharmacist-run clinic to consulting provider

At what steps in the process can pharmacists be involved?

Screening/Diagnosis
- Additional Lab Tests
- Pre-Treatment Evaluation
- Dis-Treatment Monitoring
- Post-Treatment Monitoring

New and Upcoming Gram Negative Drugs

Approved/Upcoming Gram Negative Drugs

Approved
- Ceftolozane/Tazobactam
- Ceftazidime/Avibactam
- Meropenem/Vaborbactam
- Delafloxacin
- Plazomicin

Upcoming
- Omadacycline
- Imipenem/relebactam

Ceftolozane/Tazobactam (Zerbaxa)
- FDA Indications:
  - Complicated intra-abdominal infections (cIAI): non-inferior to meropenem
  - Complicated UTIs (cUTI): non-inferior to levofloxacin
- Dose: 1.5 grams IV every 8 hours
- Activity vs. Pseudomonas and ESBL-producing organisms
- No activity against carbapenem resistant Enterobacteriaceae (CRE)

Ceftazidime/Avibactam (Avycaz)
- FDA Indications:
  - cIAI (+metronidazole): non-inferior to meropenem
c- cUTI: non-inferior to doripenem, superior to best available therapy
- Hospital-acquired Bacterial Pneumonia/Ventilator-associated Bacterial Pneumonia (HABP/VABP): non-inferior to meropenem
- Dose: 2.5 grams IV every 8 hours
- Activity vs. Pseudomonas, ESBL-producing organisms, CRE
**Meropenem/Vaborbactam (Vabomere)**

- **FDA Indications:** cUTI
- **Trial 1:** superior to piperacillin/tazobactam
- **Additional trial (cUTI, HABP/VABP/cIAI):** stopped early due to superiority over best available therapy for patients with CRE
- **Dose:** 4 grams IV every 8 hours
- **Activity vs. Pseudomonas, ESBL-producing organisms, CRE**

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**Comparison of the new Beta-lactams**

<table>
<thead>
<tr>
<th>Class of Beta-Lactamase</th>
<th>Enzymes</th>
<th>Ceftolozane/tazobactam</th>
<th>Ceftazidime/avibactam</th>
<th>Meropenem/vaborbactam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class A (Serine)</td>
<td>TEM</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>SHV</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>CTX-M</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Class B (MBLs)</td>
<td>IMP/VIM</td>
<td>None</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>NDM</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Class C (Serine)</td>
<td>Amp C</td>
<td>Variable</td>
<td>Variable</td>
<td>✓</td>
</tr>
<tr>
<td>Class D (Serine)</td>
<td>OXA</td>
<td>Variable</td>
<td>Variable</td>
<td>✓</td>
</tr>
</tbody>
</table>

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**Comparison of cUTI Trials**

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Levofloxacin</th>
<th>Doripenem</th>
<th>Best Available Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success Rate at Test of Cure</td>
<td>76.9% (vs 68.4%)</td>
<td>71.2% (vs 64.5%)</td>
<td>70.1% (vs 54%)</td>
</tr>
</tbody>
</table>

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**Delafloxacin (Baxdela)**

- **FDA Indications:** Acute Bacterial Skin and Skin Structure Infections (ABSSSI)
- **Non-inferior to vancomycin + aztreonam x 2 trials**
- **Dose:** 300mg IV or 450mg PO every 12 hours
- **Activity vs. Pseudomonas, Enterobacteriaceae**
- **Plus Gram-positives, including MRSA**
- **Ongoing trials:** Community-acquired Bacterial Pneumonia (CABP) and urinary tract infection (UTI)

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**Plazomicin**

- **New aminoglycoside**
- **EPIC trial: cUTI**
- **CARE trial: HABP/VABP or Bloodstream Infection due to CRE compared to Colistin (Both + Meropenem or Tigecycline)**
- **All-cause mortality or significant disease related complication numerically higher in Colistin arm (50% vs 23.5%, p=0.094)**
- **Dose:** 15 mg/kg IV once daily
- **Activity vs. Pseudomonas, ESBL-producing organisms, CRE**
- **Not active vs. NDM-1 isolates**

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**Ervacycline**

- **Fully synthetic fluorocycline (tetracycline-like)**
- **cIAI:**
  - IGNITE1: non-inferior to ertapenem
  - IGNITE4: non-inferior to meropenem
- **cUTI**
  - IGNITE3: inferior to ertapenem
- **Dose:** 1mg/kg IV every 12 hours
- **Activity vs. Pseudomonas, ESBL-producing organisms, CRE, Carbapenem-resistant Acinetobacter**
**Omadacycline**

- New “tetracycline” (aminomethycycline)
- OASIS-1 and OASIS-2: ABSSSI
  - Both: non-inferior to linezolid
  - OASIS-1 Dose: 100mg IV every 12 hours x 2 doses, then 100mg IV daily
  - OASIS-2 Dose: 450mg PO daily x 2 days, then 300mg PO daily
- OPTIC: CABP
  - Non-inferior to moxifloxacin
- Activity vs. ESBL-producing organisms

**Summary of New/Upcoming Drugs**

<table>
<thead>
<tr>
<th>CRE Activity</th>
<th>Other Activity/Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime/avibactam</td>
<td>Ceftolozane/tazobactam (ESBL, Pseudomonas)</td>
</tr>
<tr>
<td>Meropenem/vaborbactam</td>
<td>Delafoxacin (Gram positives)</td>
</tr>
<tr>
<td>Plazomicin</td>
<td>Omadacycline (Gram positives)</td>
</tr>
<tr>
<td>Eravaccline</td>
<td></td>
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</table>

**Summary**

- HCV treatment is available for ALL patients with HCV
- Pharmacists are key participants in many facets of HCV care
- New beta-lactam/beta-lactam inhibitors offer additional options for resistant Gram negative infections
- Keep your eyes open for more data coming soon!