#FSHP2018

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:

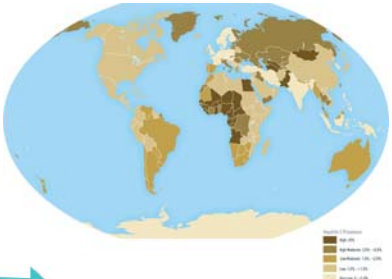
- Explain contemporary Hepatitis C Virus (HCV) antiviral treatment strategies for patients of various complexities.
- Describe and apply novel methods to expand the role of the pharmacist in treating HCV.
- Compare and contrast novel and future antibiotics, and their roles in the treatment of multi-drug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

Hepatitis C Treatment and the Role of the Pharmacist

Meet HS

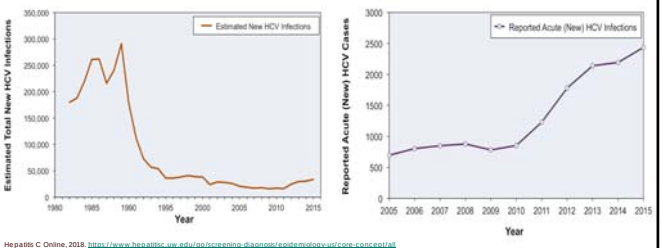
- HS is a 55 yo WM with chronic HCV
- Prior injection drug and alcohol use
- Prior relapse with peginterferon + ribavirin
- HCV Genotype 1a
- AST 80 units/mL, ALT 110 units/mL, Child-Pugh A
- HTN controlled on lisinopril and amlodipine

HCV Prevalence



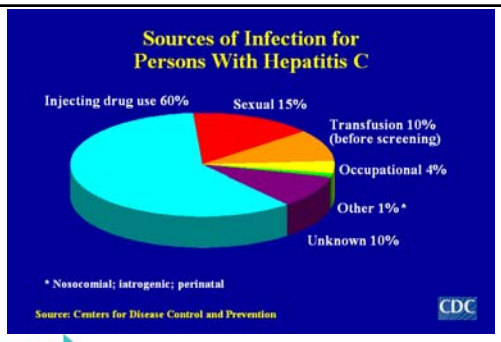
Centers for Disease Control and Prevention, 2017. https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/hepatitis-c

U.S. Incidence

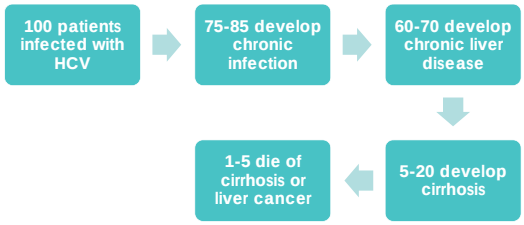


Hepatitis C Online, 2018. https://www.hepatitisc.uw.edu/go/screening-diagnosis/epidemiology-us/core-concept/all

Sources of Infection for Persons With Hepatitis C

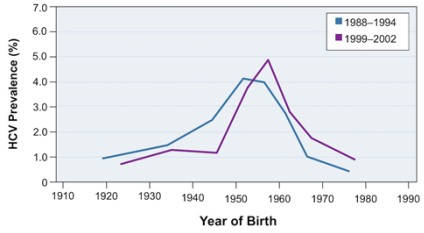


Natural History



Centers for Disease Control and Prevention, 2018. https://www.cdc.gov/hepatitis/hcv/cfaq.htm

Screening



Hepatitis C Online, 2018. https://www.hepatitisc.uw.edu/go/screening-diagnosis/epidemiology-us/core-concept/all

Diagnostic Testing

HCV Antibody	HCV Viral Load	Interpretation
Positive	Undetectable	Prior exposure Cleared acute infection or successful chronic infection treatment
Positive	Detectable	Current acute or chronic infection
Negative	Undetectable	Not exposed or infected
Negative	Detectable	???- False negative antibody test (?)

Centers for Disease Control and Prevention, 2018. https://www.cdc.gov/hepatitis/hcv/index.htm

Genotypes

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

Simmonds P. Hepatology 2005;42:962-973.

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

AASLD/IDSA. HCV Guidance, 2018. http://www.hcvguidelines.org/

Treatment Goals

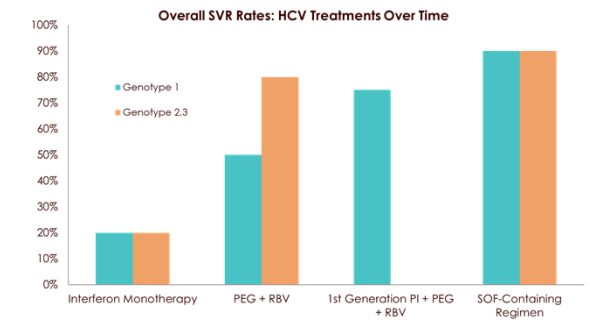
- Prevent complications
- Prevent clinical progression
- Prevent death

Ghany M G. Hepatology 2009;49:1335-74.

Virological Response

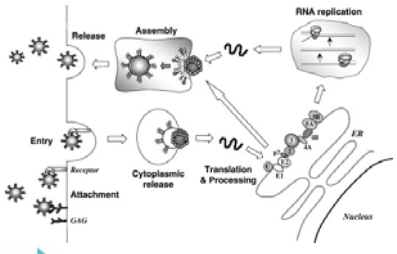
Response Name	Definition
Sustained Virological Response (SVR)	Undetectable viral load 24 weeks after end of treatment
Sustained Virological Response 12 (SVR_{12})	Undetectable viral load 12 weeks after end of treatment
Null Responder	Fail to achieve at least 2 log drop in viral load
Partial Responder	Greater than 2 log drop in viral load, but failed to achieve undetectable levels
Virological Relapse	End of Treatment Response, but detectable viral load after treatment ends
Breakthrough	Reappearance of viral load during treatment

Ghany M G. Hepatology 2009;49:1335-74.



Rosen HR. NEJM 2011;364:2429-2438., Harvoni (sofosbuvir/ledipasvir) Prescribing Information. Gilead Sciences, Inc, 2017.

HCV Life Cycle



Suzuki T. Advanced Drug Delivery Reviews 2007;59:1200-1212.

Direct-Acting Antivirals (DAAs)

- Overall well tolerated, all oral regimens
- Combination tablets

Drug Class	Mechanism of Action	Name Suffix	Examples
NS3/4A	Protease Inhibitor	-previr	Voxilaprevir, Glecaprevir, Grazoprevir
NS5A	Replication Complex Inhibitor	-asvir	Ledipasvir, Ombitasvir, Elbasvir, Velpatasvir
NS5B Nucleot(s)ide Analog	Polymerase Inhibitor	-buvir	Sofosbuvir
NS5B Non-Nucleotide Analog	Polymerase Inhibitor	-buvir	Dasabuvir

Critical Information Guiding Treatment

Information	Patient HS
Genotype	**Genotype 1a**
Treatment naïve vs Treatment experienced • If experienced, what was prior regimen(s)?	**Experienced** **Peginterferon/ribavirin**
HIV co-infection?	**No**
No cirrhosis vs. Compensated cirrhosis vs. Decompensated cirrhosis	**Compensated cirrhosis**
Post-liver Transplant?	**No**
Full medication regimen	**Lisinopril and Amlodipine**

Treatment Guidelines- Treatment Naïve

Genotype	Recommended	Recommended	Recommended	Recommended
1a or 1b	LDV/SOF x 12 weeks*	GLE/PIB x 8 - 12 weeks	SOF/VEL x 12 weeks	EBR/GZR x 12 weeks+
2	GLE/PIB x 8 - 12 weeks		SOF/VEL X 12 weeks	
3	GLE/PIB X 8 - 12 weeks		SOF/VEL X 12 weeks	
4	LDV/SOF x 12 weeks	GLE/PIB x 8 - 12 weeks	SOF/VEL x 12 weeks	EBR/GZR x 12 weeks
5 or 6	LDV/SOF x 12 weeks	GLE/PIB x 8 – 12 weeks	SOF/VEL x 12 weeks	n/a

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

AASLD/IDSA. HCV Guidance, 2018. https://www.hcvguidelines.org/

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

AASLD/IDSA. HCV Guidance, 2018. https://www.hcvguidelines.org/

Treatment Guidelines- 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

LDV = Ledipasvir, SOF = Sofosbuvir, VEL= Velpatasvir, VOX= Voxilaprevir, GLE= Glecaprevir, PIB= Pibrentasvir, DCV = Daclatasvir, RBV = Ribavirin, EBR= Elbasvir, GZR= Grazoprevir, OBV = Ombitasvir, PTV = Paritaprevir, r = Ritonavir, SIM = Simeprevir

AASLD/IDSA. HCV Guidance, 2018. https://www.hcvguidelines.org/

Treatment Guidelines- Other Special Populations

- Decompensated Cirrhotics: *Specialist referral*:
  - LDV/SOF + RBV x 12 weeks OR
  - SOF/VEL + RBV x 12 weeks OR
  - DCV + SOF + RBV x 12 weeks
- Post-Liver Transplant
  - LDV/SOF + RBV x 12 weeks OR
  - GLE/PIB x 12 weeks
- Renal Impairment
  - CrCl > 30mL/min: all regimens ok
  - CrCl < 30mL/min
    - EBR/GZR x 12 weeks OR
    - GLE/PIB x 8-16 weeks

AASLD/IDSA. HCV Guidance, 2018. https://www.hcvguidelines.org/

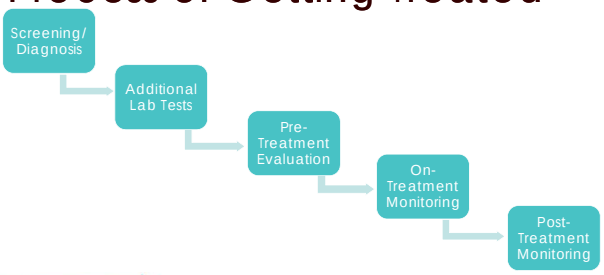
Drug-Drug Interaction Concerns with DAAs

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

Useful reference:
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

Chruscinski, Personal Communication May 2018.

Pharmacist Role in Screening

- Veterans Affairs Initiatives
  - Screen patients born between 1945 and 1965
  - Identify patients from national database
  - Call by nurse or pharmacist to arrange for screening lab
  - If positive result, pharmacist calls to explain diagnosis to patient

US Dept of Veterans Affairs. https://www.hepatitis.va.gov/index.asp
Atherton, Personal Communication May 2018.

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

Chruscinski, Personal Communication May 2018.

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

US Dept of Veterans Affairs. https://www.telehealth.va.gov/real-time/index.asp

Chruscinski, Personal Communication May 2018.

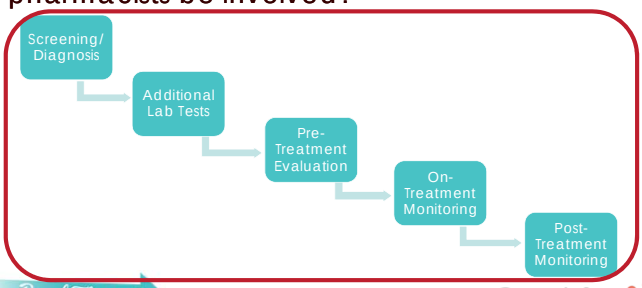
Pharmacist Role After Treatment

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

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

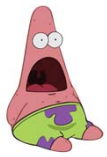
Chruscinski, Personal Communication May 2018.

At what steps in the process can pharmacists be involved?



New and Upcoming Gram Negative Drugs

Approved/Upcoming Gram Negative Drugs



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

Upcoming
- Omadacycline
- Eravacycline
- Cefiderocol
- Imipenem/relebactam

Ceftolozane/Tazobactam (Zerbaxa)

- FDA Indications:
  - Complicated intra-abdominal infections (cIAI) (+ metronidazole): 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)

Zerbaxa (Ceftolozane/tazobactam) Prescribing Information, Merck Pharmaceuticals, 2017.

Ceftazidime/Avibactam (Avycaz)

- FDA Indications:
  - cIAI (+ metronidazole): non-inferior to meropenem
  - 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

Avycaz (Ceftazidime/avibactam) Prescribing Information, Allergan Inc, 2018.

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

Vabomere (Meropenem/vaborbactam) Prescribing Information, Merck Pharmaceuticals, 2017.

Comparison of the new Beta-lactams

Class of Beta-Lactamase	Enzymes	Ceftolozane/ tazobactam	Ceftazidime/ avibactam	Meropenem/ vaborbactam
Class A (Serine)	TEM	✓	✓	✓
	SHV	✓	✓	✓
	CTX-M	✓	✓	✓
	KPC (CRE)	None	✓	✓
Class B (MBLs)	IMP/VIM	None	None	None
	NDM	None	None	None
Class C (Serine)	Amp C	Variable	✓	✓
Class D (Serine)	OXA	Variable	Variable	None

Zerbaxa (Ceftolozane/tazobactam) Prescribing Information, Merck Pharmaceuticals, 2017.
Avycaz (Ceftazidime/avibactam) Prescribing Information, Allergan Inc, 2018.
Vabomere (Meropenem/vaborbactam) Prescribing Information, Merck Pharmaceuticals, 2017.
Adapted from: http://www.gulfcoastconsortia.org/wp-content/uploads/2018/01/Current-and-Emerging-Therapies-for-the-Treatment-of-Infectious-Diseases-Kristi-Kuper-Valent.pdf

Comparison of the new Beta-lactams

	Ceftolozane/ tazobactam	Ceftazidime/avibactam		Meropenem/ vaborbactam
cUTI Trials				
Comparator	Levofloxacin	Doripenem	Best Available Therapy	Piperacillin/ tazobactam
Success Rate at Test of Cure	76.9% (vs. 68.4%)	71.2% (vs. 64.5%)	70.1% (vs. 54%)	76.5% (vs. 73.2%)
cIAI Trials				
Comparator	Meropenem	Meropenem		n/a
Success Rate at Test of Cure	83% (vs. 87.3%)	81.6% (vs. 85.1%)		n/a
Adverse Events	Nausea, diarrhea, headache	Diarrhea, nausea, vomiting		Headache, phlebitis, diarrhea

Zerbaxa (Ceftolozane/tazobactam) Prescribing Information, Merck Pharmaceuticals, 2017.
Avycaz (Ceftazidime/avibactam) Prescribing Information, Allergan Inc, 2018.
Vabomere (Meropenem/vaborbactam) Prescribing Information, Merck Pharmaceuticals, 2017.

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)

Baxdela (Delafloxacin) Prescribing Information, Melinta Therapeutics, Inc. 2017.

Plazomicin

- New aminoglycoside
- EPIC trial: cUTI
  - Non-inferior to meropenem
- 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

FDA Briefing Document for Plazomicin. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM606039.pdf

Eravacycline

- Fully synthetic fluorocycline (tetracycline-like)
- cIAI:
  - IGNITE1- non-inferior to ertapenem
  - IGNITE4- non-inferior to meropenem
- cUTI
  - IGNITE2- inferior to levofloxacin
  - IGNITE3- inferior to ertapenem
- Dose: 1mg/kg IV every 12 hours
- Activity vs. *Pseudomonas*, ESBL-producing organisms, CRE, Carbapenem-resistant *Acinetobacter*

Tetraphase Pharmaceuticals. http://ir.tphase.com/news-releases/news-release-details/tetraphase-pharmaceuticals-announces-submission-new-drug
Tetraphase Pharmaceuticals. http://ir.tphase.com/news-releases/news-release-details/tetraphase-announces-top-line-results-ignite3-phase-3-clinical

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
- Acute cystitis trial ongoing
- Activity vs. ESBL-producing organisms

Cho et al. Drugs of Today 2018;54(3):209-217.

Summary of New/Upcoming Drugs

CRE Activity	Other Activity/Role
Ceftazidime/avibactam	Ceftolozane/tazobactam (ESBL, *Pseudomonas*)
Meropenem/vaborbactam	Delafloxacin (Gram positives)
Plazomicin	Omadacycline (Gram positives)
Eravacycline	

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!

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

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