HEPATITIS C : RECENT ADVANCES IN SCREENING & MANAGEMENT

“C” Stands for Cure….

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Grant Support
- Gilead

• I will be discussing off-label use of medications
OUTLINE

• Epidemiology
• Screening guidelines
• Natural history and assessment
• Extra-hepatic manifestations
• Treatment strategies
VIROLOGY
HEPATITIS C VIRUS (HCV)

Member of flaviviridae family

- Six genotypes and subgenotypes
  - vary by region
  - important predictor of treatment response
GLOBAL BURDEN OF HCV

170 million chronically infected
3 – 4 million new infections/year
Peak incidence in early 90’s
Currently experiencing “maturation” of this peak
RECENT TRENDS IN HCV INCIDENCE (US)

Zibbell JE  Am J Public Health 2018
ALARMING TRENDS....,

• New infections ballooned nationally from 850 (2010) to 2,436 (2015)
  – highest rates among 20-29 year-olds, who inject drugs,
  – CDC estimates true number is much higher 34,000 new infections nationally for 2015
HCV BURDEN IN THE US

1.3-1.9% Ever Infected with HCV

2.7-3.9 million in US Living with Chronic HCV

12,000 Annual Deaths Associated with chronic liver disease and HCV

Hajarizadeh B. Nature Reviews Gastroenterology & Hepatology 2013 ;10, 553-562
DYNAMICS OF HCV PREVALENCE
IN THE US

Hepatitis C Prevalence

New HCV Infections
Spontaneous Clearance

Deaths
Treatment Cures
Reinfection

Source: Illustration by David H. Spach, MD
Sources of Infection for Persons With Hepatitis C

- Injecting drug use 60%
- Sexual 15%
- Transfusion 10% (before screening)
- Occupational 4%
- Other 1% *
- Unknown 10%

* Nosocomial; iatrogenic; perinatal

Source: Centers for Disease Control and Prevention
CHRONIC HCV INFECTION HAS SERIOUS CLINICAL CONSEQUENCES

CHRONIC LIVER DISEASE ~60%–70% of patients with HCV

CIRRHOSIS 5%–20% of patients infected with HCV over 20–30 years

HEPATOCELLULAR CARCINOMA ~1%–5% annually in HCV-related cirrhosis

LIVER TRANSPLANT 40% of all liver transplants are HCV-related. HCV is #1 cause of liver transplant

DEATH ~1%–5% of HCV-infected patients will die from the consequences of chronic HCV infection

PROJECTED DEATHS FROM HEPATITIS C

The graph shows the projected number of deaths from hepatitis C from 2010 to 2058. The number of deaths is expected to increase until around 2030 and then decline thereafter.
WHY SHOULD WE CARE?

TWO REASONS….
1. Hepatitis C is a major contributor to death and disease worldwide
2. It is now CURABLE

HIV
Genetic material, stored in the host cell nucleus, integrates into host DNA\(^2\)

HCV
After binding, HCV RNA remains in cytoplasm and is a target for host cell antiviral mechanisms\(^1,3\)
HEPATITIS C IS A SILENT DISEASE…

- Only 50% have symptoms in early stages
- Main symptoms
  - Fatigue
  - Nonspecific aches
  - Depression
Approximately 3.2 million in the US have chronic HCV infection\(^1,2,\)*

1.6 million (50%) diagnosed\(^3,4\)

170,000 – 200,000 (5 – 6%) were successfully treated\(^4,5\)

*Prevalence estimate based on NHANES data from 1999 through 2002.\(^1,2\) NHANES data underestimate the actual prevalence of HCV in the US by not accounting for incarcerated, homeless, hospitalized, nursing home and active military duty populations.\(^6,7\)

HCV SCREENING STRATEGIES

• Risk-based (CDC 1998)
  – Blood products before 1992
  – Intravenous drug use

• Limitations:
  – Providers reluctant to ask about risk factors
  – Patients reluctant to disclose risk

45-60% UNAWARE OF INFECTION
2012 CDC Recommendations for Birth Cohort Screening

- **Recommendation 1**
  - Adults born from 1945 to 1965 should receive one-time testing for HCV without prior ascertainment of HCV risk
  
  *Grade: strong recommendation*
  
  *Evidence: moderate-quality*

- **Recommendation 2**
  - All persons identified with HCV infection should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services for HCV infection and related conditions as indicated
  
  *Grade: strong recommendation*
  
  *Evidence: moderate-quality*

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Updated USPSTF HCV Screening Recommendations (2013)

**Risk Assessment:**

• Those at high risk for HCV infection:
  – Most important risk factor is past or current injection drug use
  – Additional risk factors include:
    • Receiving a blood transfusion before 1992
    • Long-term hemodialysis
    • Being born to an HCV-infected mother
    • Incarceration
    • Intranasal drug use
    • Getting an unregulated tattoo, and other percutaneous exposures

• Adults born between 1945 and 1965 (“Baby Boomers”)

*Grade B recommendation for persons at high risk for infection and adults born between 1945 and 1965.
Moyer VA; on behalf of the USPSTF. Ann Intern Med. 2013 Jun 11. [Epub ahead of print].
Updated USPSTF HCV Screening Recommendations (2013)

- **USPSTF Grade B recommendations regarding HCV screening**:  
  - Those at high risk for HCV infection  
  - Those born from 1945 to 1965 (one-time screening of “Baby Boomers,” regardless of risk

**The USPSTF gave this recommendation a Grade B**:  
- Grade B means there is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial

- **The Affordable Care Act**:  
  - Requires non-grandfathered private health plans to cover clinical preventive services given an A or B Grade by USPSTF without cost sharing  
  - Provides incentives for Medicaid programs to cover these services

USPSTF=United States Preventive Services Task Force.
1. Moyer VA; on behalf of the USPSTF. *Ann Intern Med*. 2013 Jun 11. [Epub ahead of print];
• Two of three Americans with HCV were born between 1945-1965
  – 5 times higher prevalence than others
  – 75% of all HCV + adults
  – 72% of HCV – related mortality
COST EFFECTIVENESS OF BIRTH COHORT SCREENING

• Six studies with prior therapies all favorable
• First study examining all-oral DAA
  • ICER* sensitive to fibrosis stage
    • $13K for cirrhosis - $173,800 for F0 per QALY **
  • ICER for new treatments $31k-$35 K per QALY

*Incremental cost effectiveness ratio
**Quality Adjusted Life Year

Cost-Effectiveness of HCV Testing vs Other Routine Preventive Services

*Birth cohort testing, 1945-1965.
2-drug treatment= PegIFN+RBV; 3-drug treatment= PegIFN+RBV+PI. QALY= quality-adjusted life-year.
Hepatitis C Virus

*Host Production of HCV Antibodies*

- HCV infects cell
- HCV proteins expressed on surface of hepatocytes
- Antibodies to HCV proteins produced by host
- HCV antibodies **DO NOT** convey immunity

Illustration by Mitchell L. Shiffman, MD.
Testing for Hepatitis C Virus

Anti-HCV Antibodies

- ELISA screening test
  - Sensitivity: 97%
  - Detects circulating HCV antibodies
- False positive reactions may occur
  - Cross-reacting circulating antibodies
  - Nonspecific binding of anti-HCV antibodies
- Positive predictive value
  - 95% with risk factors and elevated ALT
  - 50% without risk factors and normal ALT

Illustration by Mitchell L. Shiffman, MD.
HCV LINKAGE TO CARE

- Essential next step after identification of infection
- Implies access to specialized care
  - Assessment of natural history
  - Staging of liver disease
  - Triage to therapy
NATURAL HISTORY OF HCV

HCV Infection

Acute Infection, 20-30% with symptoms

Clearance of HCV RNA, 15%-25%

Fulminant Hepatitis, Rare

Chronic Infection, 75%-85%

Extrahepatic Manifestations

Chronic Active Hepatitis

Cirrhosis, 10%-20% over 20 years

 Decompensated Cirrhosis, 5-year survival rate of 50%

HCC, 1%-4% per year
Chronic Hepatitis C Virus
Extrahepatic Manifestations

- Nonspecific antibodies
- Essential mixed cryoglobulinemia
- Glomerulonephritis
- Porphyria cutanea tarda
- Leukocytoclastic vasculitis
- Mooren’s corneal ulcer
- Non-Hodgkin’s lymphoma
- Autoimmune thyroiditis
- Diabetes mellitus
- Sjögren’s syndrome
HCV and Cryoglobulinemia

Leukocytoclastic vasculitis

- Occurs in dependent areas
- Deposition of cryoglobulins in small capillaries
- Ulcerations may develop
- Pruritic
HCV and Cryoglobulinemia Manifestations

- Dermatitis (dependent areas)
- Vasculitis
- Myalgias (fibromyalgia?)
- Arthralgias (RA and/or ANA positive)
- Membranoproliferative glomerulonephritis
- Neuropathy
- Chronic fatigue syndrome (?)
HCV THERAPY
DAWN OF A NEW ERA?

Editorial | 21 February 2012
Hepatitis C: The End of the Beginning and Possibly the Beginning of the End
Harvey J. Alter, MD; and T. Jake Liang, MD
Goal of treatment

The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by an SVR.

Rating: Class I, Level A
GOALS OF HCV THERAPY

• Suppress viral RNA
• Improve liver histology
• Normalize liver biochemical tests
• Achieve sustained virological response

SVR = CURE

No viral reservoir (unlike HIV/HBV)
Hence: no reactivation
BENCH RESEARCH IN HCV PARALLELS DRUG DEVELOPMENT

HCV cDNA cloned

Jan 1990

HCV genotype classification

Jan 1995

HCV replicon developed

Jan 2000

HCV replicated in culture

Jan 2005

FDA guidance document on developing DAAs

SNPs near IL28B predict Peg-IFN + ribavirin response

Proof of concept for DAAs

Proof of concept for IFN-free regimens

IL28B added to Peg-IFN alfa-2b labeling

Clinical practice guidelines revised

Proof of concept for 4-drug regimens

DAAs boceprevir and telaprevir approved

IFN alfa-2b approved

IFN alfa-2a approved

IFN alfacon-1 approved

Peg-IFN alfa-2b approved

Peg-IFN alfa-2a approved

Jan 2010

June 25, 2018
EVOLUTION OF THERAPY IN HCV GT1

<table>
<thead>
<tr>
<th>Year</th>
<th>IFN 6m</th>
<th>IFN 12m</th>
<th>IFN/RBV 6m</th>
<th>IFN/RBV 12m</th>
<th>PEG/RBV 12m</th>
<th>PEG/R/PI 6-12m</th>
<th>PEG/R/PI 6-12m</th>
<th>All oral DAA 12-24 weeks</th>
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<tbody>
<tr>
<td>1990</td>
<td>2%</td>
<td>10%</td>
<td>15%</td>
<td>25%</td>
<td>40%</td>
<td>60%</td>
<td>75%</td>
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<td>1999</td>
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<td>2011</td>
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<td>2015</td>
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</table>
Multiple antiviral targets are available

DNA-directed RNA interference (ddRNAi)
TT-034 via Adeno-Associated Virus vector

NS3/4 Protease Inhibitors
- Simeprevir (SIM)
- Asunaprevir
- ABT-450/ritonavir (r)
- GS-9451

Entry inhibitors
- Receptor binding and endocytosis
- Fusion and uncoating
- Transport and release

NS5B Polymerase Inhibitors
- Sofosbuvir (SOF)
- GS-9669
- BMS-325
- Dasabuvir

NS5A Inhibitors
- Ledipasvir (LDV)
- Ombitasvir
- Daclatasvir (DCV)
- MK-8742

Cyclophylin Inhibitors

Antisense oligonucleotides
- Miravirsen (miR-122)

DNA-directed RNA interference (ddRNAi)
- TT-034 via Adeno-Associated Virus vector
## Antiviral All – Oral Therapies Currently Available

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Classes</th>
<th>Approved GT</th>
<th>SVR Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir+ribavirin</td>
<td>Nucleotide polymerase inhibitor + nucleoside analogue</td>
<td>1,2,3,4</td>
<td>84%</td>
</tr>
<tr>
<td>Sofosbuvir+simeprevir</td>
<td>Nucleotide polymerase inhibitor + protease inhibitor</td>
<td>1,4</td>
<td>83-94%</td>
</tr>
<tr>
<td>Sofosbuvir/ledipasvir</td>
<td>Nucleotide polymerase inhibitor + NS5A inhibitor</td>
<td>1,4,5,6</td>
<td>93-99%</td>
</tr>
<tr>
<td>Paritaprevir/ritonavir/ombitasvir/dasabuvir</td>
<td>Protease inhibitor + NS5A inhibitor</td>
<td>1</td>
<td>92-96%</td>
</tr>
<tr>
<td>Sofosbuvir+daclatasvir</td>
<td>Nucleotide polymerase inhibitor + NS5A inhibitor</td>
<td>1,3</td>
<td>86%-96%</td>
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<tr>
<td>Grazoprevir/elbasvir</td>
<td>Protease inhibitor + NS5A inhibitor</td>
<td>1,4</td>
<td>92-94%</td>
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<tr>
<td>Sofosbuvir/velpatasvir*</td>
<td>Nucleotide polymerase inhibitor + NS5A inhibitor</td>
<td>Pangenotypic</td>
<td>97-100%</td>
</tr>
<tr>
<td>Glecaprevir/pibrentasvir</td>
<td>Protease inhibitor + NS5A inhibitor</td>
<td>Pangenotypic</td>
<td>98-100</td>
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</table>
POST TREATMENT CARE
Sustained virological response 12 = CURE

<table>
<thead>
<tr>
<th>Patients with durable SVR (%)</th>
<th>All patients N=1343</th>
<th>HCV mono-infected</th>
<th>HIV-HCV co-infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy (abnormal ALT) N=166</td>
<td>99.1%</td>
<td>98.8%</td>
<td>99.0%</td>
</tr>
<tr>
<td>Combi-therapy (abnormal ALT) N=998</td>
<td>99.1%</td>
<td>99.1%</td>
<td>99.0%</td>
</tr>
<tr>
<td>Combi-therapy (normal ALT) N=79</td>
<td>100%</td>
<td>100%</td>
<td>99.0%</td>
</tr>
</tbody>
</table>

6/25/2018 39
SVR RESULTS IN IMPROVED OUTCOMES

All-cause mortality

Liver-related mortality or liver transplantation

Hepatocellular carcinoma

Liver failure

Van der Meer AJ. JAMA. 2012;308(18):2584-2593.
Reduction in Liver Transplant Waitlist in the Era of HCV DAAs

Cohort study of 47,591 adults wait-listed for liver transplant (LT WL) using the Scientific Registry of Transplant Recipients database from 2003–2015

Annual Standardized Incidence Rates (ASIR) of LT Wait-Listing per 100,000 US Population

- **Overall**
- ** Decompensated cirrhosis**
- **HCC**

The rate of liver transplant wait-listing for HCV secondary to decompensated cirrhosis has decreased by 32% in the era of DAA therapy as compared to the IFN era and is now equal to that of NASH.

MONITORING CURED PATIENTS

- HCV provider should check HCV RNA until 24 weeks after treatment (SVR24)
- No standard guidelines for further monitoring
  - Check HCV RNA if change in clinical condition
- HCV antibody remains positive for life
  - not protective
- If underlying cirrhosis/ advanced fibrosis
  - Needs surveillance for HCC / varices
WHO RESOLUTION 2017
Elimination of viral hepatitis by 2030

- 90% reduction in HCV incidence is possible by 2030
  - Depends on diagnosing at least 110,000 cases / year until 2020
  - 89,000 cases/year 2020-24
  - 70,000 cases/ year 2025-2030

- NASEM report 2017
ESSENTIAL INTERVENTIONS

• Improve treatment access
  – Universal availability of DAA
  – Build capacity to treat in primary care settings
• Expanded access to syringe exchange and opioid agonist therapy
  – PWID account for 75% of new cases

June 25, 2018
Hepatitis C in India

Cost of Sofosbuvir

<table>
<thead>
<tr>
<th>Country</th>
<th>Per tablet (400 mg)</th>
<th>24 weeks treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>1000 $</td>
<td>11.4 million Rupees</td>
</tr>
<tr>
<td>India</td>
<td>660 Rupees</td>
<td>1.2 lakh Rupees</td>
</tr>
</tbody>
</table>

Dhiman et al.
J Clin Exp Hepatol Sep 2016
WHAT IS ON THE HORIZON?

- Pan genotypic regimens
- Short duration
- High barrier to resistance
- Affordable and accessible
CHALLENGES IN HCV MANAGEMENT

• Cost of treatment
  $92 k / course

• Viral resistance

• Effective screening

• Linkage to care
SUMMARY

• Hepatitis C is widely prevalent but mainly unrecognized
• Untreated HCV has serious consequences
• Current guidelines endorse screening all baby boomers and those with risk factors
SUMMARY

• All-oral therapies now standard of care
• Ribavirin necessary for some, not all
• Cirrhosis requires longer duration of therapy, especially in treatment experienced subjects
TAKE HOME POINT

▪ HEPATITIS C IS A CURABLE DISEASE

▪ TREATMENT SHOULD BE OFFERED TO ALL THOSE INFECTED