Joint Session with ACOFP and Cleveland Clinic: Managing Chronic Disease

The Shadow Plague (Hepatitis C)

William Carey, MD
The Shadow Plague
Hepatitis C

OMED 17

William Carey MD, MACG, FAASLD
Professor of Medicine
Cleveland Clinic Learner College of Medicine/ Case Western Reserve University

[Image of an old book cover with text]
Few or no symptoms
Infection present for decades
Lethal in ~10%

Hepatitis C Virus
Goals

Brief History of HCV

Why HCV Matters

World Health Organization Position

Case Finding

Drugs

Barriers to WHO goal of Elimination by 2030

Viral Hepatitis C Pre History

• Dame Sheila Sherlock – Disease of the Liver 7th edition 1985 – Virus Hepatitis

• “There are 3 main varieties [of viral hepatitis]. Hepatitis A is a self limited, feacally spread disease. Hepatitis B is a parenterally transmitted disease that often becomes chronic. Non A Non B hepatitis is ill-defined. It contains many types, some feacally, others parenterally transmitted.”
Viral Hepatitis C Contemporary History

Michael Houghton
Hepatitis C virus (HCV): model structure and genome organisation

Expert Reviews in Molecular Medicine © 2003 Cambridge University Press

CDC Expands Hepatitis C Testing Recommendations

CDC issues broader recommendations for the prevention of Hepatitis C virus (HCV) infection and testing people at risk for HCV infection.

https://www.cdc.gov/knowmorehepatitis/timeline.htm
Realizing the potential of an all-oral cure
Outcomes such as advanced liver disease and/or hepatocellular cancer can be prevented with treatment, which is rapidly improving. New treatment options offer the potential of a cure to more patients than has been previously possible.

https://www.cdc.gov/knowmorehepatitis/timeline.htm

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Why Hepatitis C Matters

• 4/180 million in US/world infected
• Lifelong infection for 50%-80%
• Consequences for those infected
  – Decreased QOL
  – 10% > Cirrhosis and/or liver cancer

Hepatitis C-related deaths in 2013 surpassed the total combined number of deaths from 60 other infectious diseases reported to the CDC, including HIV, tuberculosis, and pneumococcal disease.
A Patient’s Perspective

October 1, 2014

Dear Dr. Carey,

In January of this year I came to see you about the new hepatitis C drugs the FDA had just approved.

I am happy to say my insurance finally approved the payment for the medication. The side effects have been mild, nothing like the side effects of the interferon treatment of 2007/08.

After only 2 weeks the viral count went from 1.4 million to undetectable. After treatment was over the viral count remained undetectable.

Needless to say, I am thrilled with the results and that, at my age, I have been given a second chance at living a healthy life. This is the best present I could ever receive. I no longer am living with the “Sword of Damocles” poised over your head. Most of the people I’ve talked to who have undergone the treatment feel this way.

Thank you from the bottom of my heart.

MEF
New York

How Is Hepatitis C Spread?

• Blood transfusion prior to 1992
• Intravenous drug use
• Intranasal cocaine
• Body piercing, tattoos
• Mother to baby (< 5%)
• Sexual transmission rare
Hepatitis C - Clinical Features

Incubation period: Average 6-7 wks
Range 2-26 wks
Clinical illness (jaundice): very uncommon
Chronic hepatitis: 70%
Persistent infection: 70%-85%
Immunity: No protective antibody response identified
Goals

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EXECUTIVE SUMMARY

Hepatitis B and C: a heavy burden of mortality that is increasing

In 2013, viral hepatitis was a leading cause of death worldwide (1.46 million deaths, a toll higher than that from HIV, tuberculosis or malaria, and on the increase since 1990) (1). More than 90% of this burden is due to the sequelae of infections with the hepatitis B virus (HBV) and hepatitis C virus (HCV) (1). Prevention can reduce the rate of new infections, but the number of those already infected would remain high for a generation. In the absence of additional efforts, 19 million hepatitis-related deaths are anticipated from 2015 to 2030 (2). Treatment now can prevent deaths in the short- and medium term.
**Box 6 Main assumptions used by WHO to cost the elimination strategy**

- Cost of treatment for hepatitis A: US$ 60/year (current price for a 2-dose in public-sector HAV programmes).
- Cost of treatment for hepatitis D: US$ 500/year (price for a 3-month course in low and middle-income countries).

**Figure 2** Estimation of the cost of the strategy to eliminate viral hepatitis B and C as public health problems by 2030 in low-income and middle-income countries.

**Table 2** Deaths prevented as a result of implementation of the Global Health Sector Strategy for Viral Hepatitis, 2015–2030

<table>
<thead>
<tr>
<th></th>
<th>Upper-income countries</th>
<th></th>
<th>Middle-income countries</th>
<th></th>
<th>Lower-income countries</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Upper</td>
<td>Lower</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAV-associated</td>
<td>520 000</td>
<td>1 390 000</td>
<td>2 680 000</td>
<td>420 000</td>
<td>5 000 000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV-associated</td>
<td>590 000</td>
<td>650 000</td>
<td>750 000</td>
<td>100 000</td>
<td>2 100 000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1 110 000</td>
<td>2 050 000</td>
<td>3 430 000</td>
<td>520 000</td>
<td>7 100 000</td>
<td></td>
<td></td>
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</tbody>
</table>
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Screening

Impact of HCV Cure

Compared to those who did not achieve cure after treatment

Hepatocellular cancer- 68-79% reduction
Death: 60-84% reduction
Liver Transplant: 90% reduction

Hill et al. Hepatology 2014; 60:219A
Birth Cohort Screening for HCV

• HCV is a major cause of morbidity and mortality in the US
• 70% of infected individuals are unaware
• 70% of infections are in those born between 1945-1965
• CDC and USPTF recommend birth cohort screening as well as for those with risk factors
• BCS alone will miss younger patients!!!

Cost- Effectiveness of Birth Cohort Screening in the US

• Retrospective review of all studies since CDC 2012 recommendation for birth cohort screening
• 6 studies
• Mean cost screening: $213
• QALYS 0.005
• ICER $39,993
• All studies found BC testing cost effective at a “willingness to pay” below $65,000 per QALY

Rein et al. Hepatology 2013; 58: 391A
Whom To Treat?

Projected Effect of Birth Cohort Screening and All Oral Therapy

Markov Model was constructed to explore relative value of 4 strategies

A. Screen for HCV based on risk and treat only if significant fibrosis on biopsy

B. Screen for HCV based on risk and treat regardless of fibrosis score

C. Birth cohort screening and treat only if significant fibrosis on biopsy

D. Birth cohort screening and treat all regardless of fibrosis score

Younossi et al. Hepatology 2014; 60: 256A
### Projected Effect of Birth Cohort Screening and All Oral Therapy

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cirrhosis</strong></td>
<td>56%</td>
<td>55%</td>
<td>6%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>** Decompensation**</td>
<td>17%</td>
<td>17%</td>
<td>3%</td>
<td>1.5%</td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td>15%</td>
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<td>3%</td>
</tr>
<tr>
<td><strong>Transplant</strong></td>
<td>7%</td>
<td>7%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Life expectancy years</strong></td>
<td>19</td>
<td>20</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td><strong>Cost per unknown HCV x 1000</strong></td>
<td>$66</td>
<td>$69</td>
<td>$71</td>
<td>$75</td>
</tr>
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</table>

Compared to strategy A, strategy D cost an extra $123 billion but produced an additional 22.9 million QALYs ($5371/QALYs).

**Conclusion:** Availability of highly efficacious and well tolerated oral agents makes birth cohort screening of baby boomers highly cost-effective with great health and economic benefit at the population level.

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### Goals

- Brief History of HCV
- Why HCV Matters
- World Health Organization Position
- Case Finding
- Drugs
- Barriers to WHO goal of Elimination by 2030
What Medicine?

Current high efficacy treatments combine drugs aimed at different HCV targets.

<table>
<thead>
<tr>
<th>PROTEASE INHIBITORS</th>
<th>POLYMERASE INHIBITORS</th>
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<th>NSSA INHIBITORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non Structural</td>
<td>Structural</td>
<td></td>
<td></td>
</tr>
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Projected Effect of Birth Cohort Screening and All Oral Therapy

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Treatment
Ideal Treatment

• Single daily dose
• Short course
• Oral administration
• Inexpensive
• Highly effective
• Infection cured
• Freedom from side effects

Seminal HCV Treatment Studies
November 30, 1989
Hepatitis C, a Silent Killer, Meets Its Match

Over the next three years, starting within the next few weeks, new drugs are expected to come to market that will cure most patients with the virus, in some cases with a once-a-day pill taken for as little as eight weeks, with only minimal side effects. That would be a vast improvement over current therapies, which cure about 70 percent of newly treated patients but require six to 12 months of injections that can bring horrible side effects. But the new drugs are expected to cost from $60,000 to more than $100,000 for a course of treatment.
**A Short History of Treatment**

<table>
<thead>
<tr>
<th>Agent</th>
<th>SVR for G1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>0%</td>
</tr>
<tr>
<td>Interferon</td>
<td>15%</td>
</tr>
<tr>
<td>Pegylated interferon</td>
<td>30%</td>
</tr>
<tr>
<td>Pegylated interferon+Ribavirin</td>
<td>45%</td>
</tr>
<tr>
<td>PIFN+R + boceprevir</td>
<td>65%</td>
</tr>
<tr>
<td>PIFN+R + telaprevir</td>
<td>70%</td>
</tr>
<tr>
<td>Current DAA agents</td>
<td>95-100%</td>
</tr>
</tbody>
</table>

http://www.hcvguidelines.org/
### Factors Influencing Treatment Selection or Outcome - Then

<table>
<thead>
<tr>
<th>Age</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>IL28B genotype</td>
</tr>
<tr>
<td>Race</td>
<td>Baseline HCV RNA</td>
</tr>
<tr>
<td>BMI</td>
<td>Renal Failure</td>
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<tr>
<td>HCV Genotype</td>
<td>Others</td>
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<td>Need for ribavirin</td>
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</tr>
</tbody>
</table>
Treatment Choices in Late 2017

HCV Drugs USA October 2017

<table>
<thead>
<tr>
<th>First Tier</th>
<th>Second Tier or niche</th>
</tr>
</thead>
<tbody>
<tr>
<td>glecaprevir/pibrentasvir (August 2017)</td>
<td>sofosbuvir/velpatasvir/voxilaprevir</td>
</tr>
<tr>
<td>sofosbuvir/velpatasvir</td>
<td>sofosbuvir/Ledipasvir (former #1)</td>
</tr>
<tr>
<td></td>
<td>daclatasvir</td>
</tr>
<tr>
<td></td>
<td>elbasvir/grazoprevir</td>
</tr>
<tr>
<td></td>
<td>ombitasvir/paritaprevir/ritonavir</td>
</tr>
</tbody>
</table>
Newest HCV Drug Combination
Glecaprevir/pibrentasvir (August 2017)

Before Discount Cost = $13,200 per month

Treatment of DAA Failures
Polaris 1, Polaris 4 studies

Patients previously treated with DAA: treatment Failures
415+ 333= 748 patients enrolled at over 100 sites across the world

Polaris 1: Cure  96%
Polaris 2: Cure  98%

Equally effective regardless of age, sex, race, HCV genotype, cirrhosis, viral load

Bourliere et al. NEJM June 2017; 376: 2134
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Cost - The Final Barrier
Expenditures on Drugs In US Increased 3-Fold in 20 Years


US prescription drug spending as high as $610 billion by 2021: Report

- Spending on prescription medicines in the U.S. will increase 4% to 7% through 2025.
- Under pressure from politicians and insurers over the cost of many branded medicines, several drugmakers have pledged to limit annual price hikes to under 10 percent.

PUBLISHED 05/17/2017 6:55 AM EDT
How much is $1 Billion?

Changing Patterns of HCV Treatment in Germany

Management of HCV by the Non Specialist

ALL must be engaged in screening for this highly treatable disease

Many should be encouraged and trained to treat HCV infected

Professional societies must advocate for removing restrictions of treating health care providers

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### Barriers to HCV Eradication by 2030

<table>
<thead>
<tr>
<th></th>
<th>US</th>
<th>Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective RX</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Prescriber Base</td>
<td>GI and ID only</td>
<td>All providers (increase 4% &gt; 19% of GPS in 2016)</td>
</tr>
<tr>
<td>Patient exclusions</td>
<td>Lack of significant fibrosis No RX</td>
<td>Rx all</td>
</tr>
<tr>
<td></td>
<td>Alcohol - No RX</td>
<td>Rx</td>
</tr>
<tr>
<td></td>
<td>Cannabis - No Rx</td>
<td>Rx</td>
</tr>
<tr>
<td></td>
<td>IV drugs – No RX</td>
<td>Rx</td>
</tr>
<tr>
<td></td>
<td>Re infection- ?</td>
<td>Rx</td>
</tr>
<tr>
<td>Negotiated Discounts</td>
<td>Limited</td>
<td>Yes- major discounts, max expenditure per year, no cap on # treated</td>
</tr>
</tbody>
</table>

Dore. J Hepatology 2017; 67:415
There are not enough HCV treating health care providers
Treatment is easy
Monitoring not time consuming
Treatment is effective
Side effects infrequent

Ideal candidate for treatment by the non specialist
A young mono-infected individual without evidence of advanced liver disease
  normal platelet count and liver tests except AST/ALT
  normal liver US
  normal renal function
  takes no medications
  anti HBc AB negative

Continue to leave to the specialist
  Cirrhosis – certain or possible
  Pre and post transplant
  HCV-HIV Co-infected
  Previously treated
  Those with anti HBc
Remaining Challenge

Creating a sustainable model for HCV treatment

Capacity
Cost
Reimbursement

Conclusions

Hepatitis C is easily curable

WHO goal of eradication by 2030 is achievable

Practitioners of all specialties are part of the team
Thank You