

## Liver Disease Research Updates

Nikunj Shah, MD  
Medical Director of Liver Transplantation  
Associate Professor of Medicine  
University of Illinois Medical Center

## Liver Disease Research

- What is research?
- Types of Research
- Research in various types of liver diseases
- Funding for research
- Future Research in liver diseases diagnosis and treatment

## What is Research?

- Main Entry: **1re·search**  
Pronunciation: ri-'s&rch, 'rE-"  
Function: *noun*  
Etymology: Middle French *recherche*, from *rechercher* to go about seeking, from Old French *recherche*, from *re-* + *cerchier*, *sercher* to search -- more at [SEARCH](#)  
**1** : careful or diligent search  
**2** : studious inquiry or examination; *especially* : investigation or experimentation aimed at the discovery and interpretation of facts, revision of accepted theories or laws in the light of new facts, or practical application of such new or revised theories or laws  
**3** : the collecting of information about a particular subject
- From Merriam-Webster Dictionary

## Types of Research

- Basic Research
- Clinical Research
- Translational Research

## Basic Research

- Research using cells like liver cells (hepatocytes)
- Research using animals (mice, chimpanzees etc.)

## Clinical Research

- Retrospective collection and analysis of data to evaluate epidemiology, prevalence natural history and outcome of treatments
- Prospective study of above information about various liver diseases
- Drug trials for efficacy of new and approved drugs

## Research: Liver diseases

- Viral Hepatitis B , C and other viruses
- Alcohol related liver disease
- Non-alcoholic fatty liver disease
- Autoimmune Liver diseases
- Complications of Cirrhosis
- Liver Cancer
- Liver Transplantation

## Research : Hepatitis B

- Vaccine
- Treatment of Hepatitis B: new drugs
- Hepatitis B and liver cancer
- Hepatitis B and liver transplantation

## Hepatitis B

- Vaccine available and protects for many yrs.
- Combination Hepatitis A and B vaccine available
- All patients with liver disease should get vaccine against Hepatitis A and B

## HEPATITIS A VACCINES

- Highly immunogenic
  - 97%-100% of children, adolescents, and adults have protective levels of antibody within 1 month of receiving first dose; essentially 100% have protective levels after second dose
- Highly efficacious
  - In published studies, 94%-100% of children protected against clinical hepatitis A after equivalent of one dose



## HEPATITIS A VACCINES

### Recommended Dosages of Hepatitis A Vaccines

Schedule Vaccine	Age (yrs)	Dose	Volume (mL)	2-Dose (mos)
HAVRIX <sup>®</sup> #	2-18	720 (EL.U.*)	0.5	0, 6-12
	>18	1,440	1.0	0, 6-12
VAQTA <sup>®</sup> ##	2-18	25 (U**)	0.5	0, 6-18
	>18	50	1.0	0, 6-18

\* EL.U. – Enzyme-linked immunosorbent assay (ELISA) units

\*\* Units

# has 2-phenoxyethanol as a preservative

## has no preservative



### HBV

### Commercially Available Recombinant Vaccines

Trade Name	Source	Manufacturer	Licensed in U.S.
Engerix-B	Yeast	SmithKline Beecham	Yes
Recombivax HB	Yeast	Merck	Yes
Bimmugen	Yeast	Kaketsuken	No
Eichi-Bi-Wai	Yeast	Green Cross	No
Heprecomb	Yeast	Berna	No
Genhevac B	*CHO cells	Pasteur-Merieux	No
r-HB Vaccine	*CHO cells	Mitsubishi	No

\*Chinese hamster ovary



## Combination Vaccines

- Combination of Hepatitis a and B vaccines
- Twinrix : 18 yrs and older, combination of Havrix(720) and Engerix(20)
- Comvax : 6 weeks to 4 yrs, combination of Recombivax (%) and Pedvaxhib
- Pediarix : 6 weeks to 6 yrs, Engerix (10), infanrix (DTaP) and IPV
- All require 3 doses

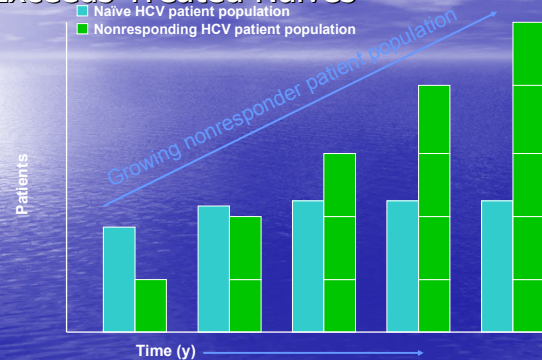
## Treatment of Hepatitis B

- Current Approved Drugs  
Interferon, Lamivudine  
Adefovir, Entecavir
- Drugs in Clinical Trials  
Tenofivir, Telbuvudine
- Combination drugs in future

## Research: Hepatitis C

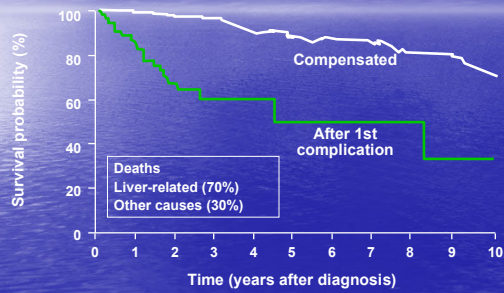
- Treatment of Chronic Hepatitis  
Current Treatment  
New Drugs
- Basic research in Virology  
Viral Kinetics  
Viral resistance
- Vaccine for prevention and treatment

## Nonresponder Growth Exceeds Treated Naïves



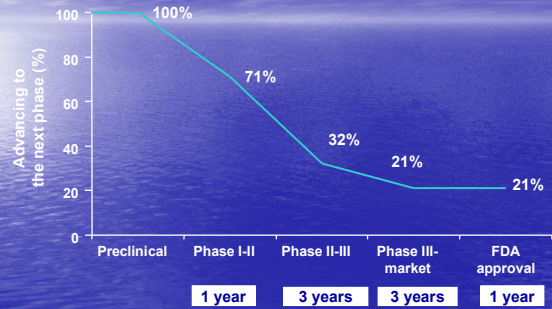
Data on file.

## Natural History of HCV Cirrhosis



Adapted from: Fattovich G, et al. *Gastroenterology*. 1997;112:463-472.

## Wait for New Agents to Be Developed: New Therapies Will Not Be On the Market for the Next Several Years



DIMasi JA, et al. *J Health Econ*. 2003;22:151-185.

## Clinical Trials: HCV Therapies in the Pipeline

Company	Product	Status	Description
IDPA	Transfersome® IFN	Ph. I	Transfersome + IFN alpha
Roche Pharmaceuticals	Mycophenolic acid	Ph. I	Mycophenolic acid
AbbVie	ANA-2515	Ph. I/II	Nucleoside
Coley Pharmaceuticals Group	Adclon™	Ph. I/II	Toll-like receptor agonist
Chiron/C3i	HCV-MF59 vaccine	Ph. I	Vaccine
VirPharma	HCV-796	Ph. I	Polymerase inhibitor
Vantex Pharmaceuticals	VX-950	Ph. II	NS3-4A Protease inhibitor
Scering-Plough	SCH 503034	Ph. II	Protease inhibitor
Human Genome Sciences	Albuteferon-Alpha™	Ph. III	Fusion albumin + IFN alpha
Amnolyt Biosciences	IFN alpha	Ph. II	Oral formulation
Amnolyt	Omega IFN	Ph. II	IFN omega
InterSine	Interferon gamma 1-b	Ph. II	IFN gamma 1-b + Interferon alfacon-1 +/- RBV
Pharmal Technologies	Medusa® interferon	Ph. II	Long-acting IFN alpha
Viragen	Multiferon™	Ph. II	Multi-subtype human alpha IFN
Idenix Pharmaceuticals	Valopicitabine (NM283)	Ph. II	Polymerase inhibitor
Innogenetics	HCV E1 vaccine	Ph. II	HCV E1 protein
Intercell	IC41	Ph. II	Therapeutic vaccine
Valeant	Interferon alfacon-1	Ph. III	IFN (daily dose) + RBV
Valeant	Viramidine®	Ph. III	RBV prodrug
Sci-Cione	Zadaxin®	Ph. III	Thymosin alpha 1 immune modulator
Ares Serono	Rebif®	Ph. III	r-IFN beta

## Research: ASH and NAFLD

- Why only some people develop?
- Associated factors for both conditions
- Diagnosis of both conditions
- Natural history
- Pathogenesis
- Treatment of ASH and NASH

## Treatment of NAFLD

- No approved treatment
- Treatments in trial: Vitamin E, other alternative medicines
- Drugs in trials: urso-deoxy cholic acid, rosiglitazone, Pentoxifylline

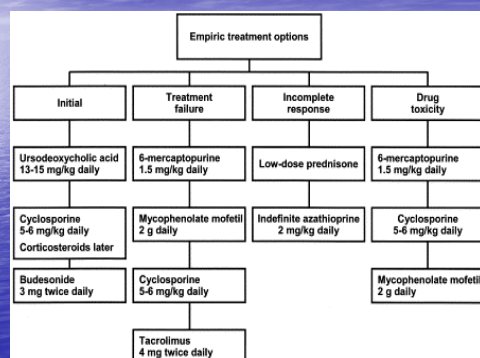
## Research: AIH and Overlap Syndromes

- Causes of autoimmune liver diseases
- Diagnosis of autoimmune hepatitis and overlap syndromes
- Treatment for both diseases

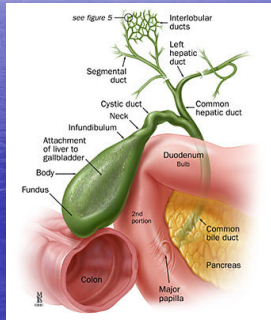
## AIH : Treatment

- Relapse after drug withdrawal
- Drug toxicity
- Treatment failure despite compliance (9%)
- Incomplete response (13%)

## AIH : Evolving Therapies



## Normal Biliary tract



## Primary Biliary Cirrhosis

- Chronic Cholestatic Liver Disease
- Female to male ratio 9:1
- Etiology unknown
- ? Autoimmune
- Genetic factors, HLA relationship
- Epidemiology: variability due to case finding

## Diagnosis Of PBC

- Lab. Tests : elevated Alk. Phosph. >3-5 times normal
- Anti-mitochondrial antibody
- Imaging Studies : normal cholangiogram
- Liver biopsy

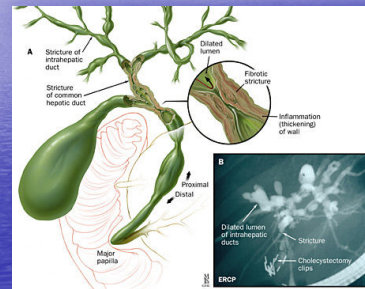
## Complications Of PBC

- Chronic Cholestasis : Jaundice, hyperpigmentation, pruritus, Steatorrhea, malabsorption of fat soluble vitamins, Osteoporosis, Osteomalacia, hypercholesterolemia.
- Biliary Cirrhosis : portal hypertension, variceal bleeding, ascites

## Treatment OF PBC

- Symptomatic: Cholestyramine  
Fat soluble vitamins
- Specific Rx : none proven  
various immunosuppressive  
agents  
Ursodeoxycholic acid
- Liver Transplantation

## Primary Sclerosing Cholangitis



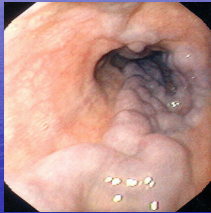
## Research: Complications of Cirrhosis

- Portal hypertension and varices
- Ascites and spontaneous bacterial peritonitis
- Hepatorenal syndrome
- Hepatic encephalopathy
- Drugs in patients with cirrhosis
- Reversal of cirrhosis

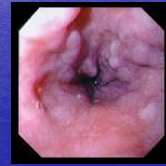
## Portal Hypertension

- Esophageal varices
- Gastric varices
- Portal hypertensive gastropathy
- GI Bleeding, anemia

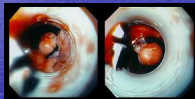
## Esophageal Varices



## Bleeding Esophageal Varices



## Variceal banding



## Portal Hypertension

- Banding of esophageal varices
- Sclerotherapy
- Oral drugs: propranolol, nadolol
- IV octreotide
- TIPS
- Surgery

#### HEPATIC ENCEPHALOPATHY

Stage	Mental State	Neurologic Signs
1	Mild confusion; ↓ attention; irritability; inverted sleep pattern	Incoordination; tremor; impaired handwriting
2	Drowsiness; personality changes; intermittent disorientation	Asterixis; ataxia; dysarthria
3	Somnolent; gross disorientation; marked confusion; slurred speech	Hyperreflexia; muscle rigidity; Babinski sign
4	Coma	No response to pain; decerebrate posture

## Hepatic Encephalopathy

- Current treatments: Lactulose, antibiotics, nutritional supplements
- New Treatments : new antibiotic rifaximin  
Sodium Benzoate,

## Research ; Liver Cancer

- Best way to screen patients at high risk
- Treatment of liver cancer and new modalities
- New drugs for treatment and prevention of liver cancer
- Role of liver transplantation
- Why some patients develop liver cancer/

## Funding for Liver Disease Research

- Various organizations  
NIH, NIDDK, ALF  
Academic centers  
Other not for profit organizations
- Drug company sponsored research  
New Drugs studies  
Approved drugs for new use  
Post-marketing study

## Internet Sites For Information

- [Liverfoundation.org](http://Liverfoundation.org)
- [Nih.gov](http://Nih.gov), [niddk.nih.gov](http://niddk.nih.gov)
- [ClinicalTrials.gov](http://ClinicalTrials.gov)
- VA sponsored research
- Academic Center websites
- [Illinois-liver.org](http://Illinois-liver.org)

Thank you for your attention