The A-B-C’s of Viral Hepatitis

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Disclosures

- I have no disclosures currently
- In the past 12 months, I have received consulting fees from Abbvie, Genentech and Gilead.

Objectives

- To understand epidemiology of viral hepatitis
- To recognize clinical presentations of viral hepatitis
- To review hepatitis screening and prevention in primary care settings
- To be aware of treatments for chronic hepatitis B and C

Clinical Scenario

A 56yo Chinese man presents to your office for a new patient appointment after getting health care coverage for the first time through the Affordable Care Act. He was born in China, has been in the US since age 6, and travels to China every 5-7 years. He is married with 2 adult children. His only lifetime sexual partner is his wife and he denies ever injecting drugs or receiving blood transfusions. He works as a cook at a local restaurant. He has no other past medical history and takes no medications or herbs. His mother died of liver cancer in China at age 50.

In addition to your other evaluations, how would you address his hepatitis risk?
<table>
<thead>
<tr>
<th>Question</th>
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<tbody>
<tr>
<td>♦ What would you do for hepatitis A?</td>
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<tr>
<td>1. Test him for immunity to hepatitis A and vaccinate if non-immune</td>
</tr>
<tr>
<td>2. Do not test him for immunity and proceed immediately to vaccination</td>
</tr>
<tr>
<td>3. Do not test him for immunity and do not vaccinate him</td>
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<table>
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<tr>
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</tr>
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<tr>
<td>♦ What tests would you order to screen for hepatitis B status?</td>
</tr>
<tr>
<td>1. Hepatitis B surface antigen</td>
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<tr>
<td>2. Hepatitis B surface antibody</td>
</tr>
<tr>
<td>3. Hepatitis B core antibody</td>
</tr>
<tr>
<td>4. Hepatitis B DNA</td>
</tr>
<tr>
<td>5. 1 &amp; 2</td>
</tr>
<tr>
<td>6. 1, 2, &amp; 3</td>
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<tr>
<td>7. 1, 2, 3, &amp; 4</td>
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<table>
<thead>
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<tr>
<td>♦ What would you do for hepatitis C?</td>
</tr>
<tr>
<td>1. Test him for hepatitis C antibody</td>
</tr>
<tr>
<td>2. Do not test him for hepatitis C antibody and proceed immediately to vaccination</td>
</tr>
<tr>
<td>3. Do not test him for hepatitis C antibody</td>
</tr>
</tbody>
</table>
Hepatitis A – Epidemiology

- Virus found in feces
- Transmitted via
  - Contaminated food and/or water
  - Direct contact with infected person’s feces
- 180,000 infections in children and adults annually in US
  - Often occurs as outbreaks
  - 6th most common reported infectious disease in US
- Reportable to local health department

Hepatitis A – Screening and Prevention

- Persons at increased risk for hepatitis A:
  - Travelers to endemic areas
  - Men who have sex with men
  - Users of injection and non-injection drugs
  - Persons with Clotting-Factor Disorders
  - Persons working with nonhuman primates
- Persons at risk for bad outcomes from hepatitis A:
  - Persons with chronic liver disease of any etiology


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Hepatitis A – Endemic Areas


Hepatitis A – Clinical Presentation

- Symptoms include extreme fatigue, nausea, fever, jaundice
  - Incubation period 15-50 days
- Always resolves – never becomes chronic
  - Average 27 days of lost work in adults
- Can lead to fulminant hepatitis with pre-existing chronic liver disease
  - Estimated 100 deaths per year in the US
- Treatment is supportive
- Preventable by vaccination
- Reportable to local health department

Hepatitis B – Epidemiology

- 2 Billion infected world-wide; 350 million chronic carriers
- Found in blood, semen, vaginal and other body fluids
- High rates of sexual transmission
  - Perinatal
  - Percutaneous
  - Noninjection drug use
- Chronic infection occurs in
  - 90% of infants infected at birth
  - 30% of children infected at age 1-5 years
  - 6% of persons infected after age 5 years
- Contributes to death in 15%-25% of chronically infected
- Preventable by vaccination

Chronic Hepatitis B in the US: Undiagnosed and Undertreated

- ~ 2 million people have chronic hepatitis B
- 400,000-600,000 diagnosed
- 200,000-300,000 entered into care
- < 50,000 are receiving antiviral treatment

Transmission of HBV

- Vertical
  - Perinatal: 80%-90% of those infected at birth progress to CHB
  - Young Children: Approximately 30% of those infected at 1-6 years of age progress to CHB
  - Older Children and Adults: <1%-12% of those infected as older children or adults progress to CHB

Global Distribution of Hepatitis B

Prevalence of HBsAg

- High ≥ 8%
- Intermediate 2% to 7%
- Low < 2%

Centers for Disease Control and Prevention. CDC Health Information for International Travel 2010

Hepatitis B – CDC Screening Guidelines

- Persons born in countries with ≥ 2% HBsAg prevalence
- US-born persons not vaccinated as infants whose parents were born in regions with high HBV endemicity (≥ 8% HBsAg prevalence)
- Persons with behavioral exposures to HBV
  - Injection drug users, MSM
- Persons needing immunosuppressive therapy
  - Chemotherapy, organ transplantation, immunosuppression for rheumatologic or gastroenterologic disorders
- Persons with elevated ALT/AST of unknown etiology
- Hemodialysis patients
- All pregnant women
- All HIV-positive individuals
- Household contact of individuals with chronic HBV


Hepatitis B – Screening

- Hepatitis B surface antigen screening is recommended regardless of vaccination history in
  - Persons born in geographic regions with HBV prevalence of ≥2%
  - U.S.-born persons not vaccinated as infants whose parents were born in regions with high HBV endemicity (≥8%)
  - Persons who received hepatitis B vaccination as adolescents or adults after the initiation of risk behaviors


HBV Screening Algorithm

- Assess HBsAg
  - Positive
    - Chronic HBV*
      - Evaluate for treatment
    - Negative
      - Assess anti-HBs
        - Positive (Antibodies present)
          - Immune to HBV
        - Negative (No antibodies)
          - Vaccinate

*Time from positive HBsAg test to diagnosis of chronic HBV is 6 mos.

Interpretation of Hepatitis B Serologies

<table>
<thead>
<tr>
<th>Serologic Marker</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg Anti-HBs, IgM Anti-HBc</td>
<td></td>
</tr>
<tr>
<td>- - (-) -</td>
<td>Never infected/exposed. Needs vaccination.</td>
</tr>
<tr>
<td>+ + (-) -</td>
<td>Chronic infection.*</td>
</tr>
<tr>
<td>- - + (-)</td>
<td>Chronic infection</td>
</tr>
<tr>
<td>- - - (-) +</td>
<td>Recovered past infection. Immune.</td>
</tr>
<tr>
<td>- + - -</td>
<td>Recovered past infection. Immune.</td>
</tr>
<tr>
<td>+ - + -</td>
<td>Chronic infection</td>
</tr>
</tbody>
</table>

* Chronic infection requires confirmation of HBsAg on two occasions, six months apart, or by absence of anti-HBc IgM in original specimen.

HBsAg = Hepatitis B surface Antigen  
Anti-HBc = Antibody to Hepatitis B core antigen  
Anti-HBs = Antibody to Hepatitis B surface antigen

Isolated anti-HBc – “Core only”

1. Resolved infection, low HBsAb – “Waning immunity.”
2. “Window Period” of acute hepatitis B
3. Surface antigen negative chronic hepatitis B – “Occult HBV”
4. False positive test
   - Generally followed up by ordering HBV DNA

Hepatitis B – Vaccination

- Standard series is 10 mcg vaccine at 0, 1 and 6 months administered IM in the deltoid
  - Response rates >90% in immunocompetent individuals <40 years old
    - Post-vaccination titers only recommended in certain circumstances
  - Lower in immunocompromising conditions
    - HIV, particularly with low CD4 counts
    - Hemodialysis
    - Chronic steroids
    - Hepatitis C infection
    - Age >60

Hepatitis B – Vaccination Recommendations

- Persons at risk by blood exposure
  - Current or recent IDUs
  - Household contacts of person with chronic HBV
  - Residents and staff of facilities for developmentally disabled persons
  - Health care and public safety workers with risk for blood exposures
  - Persons with ESRD, including dialysis

- Persons at risk by sexual exposure
  - Sex partners of persons with chronic HBV
  - Non-monogamous sexually active persons
  - Persons seeking treatment for STDs
  - Men who have sex with men

- Others
  - International travelers to endemic areas
  - Persons with chronic liver disease
  - Persons with HIV
  - All other persons seeking protection from HBV infection
**Hepatitis B Vaccine Non-Responders**

- Consider repeating 3-shot series once
  - If HIV-infection, repeat once CD4 > 200 (some suggest > 500) on ARVs
- Other strategies
  - Higher dose vaccine – 20 or 40 mcg
  - Accelerated vaccine schedule (e.g., 0, 7, 14 days)
  - Adjuvants
- Counsel on avoiding exposures and consider HBlg if significant exposure

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**Hepatitis C – Screening and Prevention**

- Traditional approach was risk-factor based screening
  - Recent/past injection drug users – even if only used once
  - Groups with high HCV prevalence
    - HIV-infected individuals
    - Hemophiliacs treated with clotting factor concentrates before 1987
    - Hemodialysis recipients
    - Patients with unexplained aminotransferase abnormalities
    - Recipients of transfusion or transplantation before July 1992
    - Children born to women infected with HCV
    - Healthcare, public safety, and emergency medical personnel following needle injury or mucosal exposure to HCV-infected blood
    - Current sexual partners of individuals infected with HCV
    - Persons who have used illicit drugs by noninjection routes

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**Hepatitis C – Screening and Prevention**

- As of August 2012, CDC now recommends one-time testing of all “baby boomers” without asking about risk factors
  - Individuals born between 1945-1965
- Rationale:
  - People born during 1945 through 1965 are 5 times more likely than other adults to be infected
    - 27% of the population, but 75% of the hepatitis C burden
  - This approach will find an estimated 800,000 undiagnosed cases and prevent more than 120,000 deaths

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**Baby Boomers Account for the Majority of HCV Cases in US**

- Estimated Prevalence by Age Group
- Number of Chronic HCV Infection (millions)

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Question

Which of the following best describes your role in managing chronic hepatitis B infection in your practice?

1. I refer all chronic hepatitis B patients to a specialist for treatment
2. I treat most chronic hepatitis B patients myself and refer complicated patients to a specialist
3. I am a specialist in chronic hepatitis B
4. Most of my chronic hepatitis B patients do not receive treatment

Question

A 27 yo foreign-born Vietnamese man is diagnosed with chronic hepatitis B infection. His ALT is 90 U/L and HBV DNA is 80,000 IU/mL. He is not cirrhotic. His father died of liver cancer at the age of 42.

Which of the following is NOT appropriate in the management of his care?

1. He should be screened for HCC starting before age 40
2. All household contacts should be screened for hepatitis B
3. Hepatitis B treatment should be initiated once his HBV DNA reaches 100,000 IU/mL
4. He should be vaccinated for hepatitis A if not immune

4 Phases of Chronic HBV Infection

Which of the following medications should NOT be used in initial treatment of chronic hepatitis B infection?

1. Lamivudine
2. Tenofovir
3. Entecavir
4. Interferon

Goals and Benefits of Hepatitis B Treatment

- Prevention of long-term negative clinical outcomes (e.g., cirrhosis, liver transplantation, HCC, death) by durable suppression of HBV DNA
- Primary endpoint
  - Sustained decrease in serum HBV DNA level to undetectable
- Secondary endpoints
  - Decrease or normalize serum ALT
  - Improve liver histology
  - Induce HBeAg loss or seroconversion in HBeAg-positive disease
  - Induce HBsAg loss or seroconversion
- Treatment is often long term or lifelong

Treatment Criteria for Chronic Hepatitis B

- Recommended HBV DNA and ALT levels outlined in the following table

<table>
<thead>
<tr>
<th>Liver Society Guidelines*</th>
<th>HBeAg Positive</th>
<th>HBeAg Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBV DNA, IU/mL</td>
<td>ALT</td>
</tr>
<tr>
<td>EASL 2009†</td>
<td>&gt; 2000</td>
<td>&gt; ULN†</td>
</tr>
<tr>
<td>APASL 2008¶</td>
<td>≥ 20,000</td>
<td>&gt; 2x ULN†</td>
</tr>
<tr>
<td>AASLD 2009¶</td>
<td>&gt; 20,000</td>
<td>&gt; 2x ULN or (+) biopsy</td>
</tr>
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</table>

*Although ALT and HBV DNA are primary tests used to determine treatment candidacy, the levels of elevation that warrant consideration of treatment are not universally agreed upon.
†Laboratory normal.
¶30 U/L for men and 19 U/L for women.
**In patients older than 40 yrs of age, 2000 IU/mL should be considered as a cutoff for treatment.

Current Guideline Recommendations for First-line Therapy

- Entecavir
- Tenofovir
- Peginterferon alfa-2a
  - Exceptions: pregnancy, chemotherapy prophylaxis, decompensated cirrhosis, acute infection

Undetectable* HBV DNA in HBV Patients After 1 Year of Treatment

*By PCR-based assay (LLD = 50 IU/mL) except for some LAM studies.

Management of Chronic HBV in the Primary Care Setting

- **After initiation of treatment**
  - Every 3 months
    - Assess adherence and toxicities
    - Check ALT and HBV DNA
  - Once ALT has normalized and HBV DNA undetectable
    - Assess every 3-6 months
  - Screening for Hepatocellular carcinoma (HCC)
    - Liver ultrasound +/- AFP every 6 months
      - Asians: males ≥40 years; females >50 years
      - African ≥20 years
      - All cirrhotic hepatitis B carriers
      - Family history of HCC

How to Use Entecavir or Tenofovir

- **Dosage and administration**
  - **Entecavir:** oral administration
    - Patients naive to lamivudine therapy: 0.5 mg QD
    - Patients who are refractory/resistant to lamivudine or HIV coinfected: 1.0 mg QD
    - Dose adjustment needed if eGFR < 50 mL/min
  - **Tenofovir:** oral administration
    - 300 mg QD
    - Dose adjustment needed if eGFR < 50 mL/min

- **Duration, based on clinical endpoints**
  - HBeAg positive: continue treatment until HBV DNA undetectable and HBeAg seroconversion achieved; continue for ≥6 mos after anti-HBe appearance
  - Close monitoring for relapse required after treatment discontinuation
  - HBeAg negative: continue treatment until HBsAg clearance

How to Use PegIFN alfa-2a

- **Dosage/administration:** 180 µg/wk by SQ injection
- **Duration of therapy:** 48 wks
- **Treatment endpoints: how to determine success or failure**
  - Finite duration therapy; not based on specific endpoints
  - Virologic response to therapy defined as decrease in serum HBV DNA to undetectable levels by PCR at end of treatment and loss of HBeAg in patients who were initially HBeAg positive
  - Favorable predictors of response to PegIFNα
    - Low HBV DNA∗; High ALT∗; Genotype A or B > C or D∗∗; Not advanced disease
  - Consider use in HCV co-infection

5-Yr Rates of Resistance With Monotherapy Oral Agents in Nucleos(t)ide-Naive Patients

- **Lamivudine**
- **Adefovir**
- **Telbivudine**
- **Entecavir**
- **Tenofovir**

Cumulative Resistance Rate (%)

- Telbivudine rate determined at Yr 2.


How to Use PegIFN alfa-2a


How to Use Entecavir or Tenofovir

**Question**

A 44yo gay man with HIV (CD4 = 788 on stable treatment for 5 years) has ALT 534 U/L on routine labs. ALT has always been normal previously, and he is asymptomatic. He has been vaccinated for hepatitis A and B. He was treated 3 months ago for rectal gonorrhea. What is the most likely cause of his ALT elevation?

1. Antiretroviral medication hepatotoxicity
2. Acute hepatitis A
3. Acute hepatitis B
4. Acute hepatitis C
5. Syphilis

**Question**

Which of the following best describes your role in treating chronic hepatitis C infection in your practice?

1. I refer all chronic hepatitis C patients to a specialist for treatment
2. I treat most chronic hepatitis C patients myself and refer complicated patients to a specialist
3. I am a specialist in chronic hepatitis C
4. Most of my hepatitis C patients do not receive treatment

**Hepatitis C**

- Blood to blood transmission
  - Percutaneous
  - Non-injection drug use
  - Transfusions, organ transplants or blood products prior to 1992
  - Perinatal
  - Low sexual transmission
- Primarily causes damage to the liver, but extrahepatic manifestations are common
- Often no symptoms
- No vaccine available

**HCV Transmission Among Men Who Have Sex with Men (MSM)**

- HCV incidence in HIV+ and HIV- MSM in Amsterdam Cohort, 1984-2011
- No incident infections among HIV-negative MSM
HCV: Worldwide Epidemiology of ~170 Million Infections

- Europe: 8.3 million (1.03%)
- Americas: 13.1 million (1.7%)
- Africa: 31.5 million (5.3%)
- Eastern Mediterranean: 21.2 million (4.9%)
- Southeast Asia: 32.3 million (2.15%)
- Western Pacific: 63.2 million (3.9%)
- Eastern Mediterranean: 21.3 million (4.6%)
- Africa: 31.9 million (5.3%)

Natural History of HCV Infection

- Stable: 75% to 95%
- Chronic HCV: 55% to 85%
- Cirrhosis: 5% to 25%
- Decompensation: 1% to 3%/yr

HCV Testing

- HCV Antibody (Ab) testing
  - Sensitivity: 97% to 100%
  - Remains positive, even after viral clearance
- Viral Load (RNA)
  - Amount of virus in per milliliter of blood
    - Copies or International units
  - Level does not correlate with disease progression
- Genotype
  - 1-6, plus subtypes
  - Useful for treatment options and treatment prognosis
  - Little impact on natural history

Patients with Chronic Hepatitis C Should be Counseled

- Alcohol use should be reduced/avoided
  - > 50 grams* per day clearly increases HCV-fibrosis progression
- Hepatitis A vaccine should be given to susceptible patients
  - Fulminant HAV infection reported in persons with underlying chronic hepatitis C
- Screen for HBV and vaccinate
- Screen for HIV
- All HCV-infected individuals should be considered for treatment

*50 grams of alcohol is approximately 48 ounces of beer, 4.5 ounces of 80 proof, or 15 ounces of wine.

References:

HCV treatment goals

- Achieve virologic clearance ("cure")
- Reduce long-term complications
  - End-stage liver disease
  - Cirrhosis
  - Hepatocellular carcinoma
  - Need for liver transplantation
- Sustained Virologic Response (SVR):
  Undetectable HCV RNA at 12 weeks after completion of treatment
  - Correlates to long-term clearance
  - Correlates to reduction in long-term complications

HCV Treatment Cascade

The Good News

HCV Treatment – Currently approved drugs

- Pegylated Interferon-α
- Ribavirin
- HCV Protease Inhibitors – for HCV genotype 1 only
  - Telaprevir
  - Boceprevir
  - Simeprevir
- HCV Polymerase Inhibitor – Pan-genotypic
  - Sofosbuvir
Adverse Events (AEs) Associated With PegIFN/RBV Therapy

- Almost all patients treated with pegIFN and RBV experience ≥ 1 AEs during therapy[1]
- AEs caused 10% to 14% discontinuation in registrational trials[2,3]
- Most common clinical AEs:
  - Influenza-like (fatigue, headache, fever and rigors): > 50%
  - Psychiatric (depression, irritability, and insomnia): 22% to 31%
  - Neutropenia (ANC < 1500/mm3): 18% to 20%[2,3]
    - Severe neutropenia* (ANC < 500/mm3): 4%
    - Serious infections are uncommon and G-CSF is rarely necessary[4]
  - Anemia (Hb < 12 g/dL): ~ 30%[3,4]
    - Nadir within 6-8 wks
    - Severe anemia† (Hb < 10 g/dL): 9% to 15%


HCV Directly Acting Antiviral (DAA) Targets

Interferon-Free Regimens

Current HCV Treatment

- Genotype 1 or 4: Sofosbuvir (SOF) 400mg po qD + weight-based Ribavirin (RBV) + Pegylated Interferon x 12 weeks
  - SVR12: GT1a-92%; GT1b-82%; GT4-96%
- Genotype 1: Consider SOF + RBV x24 if PEG-ineligible
  - SVR12: 76%
- Genotype 2: SOF + RBV x 12 weeks
  - SVR12: 95%
- Genotype 3: SOF + RBV x 24 weeks
  - SVR12: 84%
- SOF indicated for HCV mono-infection, HCV/HIV co-infection
  - Effective in re-treatment

HIV negative
HCV GT 1
90% AA

HIV negative
HCV GT 1b
Non-cirrhotic

HIV positive
HCV GT 1, T

Percent SVR12

CRCA 2014 – Abstracts #25, 26, 27LB, 29LB
Evolution of HCV Treatment

- Spontaneous clearance rates are lower
- HCV viral loads are higher
- Faster progression of liver fibrosis
- Drug-drug interactions
  - ddI and Ribavirin are contraindicated
  - AZT and Ribavirin are relatively contraindicated
  - Significant interactions between HCV protease inhibitors and antiretrovirals
- Data on new agents look good
  - Co-infected response rates almost the same as mono-infection

Hepatitis C: HIV Co-infection

- Spontaneous clearance rates are lower
- HCV viral loads are higher
- Faster progression of liver fibrosis
- Drug-drug interactions
  - ddI and Ribavirin are contraindicated
  - AZT and Ribavirin are relatively contraindicated
  - Significant interactions between HCV protease inhibitors and antiretrovirals
- Data on new agents look good
  - Co-infected response rates almost the same as mono-infection

HCC Surveillance: AASLD Practice Guideline Recommendations

- Hepatitis B
  - Asians: males age 40, females age 50
  - Africans: age 20
  - Cirrhosis regardless
  - HCC in first-degree relative (start before age 40)
- Cirrhosis from other causes, including HCV
- AASLD recommends screening with liver ultrasound at 6 month intervals
  - AFP not recommended unless ultrasound not available

Question

A 28-year-old nurse who is in good health comes to your office to seek travel advice. She is twelve weeks pregnant and is preparing to leave for a two-month trip to India and Bangladesh for a family wedding, where hepatitis E is endemic. She tells you that she very much wants to take this trip before having her child.

A. Strongly recommend postponing travel to these countries until after the pregnancy
B. Administer immune globulin to decrease the risk for hepatitis E
C. Vaccinate the patient for hepatitis E after the first trimester of pregnancy and at least 2 weeks prior to her travel
D. Provide the patient with a course of ribavirin to treat hepatitis E should she acquire it while traveling

**Hepatitis E**

- Spread by the fecal-oral route
- Clinical presentation similar to hepatitis A
  - Notable exception of a poorly understood marked increase in severity in pregnant women
  - Mortality in pregnancy is 15-25%
  - If possible, traveling to areas endemic for hepatitis E virus should be deferred until after pregnancy
- Immune globulin has no proven efficacy in the management of hepatitis E virus infection
- No vaccine for prevention
- No antiviral treatment

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**Thank You**

**Questions?**