




Occupational Liver Disease

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Introduction



- **The liver is the target organ of many occupational and environmental chemicals and plays a central role in their detoxification and elimination**
- **Hepatic injury dose not differ clinically or morphologically from drug induced damage**
- **Occupational liver disease may be of secondary importance to damage**
- **Occupational history and result of personal or workroom air sampling**

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- **Lack of sufficiently sensitive and specific tests**
 - **Effects of multiple hepatotoxic exposure**
 - **Remove the patient from exposure to the suspected workplace toxin**



Routes of Exposure

- Inhalation
 - Ingestion
 - Percutaneous absorption
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- Inhalation the most important route particularly for volatile solvent
 - Percutaneous absorption is the most important for lipophilic agent

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- **Oral intake of hepatotoxic agents is usually of importance only in the rare case of accidental ingestion**
 - **Mouth breathing and gum and tobacco chewing can increase the amount of gaseous substances absorbed during the workday.**



Physical agent induced liver disorders

- ▶ **Hyperthermia (Heat Stroke)**

- ▶ **Acute hepatic injury**

- ▶ **Centrilobular necrosis**

- ▶ **Cholestasis**

- ▶ **Ionizing radiation**

- ▶ **A cumulative dose in excess of 3000 to 6000 Rad**

- ▶ **Accidental intense exposure**

- ▶ **Hepatitis 2-6 Week later**

Chemical agents associated with occupational liver disease

Arsenic	Cirrhosis, Hepatocellular carcinoma, Angiosarcoma	Pestiside
Beryllium	Granulomatosis disease	Ceramics workers
Ccl4	Acute hepatocellular injury, cirrhosis	Dry cleaning
Dimethylnitrosamine	Hepatocellular carcinoma	Rocket mfg
Dioxin	Porphyria cutanea tarda	Pestiside
Halothane	Acute hepatocellular injury	Anesthesiology
Hydrazine	Steatosis	Rocket mfg
Nitropropane	Acute hepatocellular injury	painter
PCB	Subacute injury	Electrical utility
TNT	Acute or Subacute hepatocellular injury	Munitions workers
Trichloroethylene	Acute hepatocellular injury	Cleaning solvent sniffing
Vinylchloride	Angiosarcoma	Rubber workers

Acute hepatic injury

- Cytotoxic injury or cholestatic injury
- Latent period 24 - 48 hours
- Clinical symptoms are often extra hepatic origin
- Anorexia, nausea, vomiting, jaundice, hepatomegaly
- In massive necrosis coffee-ground emesis, abdominal pain, reduction of liver size, ascites, edema, hemorrhagic diathesis
- During 24-48 hours somnolence and coma

Carbon Tetrachloride

- Use as a liquid solvent, dry cleaning agent, fire extinguisher
- Dizziness, Headache, Visual disturbance, Confusion
- Hepatic disease occurs after 2-4 days
- Hepatomegaly, Splenomegaly, Jaundice
- Elevated serum transaminase, prolonged PT
- Hemorrhage, Hypoglycemia, Encephalopathy
- Renal failure may ensue a few days after the hepatic damage becomes manifest
- N- acetylcysteine



Sub acute injury

- **Rare**
- **Most common: necrosis**
 - **TNT, Tetrachloroethane, PCB**
- **Symptoms:**
 - **Anorexia, Nausea, vomiting, Hepatomegaly & Jaundice**

Chronic injuries

- **Asymptomatic until advanced stages**
- **Cirrhosis:**
 - Arsenicals, dimethylnitrosamine, CCL4, TNT, PCB
- **Steatosis:**
 - DMF, CCl4
- **Hepatoportal Sclerosis:**
 - VCM & Arsenic
- **Hepatic porphyria:**
 - Dioxin
- **Granoloma:**
 - Beryllium, Copper
- **Neoplastic changes:**
 - VCM, Arsenic

Infectious Agents

HAV	Nursery & kindergarten staff Sewer workers
HBV & HCV	HCWs with blood and body fluid contact
Cytomegalovirus	Pediatric health care workers
Coxiella burnetti	Animal care workers, farm workers, slaughterhouse workers
Leptospira icterohaemorrhagiae	Sewer workers, farm workers


Hepatitis A

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- **High Risk Occupations:**
 - **HCWs**
 - Emergency rooms, surgery, laundry, children's psychiatry, dentists, neonatal intensive care units
 - **Waste water treatment plant workers**
 - **Waste pickers,**
 - **home health workers**
 - **food handlers**
- **Incubation period:** 15-50 days (28-30 days)
- **Symptoms:** Abrupt onset, with fever, malaise, anorexia, nausea, abdominal discomfort, and jaundice
- **Transmission:** fecal-oral, Blood (rare)

Hepatitis A

- **Highest concentration of virus excretion in Fecal:**
 - During the incubation period
 - Early in the prodromal phase
 - It diminishes rapidly once jaundice appears
- **Greatest infectivity:**
 - 2-week period immediately before the onset of jaundice or elevation of liver enzymes
- **Not chronic carrier**


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- Fulminant hepatitis occurs rarely (<1% overall), but rates are higher with **increasing age** and in those with **underlying chronic liver disease**, including those with chronic hepatitis B or C infection.
 - Hepatitis A does not appear to be worse in HIV-infected patients when compared to HIV-negative persons

The diagnosis of acute hepatitis A is confirmed by:

- Presence of immunoglobulin IgM class anti-HAV in serum collected during the acute or early convalescent phase of the disease.
- IgG antibodies appear in the convalescent phase and remain positive for life
- **The presence of IgG anti- hepatitis A antibody indicates either previous exposure or immunization**



Treatment

- symptomatic, with rest, analgesics, and fluid replacement
 - Fulminant hepatic failure occasionally follows acute HAY infection.
 - Orthotopic liver transplantation
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Prevention

- **Hand washing**
- **Avoiding tap water and raw foods in areas with poor sanitation.**
- **Heating foods appropriately $>85^{\circ}\text{C}$ for 1 minute**
- **Chlorine, iodine, and disinfecting solutions (household bleach 1:100 dilution)**



Prevention

- **A single intramuscular dose of 0.02 mL/kg of immune globulin (immune serum globulin, gamma globulin) given before exposure or during the incubation period**

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- **Pre exposure prophylaxis in persons who plan to travel in areas with high or intermediate hepatitis A endemicity depends on the duration of the travel:**
 - up to 1 month: 0.1 mL/kg**
 - up to 2 months: 0.2 mL/kg**
 - 2 months or longer: repeat dose of 0.2 mL/kg every 2 months**
 - **postexposure prophylaxis, it is 0.1 mL/kg.**


Prevention

- ▶ Once the diagnosis of acute infection is made, **close contacts** should be given HAY vaccine and/ or immune globulin promptly within **2 weeks** of exposure to prevent development of secondary cases.
- ▶ close contacts include:
 - staff of day-care facilities
 - food handlers (in establishments with a food handler diagnosed with hepatitis A)
 - institutions for custodial care
 - hospital staff if an unsuspected patient has been fecally incontinent

- Immune globulin can be used in cases where hepatitis A vaccination is contraindicated
- where travel is imminent
- It is less protective and only for short periods of time

Routine immune globulin administration is not recommended

- **The usual office or factory conditions for persons exposed to a fellow worker with hepatitis A**
 - **Teachers with schoolroom contact**
- BUT**
- **Restaurant employees(food handlers) ,patrons**



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- Food handlers should receive immune globulin when a common-source exposure is recognized
 - Restaurant patrons when the infected person is involved directly in handling uncooked foods without gloves.

This is especially the case when the patrons can be identified **within 2 weeks of exposure** and the food handler's hygienic practices are known to be deficient

- **Pregnancy or lactation is not a contraindication to immune globulin administration.**

hepatitis A vaccine

- Persons traveling to or working in countries with intermediate or high HAV endemicity
- laboratory workers with exposure to live virus
- Animal handlers with exposure to HAV-infected primates
- Men who have sex with men (MSM),
- Illicit drug users (injections and non injection)
- Individuals with chronic liver disease,
- Individuals with clotting factor disorders
- Individuals with direct contact to others who have hepatitis A and homeless individuals.


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- **Protective antibodies remain for as long as 4 years after two-dose vaccine series**
 - **There is no need for HAV booster vaccination after completion of the primary two-dose vaccination series**
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Routine hepatitis A vaccination is not recommended for :


- Child-care workers**
- Hospital workers**
- Teachers**
- Correctional workers**
- Restaurant employees**
- sewage treatment employees,**
- Staff in institutions for the developmentally disabled.**


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- ▶ **When outbreaks are recognized in these settings:**

use of HAV vaccine and/ or immune globulin promptly within 2 weeks of exposure for persons in dose contact with infected patients or students is recommended

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- If a food handler has been in contact with an individual who is acutely infected with hepatitis A. If he has been immunized against hepatitis A with documented evidence of a completed course of hepatitis A vaccine in the past 10 years, or one dose of monovalent vaccine within the past 12 months, they can be considered immune.
 - Those who have had laboratory- confirmed hepatitis A (previous anti- HAV IgG positive, or HAV RNA positive) can also be considered immune and then no further action is required

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- If the contact with the source case of hepatitis A is within 14 days, provided they are **healthy and aged under 60**
 - the food handler should be given a first dose of monovalent hepatitis A vaccine and a second dose 6– 12 months after the initial dose.

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- Food handlers **aged 60 years and over** should be offered hepatitis A immunoglobulin in addition to monovalent hepatitis A vaccine.
 - A second dose of vaccine is recommended 6– 12 months after the first dose to ensure long- term protection.⁵

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- If the food handler has not been immunized within 14 days of exposure
 - they are at high risk of acquiring infection and should be **removed from activities** which involve preparing and handling ready- to- eat foods until 30 days post exposure.


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- If a worker is suspected of being infected with hepatitis A, should be excluded from work **until 7 days** after the onset of jaundice or
 - If there is no history of jaundice, 7 days after the onset of symptoms

Hepatitis B

- Prevalence rate of HBS-Ag in hospital staff : **1-2%**
- Prevalence rate of Anti-HBS: **15-30%**
- Prior to hepatitis B vaccine:
 - Most frequent occupational infection among health care, laboratory, and public safety workers following human blood or body fluid exposure
 - 10 times higher than general population
- **By Standard Precautions and preexposure vaccination: sharp decline**

Hepatitis B

- Blood contains the highest titers of virus in infected individual
- Low levels in other body fluids:
 - Cerebrospinal, Synovial, Pleural, Peritoneal, Pericardial, Amniotic
 - Semen and Vaginal secretions
- Viral titers in urine, feces, tears, and saliva are low enough not be routes of transmission
 - except in cases of human bites that usually involve some blood transmission

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- **HBsAg found in breast milk is also unlikely to lead to transmission,**
 - **Hence HBV infection is not a contraindication to breastfeeding.**

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- **The risk of infection with HBV depends on:
the titer of virions in the infectious fluid**

And

**correlates with the presence or absence of
hepatitis e antigen in the source patient.**

- **The risk of infection following percutaneous injury with
both HBsAg- and hepatitis B e antigen (HBeAg)-
positive blood is 22-31%;**
- **The risk of developing serologic evidence of HBV
infection is 37-62%.**

Hepatitis B

- Risk for transmission of HBV after needlestick injuries: approximately **30%**
- HBV can remain viable for **at least 1 month** on dried surfaces at room temperature
 - Individuals with open cuts or abraded skin or mucous membranes contact contaminated surfaces
 - Most occupational infections have no clear percutaneous injury leading to HBV transmission
- Over **50%** of acute infections in adults are **asymptomatic**

Hepatitis B

- Incubation period: **45 to 60 days** after exposure
- HBS-Ag can be detected in serum **30-60 days** after exposure
- Anti- HBS develops after resolve of infection

Fulminant HBV infection is uncommon(<1%)

- **10%** of acute HBV infections lead to chronic infections
 - Significant number of those with occupational infections become chronic asymptomatic carriers

Chronic Carrier State

- HBS Ag positive on at least two occasions **at least 6 months apart**
- High levels of HBS-Ag and anti-HBC
- Various levels of serum transaminases
- Progression to cirrhosis and hepatocellular carcinoma



➤ Chronic infection develops more frequently in immunosuppressed persons :

(eg, **hemodialysis** patients and persons with human immunodeficiency virus [**HIV**] infection) and persons with **diabetes**

Hepatitis B

Test	Result	Interpretation
HBS-Ag Anti-HBS Anti-HBC	Negative Negative Negative	Susceptible
HBS-Ag Anti-HBS Anti-HBC	Negative Positive Positive	Immune due to natural infection
HBS-Ag Anti-HBS Anti-HBC	Negative Positive Negative	Immune due to Hepatitis B vaccination

Hepatitis B

Test	Result	Interpretation
HBS-Ag Anti-HBS Anti-HBC Anti-HBC (IgM)	Positive Negative Positive Positive	Acutely infected
HBS-Ag Anti-HBS Anti-HBC Anti-HBC (IgM)	Positive Negative Positive Negative	Chronically infected
HBS-Ag Anti-HBS Anti-HBC Anti-HBC (IgM)	Negative Negative Positive	Interpretation unclear: 1. Resolved infection 2. False positive Anti-HBC (Susceptible) 3. Low level chronic infection 4. Resolving acute infection

Prevention

- Pre-exposure prophylaxis:
 - Vaccination in 3 doses: nearly 90% protection

- Who have received only one or two doses:
 - Not need to restart the series
 - Only need to complete the doses they did not receive

- Not immune after vaccination:
 - >45 years
 - obesity
 - smoking

Prevention

- Check for surface antibodies:
 - 4 weeks to 6 months following the primary series
- Tests negative for antibodies:
 - one additional dose of vaccine will induce antibody protection in 15-25% of non responders
 - three additional doses (for a total of six doses) will induce antibodies in 30-50% of non-responders

Prevention

- **Those who do not develop antibodies after six total doses should consider:**
 - **Changing positions at work not involving blood or blood products**
 - **Three-dose series with 40 µg of antigen with either the Merck Recombivax HB formulated for hemodialysis patients**
- **Fewer than 5% of persons receiving six doses fail to develop detectable anti-HBs antibody**
 - **May have a low level of antibody that is not detected by routine serologic testing (“hyporesponder”)**
 - **Being chronically infected**

Prevention

- Loss of detectable anti-HB levels after immunization does not imply loss of protection
- **Positive antibody response should be verified**
- **Routine booster doses of hepatitis B vaccine are not recommended**

Post exposure prophylaxis

➤ Unvaccinated:

- Source HBSAg+: HBIG & HBV vaccine series
- Source HBSAg- : initiate HBV vaccine series
- Source unknown: initiate HBV vaccine series

➤ Previously vaccinated & Ab \geq 10:

- No treatment

➤ Previously vaccinated & Ab less than 10:

- Source HBSAg+:
 - HBIG×1 & revaccination or
 - HBIG ×2
- Source HBSAg- : No treatment
- Source unknown: if high risk source treat as HBSAg+

Hepatitis C

➤ **Transmission:**

- Blood transfusion or intravenous drug abuse
- Sexual or mother to infant transmission is very low
- Risk of infection following occupational percutaneous exposure: 1.8% (0-7%)
- Mean incubation period is 6-8 weeks
- 80% cases being anicteric and asymptomatic
- Chronic hepatitis in 70% of infected person

Hepatitis C

➤ Dx:

- Anti-HCV antibodies detectable 12 weeks-6 month following exposure
- HCV RNA by PCR (1-2 w after exposure)



Prevention

- **Following percutaneous or mucosal occupational exposure:**
 - Baseline HCV Ab measurements
 - Follow-up HCV Ab measurements (6 w, 3 & 6 m)
- **Immune globulin or antiviral therapy for prophylaxis is not recommended**
- **No vaccine is currently available for HCV**



Prevention

➤ **During this follow-up period:**

➤ Health care worker should refrain from:

➤ donating blood, plasma, organs, tissue, or semen

➤ **Health care worker should not need to:**


➤ modify sexual practices

➤ becoming pregnant

➤ breast-feeding




Cytomegalovirus Infection

- **Pediatric and immunosuppressed adult units**
 - **kindergarten teachers**
 - **Child-care workers**
 - **Hepatitis**
 - **Neonate with a congenital malformation**
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Coxiella burnetii

- **Animal-care technicians**
 - **Laboratory research personnel**
 - **Abattoir workers**
 - **Farmers**
 - **Acute hepatitis occurs in up to 50% of cases and usually is self-limited.**
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Malignant Liver Disease

▶ **Hepatic Angiosarcoma**

- ▶ Vinyl chloride monomer
- ▶ Arsenic (vineyard workers)
- ▶ Copper (pesticide)
- ▶ Anabolic steroids
- ▶ Thorium dioxide (Thorotrast)





Hepatocellular carcinoma

- vinyl chloride
- Arsenic
- Dimethylnitrosamine



Adjustments at work

- In patients with oesophageal varices, there is no restriction on occupation once the varices have been treated.
- Patients with ascites may experience difficulty with lifting, bending, or stooping.
- Patients with chronic or intermittent encephalopathy should not be employed in intellectually demanding work or jobs requiring a high degree of vigilance, including :
Safety critical work or operating machinery

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- **Individuals suffering from hepatic cirrhosis with chronic encephalopathy or those who are cognitively impaired must not drive and must notify the Driver and Vehicle Licensing Agency (DVLA)**
 - **Group 1 and 2 licenses will be revoked or refused until recovery is satisfactory and other medical standards for fitness to drive (e.g. for psychiatric conditions) are satisfied.**



Implications for employment

- ▶ **patients with chronic liver disease with ongoing inflammation or liver damage should not work with hepatotoxins.**
- ▶ **All patients working with hepatotoxins should avoid alcohol misuse and enzyme- inducing agents such as anticonvulsants, in particular phenobarbitate and phenytoin.**

Medical Surveillance

➤ Biochemical tests

- AST, ALT
- ALP
- LDH
- Bilirubin
- Urine bilirubin

➤ Tests of synthetic liver function

- Alb
- PT
- Alpha fetoprotein
- Ferritin

➤ Clearance tests

- Sulfobromophthalein
- Indocyanine green
- Antipyrine test
- Aminopyrine breath test
- Serum bile acid
- Urinary D-glucaric acid



Transaminase

- **AST & ALT:**
 - Most useful indicators of hepatocellular damage
 - Sensitive not specific
 - >8-10 folds: acute injury
 - 2-3 folds chronic or mild acute
 - In alcoholics ALT>300 is uncommon
- **Positive result:** Strongly suggest liver injury
- **Negative data:** Cannot rule out it

Transaminase

- ***High levels:***
 - Viral
 - alcoholic
 - ischemic
 - extrahepatic obstruction
 - obese individuals
- **A serum AST:ALT ratio > 1 may suggestive occupational liver disease**
 - Little Prognostic value
 - Not correlate with extent of liver necrosis on biopsy



Clinical Management of OCCUPATIONAL Liver Disease

- **Occupational & medical Hx**
 - Exposure to hepatotoxins
 - PMH of liver dis, medication
 - Review of symptoms (CNS Toxicity due to solvent exposure)
 - Travel to areas with endemic parasitic or viral disease
 - Steroid use, glue sniffing, recreational solvent use
 - Previous blood transfusion, tattoos, needle sticks, IV drug ...
 - Use of protective work practices
 - MSDS
 - Ask about other employees



Clinical Management of OCCUPATIONAL Liver Disease

➤ Physical Examination

■ Acute liver disease

RUQ tenderness

Hepatosplenomegaly

Jaundice

■ **Chronic liver disease**

Spider angioma

Palmar erythema

Testicular atrophy

Ascites

Gynecomastia




Clinical Management of OCCUPATIONAL Liver Disease



- ▶ **Elevated serum transaminase level**
 - ▶ R/O non-occupational causes
 - ▶ Remove for 2-4 weeks
 - ▶ Repeat
 - ▶ A persistently elevated serum transaminase concentration suggests a non-occupational cause of liver disease or, rarely, chronic occupational liver disease.






TUBERCULOSIS

- ▶ **Transmitted by the airborne route and, depending on host factors, may lead to latent tuberculosis infection (LTBI) or tuberculosis disease (TB).**
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- **Health care settings (especially hospitals, long term care facilities, and dialysis centers)**
 - **Refugee/immigration centers**
 - **Homeless shelters**
 - **Substance abuse treatment centers**
 - **Correctional institutions**

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- After an incubation period of 4-12 weeks, infection usually remains subclinical and dormant without development of active disease,
 - But the Mantoux tuberculin skin test (TST) will become positive
 - The risk of developing active tuberculosis *is* highest in the first 2 years following infection



The risk of development of clinical disease following infection is higher:

- **In those younger than 5 years**
- **In states of undernutrition**
- **In certain immunopathologic states (eg, in persons with HIV)**
- **with certain genetic predisposition (persons with HLA-Bw15)**
- **In persons with some coexisting diseases (silicosis, end-stage renal disease, leukemia, lymphoma, upper gastrointestinal tract carcinoma, diabetes)**

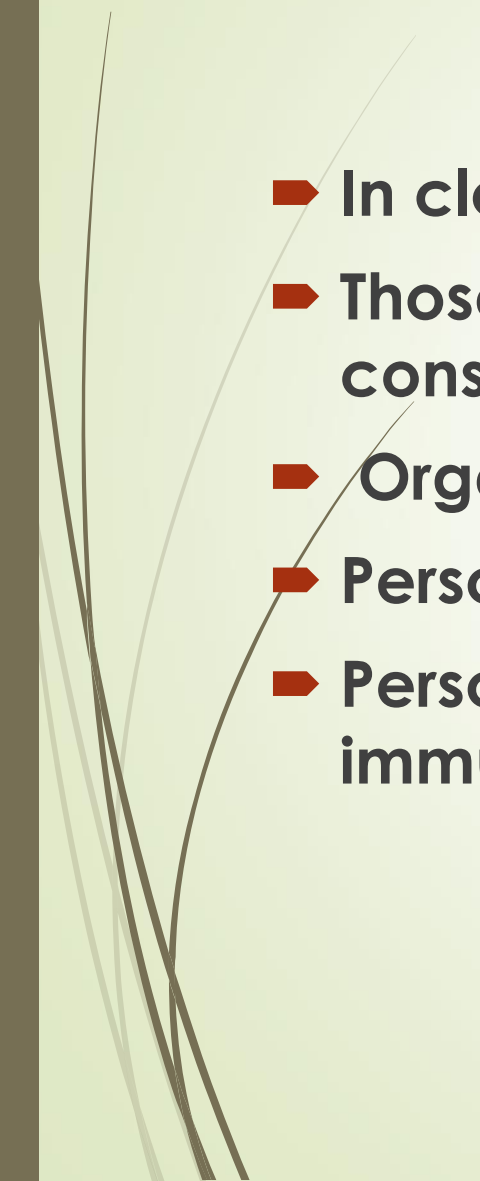


Tuberculin Skin Test

- TST skin testing is an accepted method for screening high risk populations for TB infection
- Intradermal injection of 5 tuberculin units of TST in a patient with LTBI or active tuberculosis infection results in a delayed hypersensitivity reaction manifested by induration at the site of injection within 48-72 hours



5 mm of induration

- **In close contacts of infectious patients**
 - **Those with fibrotic changes on chest radiograph consistent with prior TB**
 - **Organ transplant recipients**
 - **Persons with (HIV) infection**
 - **Persons with other types of significant immunosuppression**
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10 mm or more

- Is considered positive in high-risk occupational groups (including employees in prisons or jails, health care facilities, or mycobacterial laboratories)
- Injection drug users
- Persons who have immigrated in the past 5 years from countries with high TB prevalence
- Children younger than 5 years
- Those with the coexisting diseases



15 mm or more

- ▶ In persons with none of the previously mentioned risk factors
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The TST test may be negative in the presence of :

- Overwhelming tuberculosis
- Measles
- Hodgkin disease
- Sarcoidosis
- Immunosuppressive states
- If the initial test is negative in individuals with suspected **reduced immune response** or in those who **will be screened annually** because of occupational or other risk, **it should be repeated**

Booster phenomenon

- ▶ Some people infected with *M tuberculosis* may have a negative reaction to the TST if many years have passed since they became infected
- ▶ They may have a positive reaction to a subsequent TST because the initial test stimulates their ability to react to the test
- ▶ May incorrectly be interpreted as a skin test conversion (going from negative to positive)



Two-step method

- If the first TST result in the two step baseline testing is positive, consider the person infected and evaluate and treat the person accordingly
- If the first test result is negative, the TST should be repeated in 1-3 weeks
- If the second test result is positive, consider the person infected and evaluate and treat the person accordingly
- If both steps are negative, consider the person uninfected and classify the TST as negative at baseline testing

Blood Tests for TB infection

- Interferon-gamma release assays(IGRAs)
- whole-blood tests that can aid in diagnosing *M tuberculosis* infection
- They do not differentiate LTBI from active tuberculosis disease.
- Requiring only a single patient visit to conduct the test
- Results can be available within 24 hours
- There is no “ booster phenomenon” measured by subsequent tests
- Prior bacille Calmette-Guerin (BCG) vaccination does not cause a false-positive IGRA result





➤ **Disadvantages include :**


- **A higher false-positive rate than TSTs in relatively low-risk, serially tested workers**
- **Requirement that samples be processed within a specified time (8- 30 hours) after collection**

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- ▶ **Occupational candidates who should be given high priority for LTBI treatment include :**

Employees of high-risk congregate setting including :

- **Correctional facilities**
- **Nursing homes**
- **Homeless shelters**
- **Hospitals, other health care facilities**
- **Mycobacteriology laboratory personnel**

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- ▶ **Isoniazid (INH) plus rifapentine dosed weekly for 12 doses, rifampin dosed daily for 4 months, or INH dosed daily for 6 or 9 months.**

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- **Persons not known to have a previously positive skin test who have substantial contact with a person with infectious TB should be skin tested immediately**
 - **Then retested 8-12 weeks after the infectious contact**
 - **If conversion occurs, physical examination and chest radiography should occur to rule out acute clinical infection before beginning therapy for LTBI**