

HEPATITIS C

Hepatitis C in Children

Hepatitis C is caused by a bloodborne virus that slowly attacks the liver over many years. There is no vaccine for hepatitis C and no widely successful cure. Once a child is chronically infected with the hepatitis C virus (HCV), in most cases the infection will last a lifetime.

According to a World Health Organization (WHO) report, at least 170 million people—more than 2.8 percent of the world’s population—are chronically infected with HCV. That is nearly five times the number of people infected with HIV, the virus that causes AIDS. Over 6 percent of the world’s people are chronically infected with the hepatitis B virus.

In the United States, an estimated 3.9 million people—1.8 percent of the population—have been exposed to this virus. About 2.7 million are chronically infected with HCV, according to National Centers for Disease Control and Prevention (CDC) estimates.

An estimated 240,000 children and adolescents in the United States have been exposed to the hepatitis C virus, based on CDC estimates and a National Institutes of Health (NIH) report published in 2002. Pediatric specialists estimate that about 150,000 of these young people are chronically infected.

The latest National Health and Nutrition Epidemiological Survey (NHANES) estimates 0.2 percent of children under the age of 12 and 0.4 percent of youth ages 12 to 19 are infected with HCV. Most of the older children were exposed before America’s blood supply was screened for the virus.

Today, most new cases of hepatitis C in young children result from vertical (mother-to-infant) transmission of the virus. Between 5 to 6 percent of infants born to infected women contract the infection from their mothers, and the majority of those infants will develop a chronic infection.

In teens and adults, illegal injecting drug use with contaminated needles causes most new HCV infections.

Currently, CDC estimates there are approximately 25,000 new HCV infections each

year in children and adults.

About 15 to 25 percent of adults exposed to the virus will be able to fight off the infection and recover, but the remaining 75 to 85 percent face lifelong chronic HCV infection. Of these, 30 percent develop liver damage that ranges from mild to life-threatening, and less than 3 percent will die from chronic liver disease. There are no firm data on those infected as children.

Liver failure from chronic hepatitis C is one of the most common reasons for liver transplants in the United States. This infection causes between 8,000 to 10,000 deaths annually in the United States.

Because the virus mutates so frequently, creating slightly different versions of itself as it replicates, the virus is able to easily evade the body's immune system. This has made it extremely difficult to develop a vaccine against the virus.

Adult deaths from hepatitis C are expected to triple in the next 10 to 20 years as people reach the age and stage of the disease when serious liver complications occur. Epidemiologists have also predicted that hepatitis C will boost demand for liver transplants five-fold over the next decade.

The majority of those infected in the United States contracted the virus through blood transfusions that took place before July of 1992, which is when blood banks began effectively screening donated blood for the virus. The number of new infections has declined from an average of 240,000 per year during the 1980s to about 25,000 per year.

But the infection continues to decimate certain groups in the United States. According to a National Institutes of Health (NIH) report, HCV infects:

- One in 13 African Americans
- 39 percent of male prison inmates
- 55 percent of female prison inmates
- 40 percent of the homeless

The Identification of the Hepatitis C Virus

Acute infectious hepatitis was first recognized in 1885; the hepatitis B virus was identified in the 1960s and the hepatitis A virus in 1973. After that time, all other forms of viral infectious hepatitis were called NANBH, or non-A, non-B hepatitis, until 1989, when the hepatitis C virus was identified. Ninety percent of those with NANBH are

believed to have HCV infections.

In 1987, scientists under the direction of Dr. Daniel W. Bradley of CDC and Dr. Michael Houghton of Chiron Corp. identified the hepatitis C virus using specialized genetic chemistry that decoded the sequence of amino acids and proteins by analyzing the biochemical properties of RNA.

In 1989, scientists used molecular cloning to identify the virus in detail. In 1990, scientists developed a test that could detect hepatitis C virus antibodies in blood. While increasing the safety of the blood supply, the test was not 100 percent reliable. Because it takes 20 to 28 days after infection for the immune system to create antibodies against the virus, a newly infected person could donate blood during that window and the screening test would fail to identify any tell-tale antibodies.

Before 1986, the risk of HCV infection from blood transfusions in the United States was between 5 and 13 percent for each unit transfused. Between 1986 and 1990, when rudimentary testing of donor blood began, the risk declined to between 1.5 to 9 percent. When the second, more sophisticated generation of screening tests became available in 1992, the risk of HCV infection from a unit of transfused blood declined to 0.6 to 3 percent, according to CDC.

Today, the risk of HCV infection from a blood transfusion in the United States is estimated at less than one in 1 million units of blood due to more sensitive tests.

Blood banks today use Nucleic Acid Amplification Testing (NAT), which detects tiny hepatitis C virus RNA particles of the virus. Hepatitis C virus RNA, called HCV RNA, is present in an infected person's blood even before the immune system produces antibodies.

Canadian and European blood services began screening blood with NAT in 1999. Outside Europe and North America, the risk of contracting HCV infection through contaminated blood supplies varies, depending on each country's ability to screen donor blood and the prevalence of HCV in the population.

Where Hepatitis C Occurs Worldwide

The World Health Organization (WHO) reports there are at least 170 million people chronically infected with HCV worldwide. No one knows how many children are chronically infected.

Because HCV infection is so “silent” in children, most known and reported cases are in adults who have liver disease symptoms related to hepatitis C. HCV infection prevalence rates in adults vary dramatically around the world. The infection rate ranges from a low 0.1 percent in Canada to an extraordinarily high 18.1 percent in Egypt.

These regional summaries from WHO indicate the percentage of people who have been exposed to the virus and test positive for the HCV antibody. The antibody can represent a current or resolved infection.

Africa

The overall prevalence of HCV infection in Africa is 5.3 percent. But within Africa, the infection rate varies from Rwanda’s 17 percent rate, followed by Burundi at 11.1 percent, Guinea at 10.7 percent and Zimbabwe at 7.7 percent. On the low range, Ghana has a 2.8 percent infection rate and Ethiopia has a low infection rate of 0.8 percent.

South and Central America and Mexico

Bolivia has the highest HCV infection rate of 11.2 percent, Suriname is at 5.5 percent and Trinidad and Tobago are at 4.9 percent. On the lower range, the Dominican Republic has a rate of 2.4 percent, Peru is at 1.6 percent and Mexico has a low 0.7 percent rate.

Middle East and Southern Asia

In the Eastern Mediterranean region, the overall prevalence is 4.6 percent, second only to Africa for regional infection rates. Egypt has the region’s highest rate, with 18.1 percent of the population infected with HCV. Kuwait has a 3.3 percent rate, Pakistan 2.4 percent, Saudi Arabia 1.8 percent and Morocco’s rate is 1.1 percent.

Europe

Europe has an overall prevalence of 1.03 percent. On the high end, in Romania, the rate is 4.5 percent, Russia has a 2 percent rate, and Turkey and Greece both report a rate of 1.5 percent. The United Kingdom has a 0.02 percent rate, as do Finland and Denmark.

Asia and the South Pacific

Southeast Asia has an overall prevalence rate of 2.15 percent. Thailand’s rate is 5.6 percent, Vietnam 6.1 percent and Cambodia 4 percent. India is at 1.8 percent and Nepal is at 0.6 percent. Mongolia has the highest rate in Asia, with a 10.7 percent prevalence,

while China has a 4 percent rate and Japan has a 2.3 percent rate. Australia and New Zealand both have just 0.3 percent of the population infected.

HCV transmission in those countries results primarily from the use of improperly sterilized needles and syringes and injecting drug use.

North America

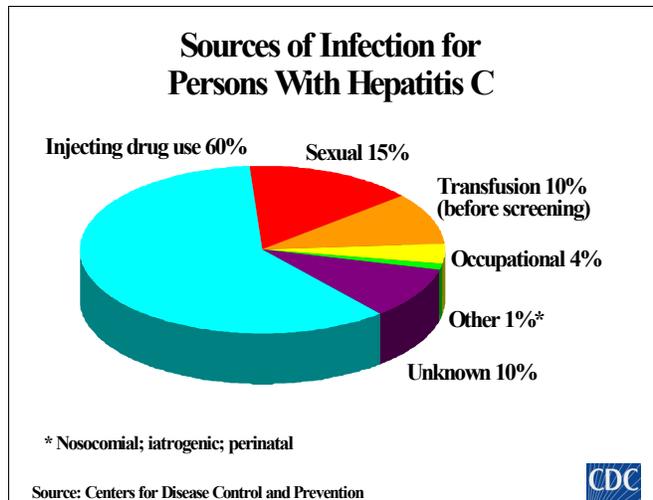
The prevalence of chronic infection in the United States is 1.8 percent while Canada’s rate of infection is estimated at 0.1 percent.

HCV Infection in the United States

Hepatitis C is the most common bloodborne infection in the United States, according to reports presented at the 2002 NIH Consensus Development Conference on hepatitis C. But finding the exact number of infected children and adults is difficult because hepatitis C usually presents no symptoms for decades after initial infection.

According to the third National Health and Nutrition Examination Survey (NHANES), a national survey of a representative portion of the U.S. population, an estimated 3.9 million Americans have been infected with HCV. Of this population, 2.7 million are thought to be chronically infected.

Epidemiologists struggle to report the precise numbers of newly infected children and adults in the United States each year. “Cases of hepatitis C reported to CDC are considered unreliable because 1) no serologic marker for acute [new hepatitis C] infection exists, and 2) most health departments do not have the resources to determine if a positive laboratory report for HCV infection represents acute infection, chronic infection, repeated testing of a person previously reported or a false-positive result,” wrote CDC epidemiologists when summarizing hepatitis C infection rates in the United States during 2001.



According to CDC calculations, made after adjusting for underreporting and asymptomatic infections, they estimated the annual number of new HCV infections to be about 25,000 cases in 2001. This represents almost a 90 percent decline in new infections since the 1980s, when new HCV infections each year averaged 230,000.

But while the number of new infections is declining, the prevalence of liver disease caused by HCV is on the rise. According to CDC, hepatitis C ranks just slightly behind alcoholism as the leading cause of chronic liver disease, liver failure and liver cancer in adults in the United States.

The NIH reports hepatitis C alone, or in combination with alcohol abuse, is responsible for almost half of all adult transplants in the United States today. Because of the slow progression of the disease, hepatitis C is responsible for very few pediatric transplants. During 2002, 11 liver transplants were performed on children with hepatitis C under the age of 18.

Infection by Age

The age of those infected with HCV varies around the world. The infection rate in Egypt increases steadily with age, with the 50 and older age group facing a 45 percent infection rate. About 30 percent of Egyptians ages 30-39 are infected and 5 percent of Egyptian children age 9 and younger are infected.

The reason for this age curve of infection was a mass inoculation with reused, contaminated syringes that took place in Egypt from 1960 to 1987. In an attempt to stop schistosomiasis (an illness caused by parasitic worms in the blood, resulting in intestinal disease), many people were immunized. Oral treatment to prevent the parasitic infection became available in 1982.

The practice of reusing syringes in medical settings has played a significant role in transmitting bloodborne viruses in many countries, including Romania, Moldova and Pakistan. In Japan, there is a demographic disease curve similar to that in Egypt. There is a 10 percent HCV infection rate among those 50 and older and a 5 percent infection rate in those ages 30 to 39. The infection rate is nearly zero in children age 9 and younger.

According to NHANES, a survey conducted by CDC's National Center for Health Statistics, the highest HCV infection prevalence in the United States is among the 30 to 39 age group, which has an infection rate of about 5 percent. Illegal injecting drug use is believed to cause most infections in this age group. The infection rate decreases to 1

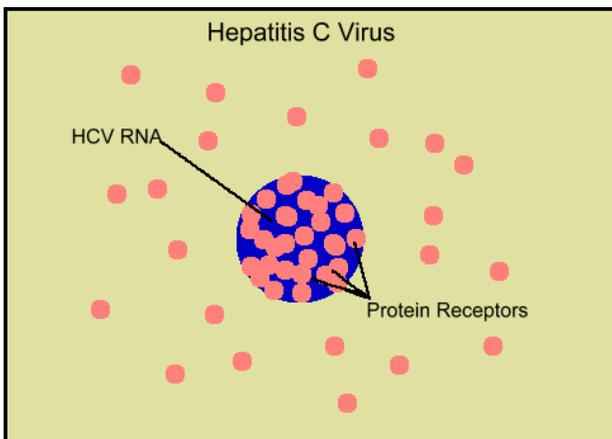
percent in those 50 and older.

HCV infection in very young children in developing countries results primarily from improperly sterilized syringes and medical equipment and vertical transmission.

What Is the Hepatitis C Virus?

The hepatitis C virus is an RNA virus of the Flaviviridae family. Other viruses in the Flaviviridae family include West Nile virus, yellow fever, Dengue fever, and Japanese encephalitis. The hepatitis C virus is not related to the viruses that cause hepatitis A, B, D or E infections.

The virus is a linear single-strand RNA (ribonucleic acid) virus, about 50 nanometers in diameter. (A nanometer is one-billionth of a meter.) The virus consists of a core of



genetic material, its RNA, surrounded by a protective shell of protein (nucleocapsid), coated with an outer envelope of fatty cellular material.

The RNA viruses are unique in that their genetic information is stored in the RNA, and not the DNA, as is the case with most living things. In organisms other than RNA viruses, the RNA is only a messenger of information, with permanent genetic information stored in the

DNA.

A DNA molecule is a stable molecule, and in the process of copying the molecule, very few mistakes are made. This makes it an ideal molecule for storing genetic information. In contrast, an RNA molecule is an unstable molecule that makes frequent mistakes during its replication process, which makes it poorly designed for storing genetic information. However, this changeability makes RNA ideal for storing viral information.

Normally, when the immune system recognizes an infecting virus, it makes antibodies to quickly destroy the viral invader. Because RNA makes slightly different copies of itself as it replicates millions of times each day, antibodies have a much harder time recognizing and killing the viruses in their various mutations. In most cases, the

antibodies are not made fast enough, and they lack the flexibility and diversity to defeat all the infecting viruses.

This reproductive mutation strategy in RNA viruses makes HCV a powerful virus when it comes to escaping the body's immune system.

While the virus evades the immune system, it is alive and well and uses the liver cell's resources to replicate very efficiently.

Because of its mutations, scientists are struggling to find an effective drug to combat the virus and a vaccine to prevent its numerous genetic variations.

Hepatitis C Genotypes

In addition to its ability to mutate or change its structure within a liver cell, around the world there are several genotypes or strains of the virus. These genotypes can vary in genetic composition by as much as 35 percent. Genotype classification is used to identify the distinct genetic (and sometimes regional) variations of the virus.

So many subtypes within individual genotypes have been discovered recently that to date researchers have identified and named 11 genotypes and more than 50 subtypes of HCV. The most common genotypes are 1, 2, 3, 4, 5 and 6. A letter after the genotype number indicates the subtype. The normal mutations that occur in these flexible viruses during viral replication occur within each genotype.

One way to look at genotypes is to compare the virus to dogs. Many different groups or "genotypes" of dogs exist. A group of dogs, like terriers, could be thought of as a single genotype, such as Genotype 1, and hounds could be Genotype 2. Within each group or genotype, there are several breeds, just like the subtypes within each hepatitis C genotype.

Under the Genotype 1 of terriers, there are wire-haired fox terriers (1a), Jack Russell terriers (1b) and so on. Even within "purebred" breeds, there are slight variations, such as smooth coat versus a wiry coat. These minor variations, within each genotype, are the mutations the hepatitis C virus creates every time it replicates.

"Mixed breeds" within genotypes, such as 1a/1b, and even a mixture of two different genotypes, such as 1a/3, occurs in 2 to 4 percent of infected people.

The specific characteristics of each genotype are not well understood. Medical

researchers are just starting to discern the clinical nuances between these viral genotypes. They have found that Genotypes 2 and 3 appear more likely to respond to treatment with interferon alpha, or interferon combined with ribavirin, than does Genotype 1. Genotype 1b seems to be associated with a faster progression to cirrhosis than other genotypes.

In a study published in the May 2001 issue of the *European Journal of Gastroenterology and Hepatology*, 2,307 adult patients with HCV infections were evaluated for genotype and severity of the disease. The overall survival of patients with Genotype 1b was poorer than of patients with other genotypes. Additionally, those with Genotype 1b had a higher rate of cirrhosis, serious scarring of the liver.

A person's genotype does not significantly change during the natural history of his or her infection. However, a person with a resolved HCV infection can be re-infected with the same genotype, or a different genotype of HCV. According to Dr. Miriam Alter of CDC, a formerly infected person's immune system often cannot recognize a virus from the same genotype again, due to the rapid mutation of the virus.

Within a single genotype, the viral particles are all slightly different from one another, which renders the hepatitis C antibodies powerless in fighting the ever-mutating viruses. The ever-changing composition of the virus also renders people vulnerable to new HCV infections or re-infections.

Known Genotypes of HCV

According to an article in the *Journal of General Virology*, the hepatitis C virus probably developed 500 to 2,000 years ago, based on study of the origins of the major genotypes, combined with data about other RNA viruses. The most recent variations of genotype 1b are believed to have evolved 70 to 80 years ago. Numerous subtypes are believed to have developed over 300 years in certain geographic regions, while others have emerged more recently. The current geographic distribution of various genotypes and subtypes offers clues into this viral evolutionary process.

Within the six main genotypes, there are subtypes ranging from one to five subgroups within a single genotype. Some genotypes can be found anywhere in the world, but there are some geographic trends worth noting:

- Genotype 1a is found primarily in North and South America and Australia. About 70 percent of patients in the United States are infected with genotype 1. Genotype 1a is common in the United Kingdom. Genotype 1b is mostly found in Europe and Asia,

and common in Japan. Unfortunately, studies show genotype 1 is more resistant to therapy than genotypes 2 or 3.

- Genotype 2a is the most common in Japan and China. In Japan, Taiwan and China, 1b and 2b are also found. Genotype 2b is the most common subtype of genotype 2 in the United States and Northern Europe. Genotype 2c is the most common subtype of 2 in Western and Southern Europe.
- Genotype 3 is prevalent in Scotland and other parts of the United Kingdom, Europe and to a lesser degree in the United States. Genotype 3a is highly prevalent in Australia and Southern Asia.
- Genotype 4 is the most common genotype in the Middle East and Northern and Central Africa. Genotype 4a is prevalent in Egypt. Genotype 4c is highly prevalent in Central Africa.
- Genotype 5a is prevalent only in South Africa.
- Genotype 6 is found mainly in Asia and in Hong Kong. Genotype 6a is restricted to Hong Kong (it accounts for one-third of those infections), Macau and Vietnam.
- The lesser-known genotypes 7a and 7b are common in Thailand.
- The lesser-known genotypes 8a, 8b, and 9a are prevalent in Vietnam.
- The lesser known genotypes 10a and 11a are found in Indonesia.

Response to Treatment May Depend on Genotype

Which genotype a child or adult has usually dictates how he or she will respond to conventional interferon, pegylated interferon and ribavirin—the only available therapies to treat HCV infections. That is why it is important to find out what a child’s genotype is if treatment is being considered.

Historically, children with genotypes 2 and 3 have a high rate of viral clearance (70 percent) when they are treated with interferon.

In contrast, those with genotype 1, who make up most of the children infected with HCV in the United States, have a much lower rate of clearing the virus (26 percent) when treated with just interferon, according to NIH reports.

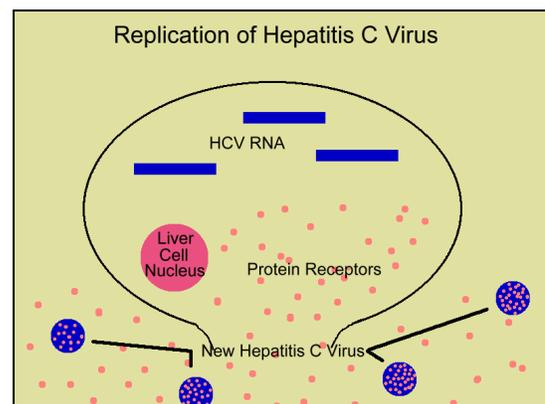
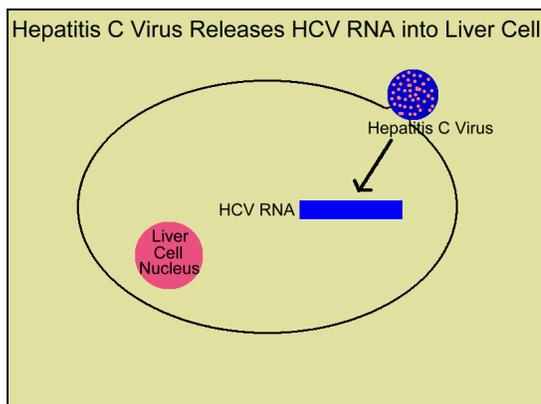
HCV genotype is determined by an enzyme immunoassay (EIA) test that identifies the viral genotype by examining the make-up of the hepatitis C antibodies. The test will identify only a main genotype (genotypes 1 to 6), but not the subtype of HCV. To date, no HCV genotyping test has been approved by the FDA.

Currently, doctors will test a child's genotype only if they are considering treating the child for liver damage or if a parent requests it.

How the Hepatitis C Virus Infects Individuals

The bloodborne virus enters the bloodstream through a laceration of the skin, contaminated needles, or through a break in the mucous membranes around the eyeballs, nose, mouth or genitals and travels to the liver, where cells have the biochemical properties the virus needs to set up shop and replicate.

Once in the liver, the virus invades and occupies liver cells, using each cell's resources to replicate thousands of times. Eventually, the liver cell dies from having its resources exhausted by this viral replicating machine. Liver cells are also killed by the immune system's attempt to eradicate the infection. Because the virus is embedded inside the liver cell, the body's defenses hammer at the liver cell itself in an attempt to kill the virus.



Because scientists have not been able to culture or isolate hepatitis C viruses in a laboratory setting, the exact mechanism of how the virus enters liver cells is not known. But based on observations of viruses similar to HCV, researchers hypothesize that when the HCV particle reaches a liver cell, it attaches itself with special proteins (receptors) on the liver cell's outer coat. The virus is then taken up by the cell. The RNA of the virus

then sheds its protective coating, giving it full access to the liver cell.

The RNA takes over the functions of the liver cell in order to replicate itself. The liver cell is tricked into reproducing the virus as part of its normal cell function. In some cases, other functions of the cell are shut down in order to conserve energy for viral reproduction.

The RNA is copied thousands of times, making genetic material for new viral particles. However, every time the RNA is copied, there are numerous, slightly different versions of the viral genetic information made.

The virus then uses the cell's own resources to create the other components and proteins that the virus needs to assemble new viruses.

The newly-formed viruses are released through a budding process. Either an intracellular membrane or the plasma membrane encircles the virus and provides its lipid coating during the release process.

Since the lipid coating on each viral particle was created under the direction of the RNA within the cell, each coating is slightly different, which makes it hard for antibodies to identify and attack each virus. This mutation, along with the virus's prolific replication rate, makes it successful and virulent.

The virus's ability to evade the immune system so effectively is why most children and adults infected with HCV cannot fight off the infection.

When the infection continues for more than six months, it is considered chronic.

During chronic HCV infection, the viruses replicate in liver cells at fluctuating rates. Initially, during the first 10 or 20 years of the disease, there may be little liver damage. But over time, the immune system's repeated attacks on infected cells can seriously damage the liver. The more serious liver damage and intense scarring of the liver, called cirrhosis, generally occur after decades of infection in 20 to 25 percent of those chronically infected.

HCV Infection in Children

In a study published in *Blood* in 1997, researchers followed 56 HCV infected children who had detectable HCV RNA levels, which indicates an active infection. These children had been infected by blood or blood products used in treatment of childhood leukemia prior to the implementation of blood screening.

Seventeen years after the initial detection of hepatitis C antibodies, 16 of the 56 children had no detectable HCV RNA in their bloodstream. This group experienced a 28 percent clearance rate, which means 72 percent of the children became chronically infected.

A study by Dr. M. Vogt published in *The New England Journal of Medicine* followed 67 children with HCV antibodies who had undergone cardiac surgery 17 years earlier. Of these children, 37 patients or 55 percent, still had HCV RNA (an active infection) 17 years after the surgery.

While these two studies indicate children might have a slight advantage over adults in clearing the virus, there is insufficient data to draw strong conclusions at this time.

Progression of HCV Infection

Within seven to 21 days after exposure to HCV, the virus's RNA (HCV RNA) can be detected in the blood. However, HCV antibodies to the virus can take 20 to 150 days to appear, with an average of 50 days.

According to Drs. Harvey Alter and Leonard Seeff, authors of *Recovery, Persistence, and Sequelae in Hepatitis C Infection: A Perspective on Long-term Outcome*, in 80 percent of acute infections, the antibodies are detectable within 15 weeks. In rare cases, it may take as long as six to nine months for antibodies to appear, however that may not indicate chronic infection.

In acute or short-lived infections, the body's immune system succeeds at fighting off infection, and the HCV RNA disappears within a few weeks. In chronic HCV infection, the body's immune system is unable to completely clear the virus over the course of several months and the HCV RNA usually persists for a lifetime.

Most pediatric gastroenterologists report they never or very rarely diagnose acute cases of HCV infection in children because most young people are asymptomatic during acute phases. Typically, the infection is diagnosed when a child is screened because the mother is diagnosed with HCV infection or when it becomes a chronic condition and causes enough liver damage to produce symptoms.

HCV antibodies persist in all who are infected, although they may not be detectable, no matter if the infection is cleared quickly or becomes chronic. The antibodies appear to do little to actually fight the infection because of the virus's ever-mutating composition.

According to Dr. Maureen Jonas, a pediatric gastroenterologist at Children's Hospital

Boston who reported on hepatitis C and children to the NIH Consensus Development Conference on hepatitis C in 2002, researchers have had two populations of children infected with HCV to study.

- One group contracted HCV infection through tainted blood transfusions before initial screening began in 1990.
- The second group was infected by their mothers at birth.

“Independent effects of age at acquisition and mode of acquisition on natural history are difficult to separate in pediatric studies,” she reported to NIH. “In addition, the natural history of transfusion-associated HCV infection may differ according to the underlying disease for which transfusion was required.

“Some children who were transfused at the time of surgery for congenital heart disease developed chronic hepatitis, but others cleared the infection,” she reported. “Children treated for leukemia prior to 1990 have a very high rate of HCV infection, but one ... prolonged follow-up study did not commonly reveal serious liver disease.

“In contrast, an American study of individuals treated for childhood cancer revealed one death from liver disease and two deaths due to [liver cancer] in the decades following HCV acquisition,” Jonas added. “Clearly, some cases of HCV infection acquired in childhood by transfusion are associated with serious liver disease in the decades following infection.”

Jonas and others have pointed out that no one knows yet whether the natural history of HCV infections acquired perinatally—from an infected mother—will be different from HCV infections acquired through transfusion.

“Vertically infected infants typically have elevated alanine aminotransferase [ALT] levels [which appear when liver cells are injured or die] for a few years, and those levels often become normal,” Jonas added. It appears that children who acquire it vertically experience some liver injury early in life, but most show signs of only a mild liver disease during their early decades.

“However,” added Jonas, “in some children the infection takes an aggressive course leading to cirrhosis and even end-stage liver disease during childhood; the factors responsible for this are as yet unidentified.”

What doctors are certain of, however, is that when children are coinfecting with HCV

and hepatitis B or HIV, these dual infections usually produce more severe symptoms and, as with coinfecting adults, a more rapidly progressing liver disease.

Liver biopsies, in which a biopsy needle extracts liver cells, provide the best insight into the impact and progression of HCV infection in children. According to an article by Dr. David Kleiner, published in *Hepatitis C, Biomedical Research Reports, 2000*, studies of liver biopsies from large groups of infected children show the pattern and progress of liver injury over time are similar in children and in adults.

In *Hepatitis C, 2000*, Drs. Jay Hoofnagle and Giovanna Fattovich reviewed five studies of children's biopsies. They found children had less fibrosis (liver scarring) and inflammation than adults, and only about 3 percent of children experienced cirrhosis (severe scarring of the liver). However, they noted that because children haven't been infected for the same length of time as adults, it is difficult to compare pediatric patients to adult patients.

In a German study of children who tested positive for HCV antibodies after cardiac surgery, 17 of the chronically infected patients with HCV RNA underwent liver biopsies. Two (12 percent) had fibrosis or some scarring in their livers. One of the patients, who was also coinfecting with the hepatitis B virus, had a more serious level of cirrhosis. The remaining 14 patients had little or no liver damage. This study shows a relatively benign course of the disease in transfusion-infected children over a 17-year period. If the patient with the coinfection was excluded, only two of the remaining 16 or 12.5 percent of the children had fibrosis or some type of scarring 17 years after infection.

According to Drs. Harvey Alter and Leonard Seeff, it is unclear whether the impact of HCV infection in children is milder, or whether the disease simply has not progressed in their short life spans. To date, doctors generally agree that the majority of infected children do not develop advanced liver disease during their first 20 years of life.

It appears from these studies that after 17 to 20 years of infection, about 12 percent of the children may experience some liver injury, while 3 to 4 percent will progress to more serious liver disease, such as cirrhosis. Very rarely will a child progress rapidly to cirrhosis. There is no data on how the disease progresses beyond 20 years in those infected as children.

Because the disease appears to be very mild during the first 15 to 20 years of infection, doctors expect most children chronically infected will not experience adverse effects until they reach adulthood.

T-cells and the Battle Against Infection

In a report published in *Hepatology*, Dr. Kyong-Mi Chang and associates examined the responses of two types of T-cells that play a critical role in fighting and defeating HCV infections. T-cells are lymphocytes or white blood cells that fight infection.

Dr. Chang studied two types of T-cells, CD4 and CD8, in three groups of adults: those with chronic hepatitis C who had both the HCV antibody and HCV RNA in their bloodstream, those who had recovered from HCV infection and had only antibodies in their blood, and a test group of uninfected people. They analyzed the T-cells in each group.

They found people who recovered from HCV infection maintained a steady and vigilant CD4 T-cell response indefinitely. Their immune systems were always prepared to swing into action and defeat the virus all over again. But in chronically infected patients, the CD4 response was very weak. Only the CD8 T-cells rallied, though unsuccessfully, against the viruses. These results suggest that a strong CD4 T-cell response may be critical to clear the hepatitis C virus and maintain recovery.

Progression of HCV Infection

The progression of HCV-related liver disease may be accelerated by alcohol consumption, coinfection with other viruses or other factors, such as method of infection or age at infection.

One of the biggest factors in the severity of liver disease in children with HCV infection appears to be coinfection.

Alcohol abuse plays a critical role in liver health, according to a 1998 article in *Hepatology*:

- If an adult is healthy, but drinks heavily, consuming more than four drinks (6.1 ounces or 175 g) of alcohol per day, the chance of developing cirrhosis increases to 15 times that of a healthy non-drinker.
- If an adult does not drink and has HCV infection, the chance of developing cirrhosis is 9.2 times greater than a healthy person who does not drink.
- If an adult is a heavy drinker and also has chronic HCV infection, the chance of developing cirrhosis is 147 times that of a healthy non-drinker.

The timetable and development of liver disease in children with hepatitis C is difficult to track because most children have not been diagnosed and therefore data are not yet available.

Researchers are currently studying whether children who contracted the virus through transfusions fare better than those who contracted it perinatally. In adults medical researchers have associated the following factors with a more rapid progression to liver disease:

- Contracting the infection at age 40 or older
- Moderate to heavy alcohol consumption
- Male gender
- Genotype 1b, which may be a more virulent strain

Hepatitis C Symptoms

Identifying symptoms of HCV infection in children and adults is challenging. Most people infected with HCV don't know it, and years pass before doctors diagnose and start tracking the disease. There are no symptoms in more than half of those infected with HCV. It often takes 15 years or longer for symptoms to develop, if they ever do.

Symptoms of acute HCV infection are similar to other forms of acute hepatitis and include jaundice, nausea, dark urine and appetite loss.

Only 5 to 25 percent of people acutely infected with the virus recall experiencing any symptoms at all because acute symptoms are generally mild. Dr. Regino González-Peralta, a pediatric gastroenterologist with the University of Florida, reports he has diagnosed no children with acute HCV infection, which illustrates what many other pediatricians report—that acute HCV infections in children are either undetected, or lack symptoms significant enough to prompt medical attention.

According to Dr. González-Peralta, symptoms such as fatigue, pruritus (itching, sometimes severe), ascites (swelling due to accumulation of fluid), coagulopathy (disorders in blood-clotting ability), esophageal varices (enlarged blood vessels in the esophagus), and hypersplenism (swollen spleen), only appear in the rare cases when HCV infection progresses to severe liver disease and cirrhosis during childhood. Dr. González-Peralta notes the “average hepatitis C child” has mild symptoms, if any.

Extrahepatic Manifestations

Most of the extrahepatic manifestations (disorders and diseases that occur outside the liver) associated with HCV infections are rare in children and adults. Because children are infected for a shorter period of time than most adult patients who have been studied, doctors say it may be many years before they experience any of these problems.

One health problem linked to chronic HCV infection in adults is cryoglobulinemia. About 1 to 2 percent of adults get this complication that produces skin rashes, joint and muscle aches, and kidney disease. However, according to Dr. Philip Rosenthal, pediatric hepatologist and medical director of the Pediatric Liver Transplant Program at the University of California, San Francisco, this symptom has not been observed in children with HCV infections.

Another symptom is glomerulonephritis, a disease of the kidneys that can lead to kidney (renal) failure. Dr. Maureen Jonas, an expert in pediatric HCV infections, reported she has seen one child with hepatitis C with this condition.

Another less well-documented complication is sicca syndrome, an autoimmune disease where the body attacks its own moisture-producing glands.

How Is HCV Transmitted?

Before 1990—1992, most children acquired HCV infection through infected blood transfusions or contaminated blood products. This included transfusions for:

- **Thalassemia**, a disorder resulting from an imbalance in the production of amino acids in the blood.
- **Sickle cell anemia**, a disease characterized by sickle-shaped red blood cells and chronic hemolytic anemia.
- **Congenital anemia**, a disease that occurs when a defective gene results in an abnormal red cell membrane.
- **Hemophilia**, a bleeding disorder caused by a deficiency in one of the blood clotting factors.
- **Hemodialysis**, a process where toxins are mechanically filtered from the blood when the kidneys no longer function adequately.

Because many children who became infected through transfusions and blood products had other serious diseases as well, this has made it difficult to study the natural course of the disease in otherwise healthy children.

Immune globulin made with contaminated plasma is responsible for some infections during 1993 and 1994. Since December 1994, all immune globulin produced in the United States is tested prior to release.

Currently, the most common route of adult transmission of HCV in the United States is through injecting drug use. Approximately 43 percent of acute cases of hepatitis C today are related to illegal injecting drug use.

Improperly sterilized hypodermic needles are a highly efficient method of transmitting the hepatitis C virus. About 60 to 90 percent of illegal drug users in the United States become infected within a few months of injecting drugs. After five years, about 90 percent of injecting drug users test positive for HCV antibodies, according to CDC. Cocaine users who have open sores and ulcers in their noses may also transmit the virus through shared straws, though this transmission route has not been well documented.

Another conduit is sexual transmission, although the efficiency of sexual transmission is low. Scientists hypothesize infection between long-term, monogamous heterosexual partners is rare because of low levels of HCV in semen and/or because the cells lining the vaginal wall are not efficient receptors for the virus.

In a study of 234 couples in Japan published in the *Journal of the American Medical Association* in 1995, both partners tested positive for HCV antibodies in only 17 couples. In the 11 couples whose genotype was determined, only half had similar genotypes, indicating HCV transmission in half of the cases was from a source other than the spouse.

In a study published in the *Journal of Infectious Diseases* in 1995, heterosexual couples in the United States who used sexually transmitted disease clinics were studied. Females whose sexual partners were infected with HCV were 3.7 times more likely to also be infected than females whose partners were negative. Males' HCV status was not at all impacted by their female partners' status. This suggests male-to-female transmission is much more efficient than female-to-male transmission, as is the case with HIV.

The CDC currently does not advise people with HCV infection in long-term monogamous relationships to change their sexual practices. But the risk of sexual transmission exists and underscores the importance of teaching safer sexual practices to adolescents

and even pre-teens to prevent all sexually transmitted infections and diseases.

Household transmission from an infected family member to an uninfected member through regular daily contact is rare. According to CDC, no transmission of HCV to healthcare workers has ever been documented when either intact or bruised or chapped skin was exposed to blood infected with HCV. Unlike hepatitis B, the virus does not survive long outside the body.

However, transmission can happen through contact with infected blood by sharing toothbrushes, nail clippers, razors, manicuring tools and other personal care items.

CDC recommends the following people be screened for HCV:

- Anyone who ever injected illegal drugs
- Anyone who received a blood transfusion or organ transplant before July 1992
- Anyone who received clotting factor concentrates before 1987
- Anyone who was ever on long-term dialysis
- Children born to HCV-positive women

Adolescents who engage in high-risk sexual behavior and body piercing or tattooing in an unregulated or non-sterile environment are also vulnerable to the virus. Any child with abnormal Liver Function Test results, which may be performed for reasons unrelated to viral hepatitis, should be tested for HCV infection.

Perinatal Transmission of HCV

Vertical transmission (from mother to infant) of hepatitis C infections occurs in just 5 to 6 percent of births to infected mothers, according to CDC. Of those children who are infected at birth, approximately 75-85 percent of them will develop chronic infections and the remaining 15-25 percent will resolve their acute infection.

There is still confusion about what exactly causes some, but by no means all, pregnant infected women to transmit the infection to their newborns.

Researchers to date have found no difference between women who transmitted the virus to their newborns and those who did not when it came to their age, ALT levels, HCV

genotype or whether or not the mothers breast-fed.

Some key factors that may play a role when it comes to perinatal transmission are:

- The amount of viruses (HCV RNA) circulating in the mother's bloodstream during pregnancy. Researchers suspect that the higher the mother's viral load (the amount of HCV RNA in her bloodstream) at various stages of pregnancy and time of delivery, the more likely the chance of infection.
- Whether she is coinfecting with HIV. Transmission is much more likely if mothers are coinfecting with HIV. Infants born to mothers who test positive for both HCV RNA and HIV face a 17 percent chance of contracting HCV.
- Injecting drug use history. Doctors have reported in some studies that they have found a higher transmission rate in women who are injecting drug users—even when they have no HIV coinfection.
- Whether certain immune cells called peripheral blood mononuclear cells are infected with the virus. The result of one study published in an edition of *Blood* magazine showed that when peripheral blood mononuclear cells of pregnant women contained strands of HCV RNA, the infection was passed to the newborn.

One study of 441 infected mothers in the United Kingdom, published in *The Lancet*, found no child delivered by elective C-section contracted the virus, while 7 percent of those delivered vaginally or by emergency C-section (after membranes ruptured) contracted the virus. These researchers suggested that avoiding rupture of the membranes in elective C-section procedures could avert perinatal transmission of the virus.

Another study suggests doctors refrain from performing an amniocentesis on pregnant, infected women because there is a risk of introducing the mother's blood into the baby's amniotic sac.

According to Dr. Maureen Jonas, it is also recommended that doctors refrain from using a fetal monitor, which is usually attached to the infant's scalp during delivery, to avoid transmission.

At this time, there are no studies documenting the transmission of hepatitis C to infants through breast milk. Women with HCV infection who are not coinfecting with any other virus may breastfeed, according to CDC. The majority of studies demonstrate similar

infection rates among breast-fed and non-breast fed infants. Women should take care that their nipples do not develop any open sores that could expose the baby to their blood.

All children born to infected mothers will temporarily carry their mothers' HCV antibodies, but these maternal antibodies usually disappear after 12 to 15 months. However, it is possible to determine if a baby is truly infected with HCV by testing for HCV RNA using an RNA Polymerase Chain Reaction (PCR) test. If HCV RNA are present, then the child is infected with HCV.

HCV infection is not spread through coughing, sneezing, shaking hands, hugging, sharing food, using the same toilet, swimming in the same pool or drinking from the same water fountain. It is not spread by mosquitos. The virus must enter the body through an opening in the skin, or through a mucus membrane, to reach the liver and cause infection.

What Tests Are Used to Diagnose an HCV Infection?

Two types of tests are used to diagnose and monitor HCV infections in children and adults. One test looks for the presence of hepatitis C antibodies, and the other looks for the presence of HCV RNA, which indicates an active hepatitis C infection.

After initial diagnosis, doctors may also conduct a third test to determine the genotype of a patient's virus.

Hepatitis C Antibody Tests

An HCV antibody test, conducted on blood drawn from a patient, determines if any HCV antibodies are present in the bloodstream. An enzyme immunoassay (EIA) test is used to detect HCV antibodies. According to reports made to NIH in 2002, the test is 99 percent accurate in detecting antibodies if someone has a healthy immune system.

Initially, an HCV antibody positive reading in a child could indicate:

- An existing HCV infection
- A resolved infection
- Passively-acquired maternal antibodies in infants
- On rare occasions, a false positive result

In infants born to infected mothers, doctors usually test for the HCV antibodies after an

infant has reached 12 to 15 months of age. However, these antibodies can linger up to 18 months. Testing for HCV antibodies prior to this age may produce “false positive” test results due to the presence of the mother’s antibodies in the baby. These antibodies can be passed on even if the mother has cleared the infection.

In toddlers and older children, doctors can test for HCV antibodies without risking a misdiagnosis because the mother’s residual antibodies will not be present.

To learn if a child has an active hepatitis C infection, doctors test for HCV RNA.

HCV RNA Tests

To truly determine if a child is infected with hepatitis C, doctors look for the presence of the active virus—the HCV RNA.

In infants born to infected mothers, a test for HCV RNA should generally be conducted twice, according to the 2002 NIH Consensus Development Conference report. The first test can be conducted when the baby is about two months old, and the second three to four months later.

In toddlers and older children, doctors test for HCV antibodies first if they suspect HCV infection. If a child tests positive for HCV antibodies after 15 to 18 months of age, usually doctors will then conduct an HCV RNA test to determine if an active infection is present.

A determination of whether the HCV RNA is present and in what volume in the blood-stream, called viral load, can be made through an RNA PCR test. There are two types of HCV RNA tests that doctors perform: qualitative HCV RNA tests and quantitative HCV RNA tests.

Qualitative HCV RNA Tests

A qualitative RNA PCR test produces either a positive or negative result, indicating whether or not the HCV RNA is detected. This is the more sensitive of the two tests and can identify viral particles that are so few that a quantitative RNA PCR test misses them. However, a qualitative test does not reveal the number of viruses circulating in the blood, called viral load.

Quantitative HCV PCR Tests

A quantitative RNA PCR test reveals the number or viral load of HCV RNA in the bloodstream. But if HCV RNA levels are extremely low, it may miss them completely and report HCV RNA to be undetectable.

An undetectable result from a quantitative PCR test could mean:

- The virus is no longer present in the body.
- The level of the virus is very low and not detectable with this test.
- A false positive antibody test result. If repeated quantitative viral load testing remains at undetectable levels, the patient either has a resolved infection, or a false positive antibody test.

A quantitative RNA PCR test result is often reported as a number (or quantity), in scientific notation form, such as 3.2×10^6 . The patient with this result would have a viral load of 3.2 million copies per milliliter of the virus in his or her system.

Generally, in adults, a quantitative result below 1 million per milliliter is considered a low viral load and 5 million per milliliter or higher is considered a high viral load. However, viral load may not be directly related to the extent or rate of liver disease in people with HCV. Viral loads can fluctuate extensively over the course of an infection.

People who clear their bodies of viruses during an acute infection would produce a negative RNA PCR, or an undetectable level of HCV RNA. Patients who clear the infection as a result of therapy have similar test results.

In the past, there have been many versions of HCV RNA tests, all using different units of measure and different technologies. As a result, tests performed by different labs were difficult to compare.

Today, all HCV RNA tests should use standard global units defined by the World Health Organization.

There are a number of companies that have developed very sensitive quantification HCV RNA tests. In 2002, two companies had submitted applications for sensitive viral load tests for HCV RNA to the U.S. Food and Drug Administration for approval.

The first test submitted to FDA during 2002 was a HCV bDNA test using branched DNA (bDNA) signal amplification technology. The second FDA submission was for a test using Transcription Mediated Amplification (TMA) technology. The TMA technology produces an ultra-sensitive test for HCV RNA.

No virologic test, such as HCV RNA or viral load or genotype, can measure the severity of liver disease or fibrosis. They simply indicate the status of the hepatitis C infection.

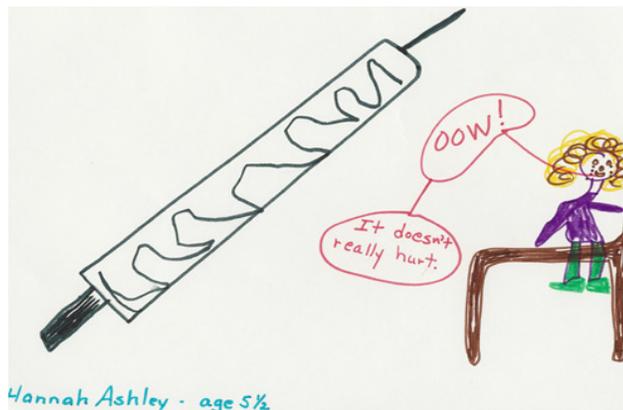
Additional Tests for Children with HCV Infection

In addition to the viral tests performed, doctors also examine a patient's blood for certain liver enzymes. When liver cells are damaged, they release enzymes such as aspartate aminotransferases (ASTs) and alanine aminotransferases (ALTs). However, these enzymes can appear normal even when liver damage occurs as a result of HCV infection.

When children are chronically infected with hepatitis C, liver enzyme tests (for ALT or AST) are usually repeated every six to 12 months. The HCV RNA test is repeated every six months or every year.

To date, there are no clear or definitive recommendations on what other types of tests should be performed on asymptomatic children with chronic HCV infection and with what frequency. However, the country's leading pediatric hepatologists recommend ALT, AST, HCV RNA and HCV antibody testing every six to 12 months, or more frequently if there are signs of liver damage or if a child is being treated.

An alpha fetoprotein test, which reveals the presence of liver cancer or tumors, may be performed once a year or more frequently if liver enzymes are elevated.



artwork by Hannah

Here is a summary of the viral tests performed for hepatitis C:

<p>Antibody to Hepatitis C Virus (Anti-HCV or HCVAb)</p>	<ul style="list-style-type: none"> • False-positive results may appear in patients with autoimmune chronic active hepatitis, alcoholic liver disease and other disorders relating to hypergammaglobulinemia. • The presence of an HCV antibody may be due to acute or chronic infection or a resolved infection. • An infant under 12 months of age may have passively acquired the antibody from his/her mother. • The presence of an HCV antibody does not mean a patient is immune to the virus.
<p>Available HCV RNA Tests:</p> <ul style="list-style-type: none"> • Branched-Chain DNA Assay (Quantiplex HCV RNA) • Reverse-Transcription PCR for HCV RNA (Cobas Amplicor HCV Monitor, HCV Superquant) 	<ul style="list-style-type: none"> • These specialized tests are considered the gold standard to assess chronic infection. They are also used for research or to assess drug therapy results. • They are used to determine the presence of HCV RNA circulating in the blood, which indicates the volume of viral replication in the liver. • Because they measure viral load, these tests may reveal how infectious a patient is. • These tests may be used during the early infection period before the body's immune system has produced HCV antibodies.

Importance of Hepatitis A and B Vaccines in Children with HCV Infections

Most children ages 2 and older with chronic HCV infection should be vaccinated against hepatitis A, and most children of any age with chronic HCV infection should be vaccinated against the hepatitis B virus. Those with chronic HCV infections who become infected with hepatitis A or B are at risk of fulminant hepatitis (a sudden and severe form of hepatitis).

Like all forms of viral hepatitis, the hepatitis A and B viruses cause acute inflammation of the liver. If children with HCV infections become infected with hepatitis A or B viruses, they face serious liver damage due to the additional virus infecting their inflamed or vulnerable livers. Their liver disease is usually accelerated and their chance of developing cirrhosis and liver failure much higher. At this time there is no hepatitis A vaccine licensed for children under the age of 2.

Status of the Hepatitis C Vaccine

Researchers are working to develop an effective hepatitis C vaccine, but development of an effective vaccine is still years away.

The main obstacle to developing a vaccine is the diversity of hepatitis C virus mutations. The ability of the virus's envelope protein to mutate and change itself makes it a complicated target to develop a vaccine against.

When researchers have isolated antibodies that can neutralize HCV, they find they are often effective only against one strain of HCV.

And, scientists are still researching why some people's immune systems are able to eradicate the virus after infection and prevent the development of a chronic infection. If they knew more about what made certain immune responses to the virus successful, they could use immune response to develop an effective vaccine.

But finding that critical immune response is a challenge. To date, scientists have not been able to develop a cell culture system or a small animal model for hepatitis C to use for vaccine experimentation. They have only been able to use chimpanzees to study HCV infection, and they are few in number and expensive to use.

The development of an HCV vaccine poses a great challenge due to the virus's various strains and mutations, and its ability to establish a persistent or chronic infection by effectively avoiding the immune system.

Studies performed in humans and chimpanzees suggest that defeating an HCV infection hinges on a strong immune response. Because the hepatitis C virus may cause serious liver damage after a lengthy infection, a vaccine that spurs the immune system into action early after infection first occurs is one of the important research goals, according to a report on the status of the HCV vaccine published in the *Journal of Hepatology* in 2002.

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