RGA®

ReFlections

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LETTER FROM THE EDITOR

Dear Readers:

In Volume 15 (September 2005) of ReFlections, I wrote an article entitled "Weighing-In on Obesity" in which I discussed the prevalence of obesity and its relationship to mortality. In this edition of ReFlections, I have revisited this topic to bring you up to date on RGA's involvement in understanding the epidemiological trends relating to obesity, which hopefully will contribute to a reversal of the observed patterns.

This issue of ReFlections also explores three other important topics: Prostate Cancer and PSA, Viral Hepatitis B and C, and MRSA. I hope you enjoy all of these articles.

J. Carl Holowaty M.D., D.B.I.M.

OBESITY REVISITED

By Dr. J. Carl Holowaty M.D., D.B.I.M.

Obesity Revisited

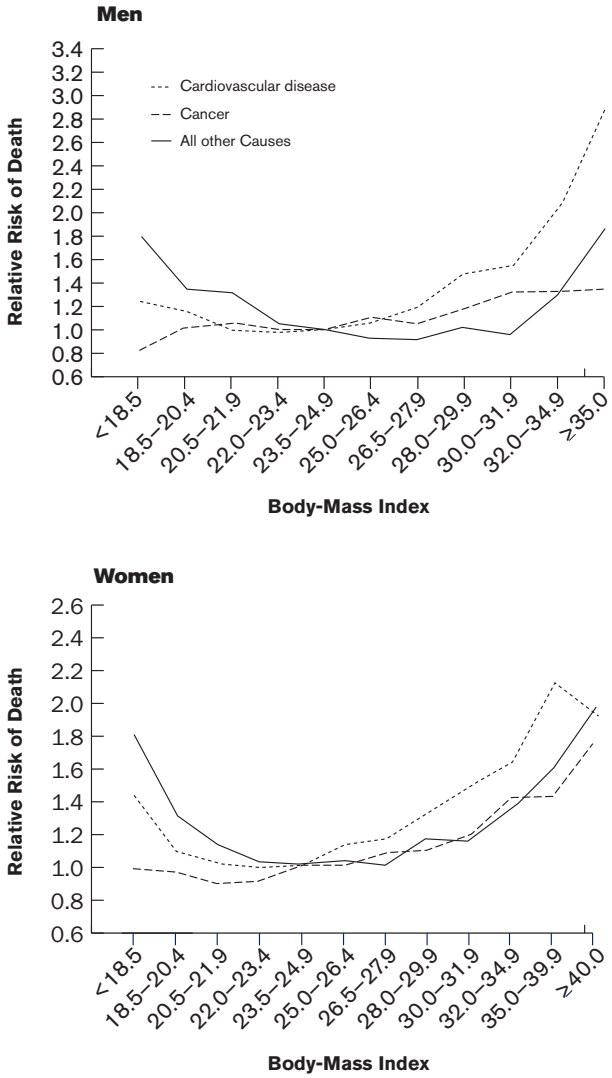
Obesity and a sedentary lifestyle have been linked to excess cardiovascular and all–cause mortality in both males and females as the charts below indicate.

While it may be possible to refine the mortality expectations based on the above tables, through the process of risk selection, the evidence linking obesity to excess mortality and morbidity remains a serious health and financial concern to individuals, insurers and healthcare providers.

Here are a few facts and figures provided by the Campaign to End Obesity:

- According to the Health Affairs Journal and RAND, 83 cents of every health dollar in America is spent on a patient who is overweight or obese.
- According to the U.S. Department of Health and Human Services, the total cost of obesity in the United State is $117 billion each year.
- The National Business Group on Health indicates that obesity was responsible for 39 million lost work days and 63 million physician visits.
- Obesity is associated with increased risk for cardio-vascular disease, hypertension, diabetes and a variety of cancers.

Risk Selection

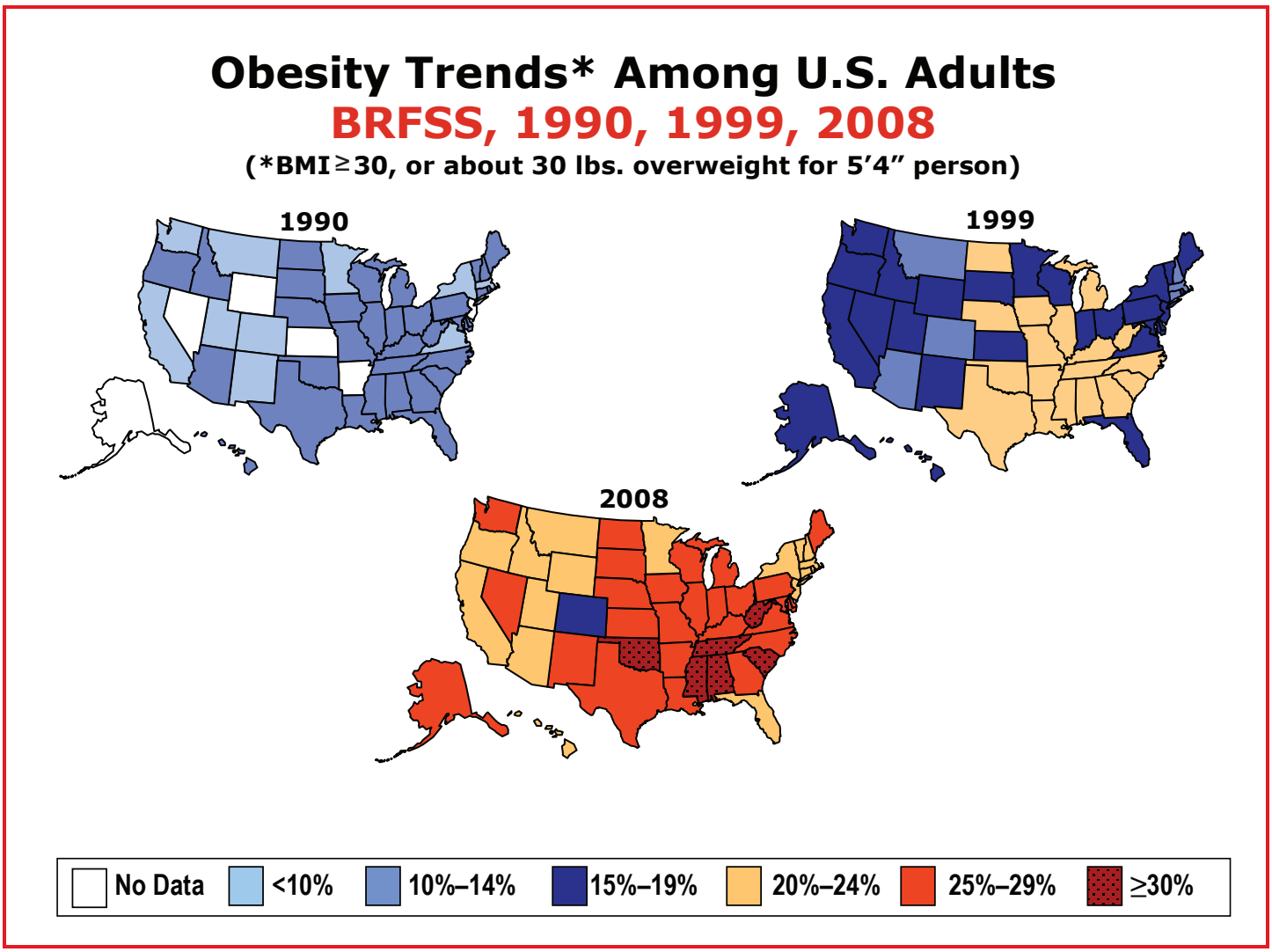


Multivariate Relative Risk of Death from Cardiovascular Disease, Cancer, and All Other Causes among Men and Women Who Had Never Smoked and Who Had No History of Disease of Enrollment, According to Body-Mass Index. The reference category was made up of subjects with a body-mass index of 23.5 to 24.9.

In spite of this knowledge, which is readily available to health care providers, individuals and government agencies, the level of obesity in America and many other countries continues to increase.

In RGA's role as mortality experts, it is important for us to not only be aware of the impact of obesity, along with its trends and prevalence, but also, if possible, to contribute to the understanding of the cause and resolution of the current obesity "epidemic." As such, RGA has provided funding for a variety of projects that hopefully will lead to improvements in mortality and morbidity related to this condition.

In 1999, RGA entered into a partnership with Washington University in St. Louis, Missouri to form the Longer Life Foundation (LLF), whose mission is "to fund studies to help the public live longer and better quality lives and to find better ways to prognosticate disease." During the subsequent 11 years of the foundation's existence, RGA has successfully encouraged the funding of a variety of studies that pertain to obesity in both adults and children. The current group of successful grant applicants includes researchers in this field who continue the work of the initial researchers. A complete list of grants, as well as additional information on the foundation, is available at www.longerlife.org.



Source: CDC Behavioral Risk Factor Surveillance System

RGA has also recently contributed to the Campaign to End Obesity, which is an umbrella group of individuals and organizations who are "collaborating in the fight to reverse America's costly obesity epidemic through engagement with and education of policy makers, public awareness initiatives and collaborative programs between and among leading stakeholders." This consortium of interests includes representatives from medical schools, pharmaceutical companies, the American Heart Association, public broadcasting interests, sporting good manufacturers and strategists. RGA has been invited to provide support and representation from the life insurance industry in this venture. More information about this group can be found at http://obesitycampaign.org.

I hope to one day publish an article in ReFlections that illustrates decreasing rates of obesity in America to levels that are consistent with optimal health which also contribute to mortality improvements from declining levels of heart disease, diabetes and all the other various conditions that are associated with obesity. Until such time, we will continue to monitor the phenomenon of the obesity epidemic and attempt to contribute to its resolution. ▪

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PROSTATE CANCER AND PSA

By Dr. Robert Coates M.D., D.B.I.M, FLMI

Prostate cancer is the second leading cause of cancer deaths in men. In the U.S., it is estimated that in 2009 more than 192,000 men will be diagnosed with prostate cancer and more than 27,000 men will die from the disease.

Not only is it the second leading cause of cancer deaths in men, it is the most common non-skin cancer in men. This article discusses prostate cancer and its implications for underwriting.

Table #1 below shows the 2009 American Cancer Society estimates for the three leading causes of new cases of male cancers and the three leading causes of male cancer deaths.

Table 1

2009 Cancer Statistics Estimates	
Male-New Cancer Cases	**766,130**
Prostate	192,280
Lung	116,090
Colon/rectal	75,590
Male-New Cancer Deaths	**292,540**
Lung	88,900
Prostate	27,360
Colon/rectal	25,240

The prostate gland is part of the reproductive system of all mammals. At puberty, under the stimulation of the androgen dihydrotestosterone, the prostate enlarges to the adult size of 20 grams by age 20. Around age 45, the prostate begins a second growth phase called BPH. The cause of BPH is unknown. It occurs in 90% of men by age 70. The epithelial cells of the acinar units of the prostate produce prostate-specific antigen (PSA).

The prostate gland is divided into three zones: the central zone (CZ) which surrounds the ducts draining the seminal vesicles and the vas deferens which drains the testicles; the transition zone (TZ) surrounding the urethra as it exits the bladder; and the peripheral zone (PZ) which includes the remaining portions of the prostate. See Figure 1. Not labeled in the diagram is the apex portion of the prostate, which surrounds the urethra as it exits the prostate.

Figure 1

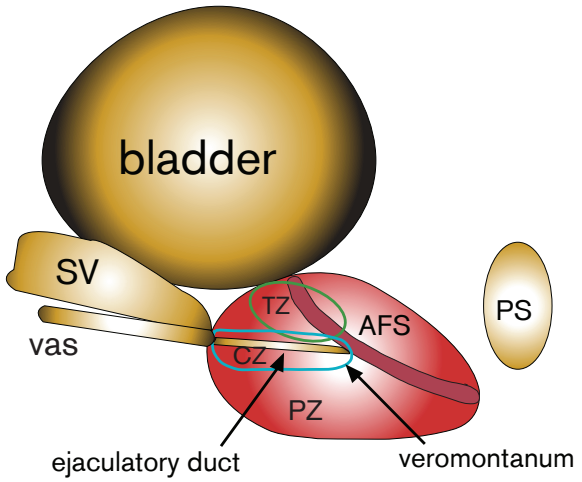


Figure 1-Normal prostate anatomy
SV=seminal vesicle, vas=vas deferens, PS=pubis symphysis; prostate is oval structure, urethra is the red tube from bladder through prostate.

The transition zone (TZ) of the prostate comprises 5 to 10% of prostate tissue in young men. It gives rise to BPH as men age. About 20% of prostate cancers occur in the transition zone. The central zone (CZ) comprises 25% of prostate tissue in young men. Only 1 to 5% of prostate cancers originate in the central zone. The peripheral zone (PZ) makes up the majority of prostate tissue. Approximately 75% of prostate cancers originate in the peripheral zone. This is the area of the prostate that can be felt on exam.

The incidence of prostate cancer in the U.S. is 175 per 100,000 males. In Sweden the incidence is 55 per 100,000 and in Israel the incidence is 24 per 100,000. In the U.S., for various ethnic groups, the incidence of prostate cancer per 100,000 males is 255 for African Americans, 161 for Caucasians, 140 for Hispanics, and 96 for Asians. The median age at diagnosis of prostate cancer is 68. About 71% of prostate cancer deaths occur in males age 75 and older.

Mortality from prostate cancer decreased 4% per year from 1999 to 2003, presumably due to earlier diagnosis and treatment. In 1982, 33% of prostate cancer cases had metastatic disease at the time of diagnosis. In 2008, less than 5% of prostate cancer cases had metastatic disease at the time of diagnosis. This data again shows diagnosis of prostate cancer is occurring at earlier stages. The goal of all cancers is to diagnose the cancer early before it has spread.

The exact cause of prostate cancer is unknown. Testosterone must be present because eunuchs do not develop prostate cancer. The current theory is that somatic genetic mutations develop in the prostate over a man's lifetime, eventually leading to cancer. About 10% of prostate cancer cases are due to inherited genetic conditions, such as BRCA2, and alterations described on chromosomes 1, 17 and X. Only BRCA2 testing is available clinically at this point in time.

There are three strong risk factors for developing prostate cancer and four less strong prostate cancer risk factors. The three strongest risk factors are advancing age, family history of prostate cancer and African American ethnicity. It is estimated 29% of men ages 30-40 have small foci of prostate cancer, 64% of men ages 60 to 70 have prostate cancer (mostly non-invasive) and 75% of men age 80 and older have prostate cancer. About 70 to 75% of prostate cancer is diagnosed in men age 65 and older.

If a male has one first-degree relative with prostate cancer, his risk of getting prostate cancer is two times higher than males without a first-degree relative with prostate cancer. If a male has two or more first-degree relatives with prostate cancer, his risk increases four times or more over males without any first-degree relatives with prostate cancer.

Additionally, as referenced earlier, 10% of prostate cancer cases may have inherited genetic mutations. African American males have a higher incidence of prostatic intraepithelial neoplasia (PIN) prostate cancer and more aggressive prostate cancer with higher Gleason scores. Young African American males have 15% higher testosterone levels compared to young white males. However, the exact reason why African American males have a higher incidence of PIN and prostate cancer is unknown. The four lesser risk factors for developing prostate cancer include increased dietary fats and red meat, chronic inflammation, reduced sexual activity and unknown environmental factors. Evidence that supports the theory for unknown environmental factors includes Asian males who move to Western countries develop an increasing incidence of prostate cancer.

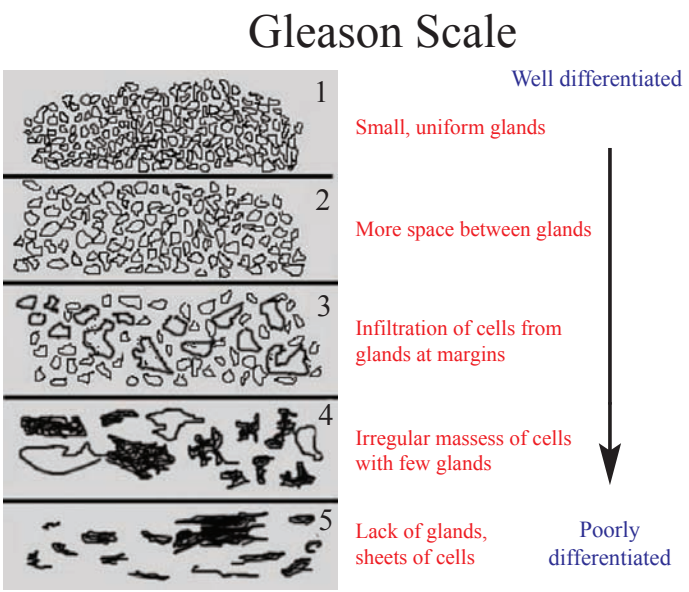
Factors not associated with an increased risk of prostate cancer include smoking, alcohol, BPH (benign prostatic hypertrophy/hyperplasia) and vasectomy. Dietary factors which may be helpful in preventing prostate cancer include soy, antioxidants (vitamin E, selenium) and lycopenes (tomatoes).

The pathology of prostate cancer is pertinent to an understanding of both the treatment and the rating of prostate cancers by life insurers. Approximately 95% of prostate cancers are adenocarcinomas; about 4% have transitional morphology and are thought to arise from the prostatic urethral area; and less than 1% are sarcomas or lymphomas. As mentioned previously, less than 75% of prostate cancers are located in the peripheral zone; less than 20% in the transitional zone; and about 1 to 5% in the central zone. More than 75% of prostate cancers are multifocal with 41% having two cancer foci, 28% having three cancer foci; and 9% having four or more cancer foci; and are heterogeneous, that is, with different grades or degree of differentiation.

The Gleason method of histological grading is the most accurate grading method of prostate cancer differentiation. The areas of cancer are graded 1 through 5 (1 is well differentiated and 5 is poorly differentiated) for both the most common and the second-most common cancer cell types. The two numbers added together equal the Gleason score.

The Gleason scoring system is as follows; 2-4 is well differentiated, 5-6 is moderately differentiated, 7 is gray zone-moderate vs. poorly differentiated and 8-10 is poorly differentiated. Dr. Don Gleason is a pathologist from Minnesota who devised the grading system (on the following page) for prostate cancers that is used around the world.

Figure 2



All solid cancers of the body use the TNM method of pathology and staging which aids in determining both treatment and prognosis. The TNM system is the most widely used system in the United States for staging prostate cancer. It describes the extent of the primary tumor (T stage), the absence or presence of spread to nearby lymph nodes (N stage) and the absence or presence of distant spread, or metastasis (M stage).

Table 2 below shows the American Urologic Society and the TNM staging of prostate cancer.

Table 2
AUS and TNM Prostate Cancer Staging Systems

AUS	TNM	STAGE	LESION
A-1—focal	T0NxM0	I-A	A-1—focal
A-2—diffuse	T0NxM0	I-B	A-2—diffuse
B	T1-2NxM0	II	B
C	T3NxM0	III	C
D-1	TanyN+M0	IV	D-1
D-2	TanyNanyM+	IV	D-2

The three most important prostate cancer prognostic factors are the stage of the cancer, the Gleason score and the pretreatment PSA level. The lower stages of prostate cancer have a better prognosis. That is, T0 and T1 prostate cancers have the most favorable survival statistics. Some statistics that amplify this point further are: T1a — progression over 10 years uncommon; T1b — 10% tumor-related death in 10 years; T2 — well differentiated 10-year metastasis-free survival is 81%, moderately differentiated is 58% and poorly differentiated is 26%; T3 — disease-free survival is 25%; with distant metastasis and 10-year survival is 10%.
The same is true of Gleason scores. That is, lower Gleason scores have a more favorable prognosis. Gleason scores of 2 to 6 are favorable, a Gleason score of 7 is a gray zone and Gleason scores of 8 to 10 are unfavorable. A pretreatment PSA<10 ng/ml is the most favorable PSA prognostic level, while pretreatment PSA >20 ng/ml is the most unfavorable PSA prognostic level.

There are seven general treatment options for prostate cancer: watchful waiting, androgen deprivation therapy, cryotherapy, photodynamic therapy, high-intensity focused ultrasound (HIFU), surgery and radiation. Surgery and radiation offer hope for a cure. Generally, surgery (radical prostatectomy) has better long-term survival than radiation treatment. See Table 3 for data showing prostate cancer and survival data with various treatments. There are two types of radiation treatment: external beam radiation or radioactive seed implants, also called brachytherapy.

Treatment of prostate cancer is recommended for younger men, if the tumor is more aggressive as determined by Gleason score and stage, and if the man is likely to live more than 10 years.

Table 3
Prostate Cancer Treatment Results

10 year all-cause mortality survival:	
prostatectomy	81%
prostatectomy and radiotherapy	68%
radiotherapy	61%
watchful waiting	51%

5,845 men ages 65 to 74 diagnosed with local or regional prostate cancer potential prostatectomy candidates in 1992 from SEER data, median follow-up 11 years.

Liu, et al: J Clin Oncol 2008; 97:583

All treatment options for prostate cancer have complications. The main complications of surgery/radical prostatectomy are varying degrees of sexual dysfunction/impotence and urinary incontinence. The main complications of external radiation and brachytherapy treatment are damage to the bladder or bowel (urethritis, proctitis) and varying degrees of sexual dysfunction/impotence. The main complications of watchful waiting are metastatic progression of prostate cancer and the psychological effects of anxiety, depression and suicide risk, due to knowing cancer is present and not being treated.

Since survival is best when cancer is confined to the prostate, early diagnosis is crucial to decrease mortality from prostate cancer. The two commonly used screening tests for prostate cancer are the digital rectal exam (DRE) and the prostate specific antigen (PSA). Prostate biopsy is the definitive diagnostic method for prostate cancer. DRE and PSA will be discussed in an upcoming issue of ReFlections.

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Dr. Robert Coates is an insurance medicine specialist with more than 25 years of experience, including 18 years in internal medicine practice. Prior to joining RGA, Dr. Coates worked at Allianz Re and Metropolitan Life. He is a member of the Midwestern Medical Directors Association and the American Academy of Insurance Medicine (AAIM), where he serves as the secretary-treasurer. He also was a faculty member on the AAIM Triennial Course in insurance medicine in 1997, 2000 and 2003. Dr. Coates has written articles for the Journal of Insurance Medicine and has been a featured speaker at insurance industry conferences. He received B.Sc. and M.D. degrees from the University of Minnesota.

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REVIEW OF VIRAL HEPATITIS

By Dr. Oscar A. Cartaya M.D., M.P.H., M.S., D.B.I.M

The term "viral hepatitis" refers to a collection of different viral disorders affecting the liver. These are disorders with significant differences in their natural histories. The only thing these disorders have in common is their target organ, the liver, and the kinds of damage they cause to it.

The goal of this article is to present the natural history of these viral disorders emphasizing hepatitis B and C, trying to clarify their nature over time. I will review the immune reactions associated with these disorders and how they are used for diagnostic purposes. The common progression of these disorders to end-stage liver disease will be reviewed as well. The subject of viral hepatitis has historically been a cause of confusion among those trying to evaluate mortality risks. I hope this review will facilitate the reader's evaluation of mortality risk for these disorders.

What is Hepatitis?

Hepatitis is a broad term referring to any inflammatory disorder or state of the liver. This inflammatory state of the liver can be due to a primary liver disorder (like one of the various types of viral hepatitis) or to a secondary manifestation of a different disease (like mononucleosis). There are many different causes for primary hepatitis, among them chemicals (most commonly alcohol), medications (like Dilantin), autoimmune disorders and infectious disorders. The infectious disorders affecting the liver cover the whole spectrum of infectious agents from parasites (amebic abscesses) to viruses which may target the liver either primarily (viral hepatitis) or secondarily (yellow fever). The spectrum of infectious disorders affecting the liver is very broad; however, among these the most common cause of infectious hepatitis are the viruses causing viral hepatitis B and C.

Viral Hepatitis

The hepatitis B and C viruses are the most common but they are by no means the only viruses infecting the liver as their primary target site. Currently, five distinct primary hepatitis viruses have been identified, all of which are entirely different viruses from different families of viruses with different characteristics, as follows:

1) Hepatitis A virus belongs to the picornavirus family. It contains single stranded RNA, and is naked with no envelope. This virus causes an acute form of hepatitis which is generally well controlled by the body's defenses with the vast majority of patients recovering fully and developing permanent immunity to reinfection by this virus. In a very small number of cases, acute hepatitis A infection can take a fulminating course and cause death during the acute period of the infection. Hepatitis A does not cause chronic hepatitis.
2) Hepatitis B virus belongs to the hantavirus family. It contains double stranded DNA and has an envelope. This virus causes a highly prevalent infection which can become chronic and cause long-term liver damage.
3) Hepatitis C virus belongs to the flavivirus family. It contains single stranded RNA and has an envelope. This virus causes a highly prevalent infection which usually becomes chronic and causes long-term liver damage.
4) Hepatitis D virus belongs to the deltavirus family. It contains defective single stranded RNA which is non-self-reproducing, and requires coinfection with hepatitis B virus to be able to reproduce. This virus is only found in dual infections with hepatitis B which carry a worse prognosis than infection with hepatitis B alone. Elimination of and immunity to hepatitis B effectively controls all infection with hepatitis D.
5) Hepatitis E virus belongs to the calciviurs family. It contains single stranded RNA and has an envelope. This is a water borne virus associated with epidemics of hepatitis which can be extensive and can cause occasional death. It is primarily found in locales with poor sanitation and polluted water.

Among these infections, the most important ones, in terms of their prevalence and overall mortality risk impact, are hepatitis B and C. There are more than 350 million estimated cases of hepatitis B in Asia, and a smaller but significant number of hepatitis C cases throughout the world. These are chronic infections which increase the risk for cirrhosis and hepatocellular cancer. The mortality risk caused by hepatitis B and C is considerable.

These disorders, with the exception of the perinatal infections found in carriers of hepatitis B, go through an acute phase before transitioning into chronic hepatitis. The acute phase of viral hepatitis has a prodrome of variable length with non-specific symptoms, which may include fatigue, lower exertional tolerance, pains and aches, fever, and, in some cases, weight loss. A clinical diagnosis of acute hepatitis is generally not made during this period. Later on in the course of the infection, liver specific signs appear like hepatomegaly, elevations of the liver enzymes,

and sometimes jaundice with dark urine. Any of these liver specific signs may trigger immune testing for viral hepatitis, which confirms the diagnosis. Each type of viral hepatitis has its own typical natural history timeframe.

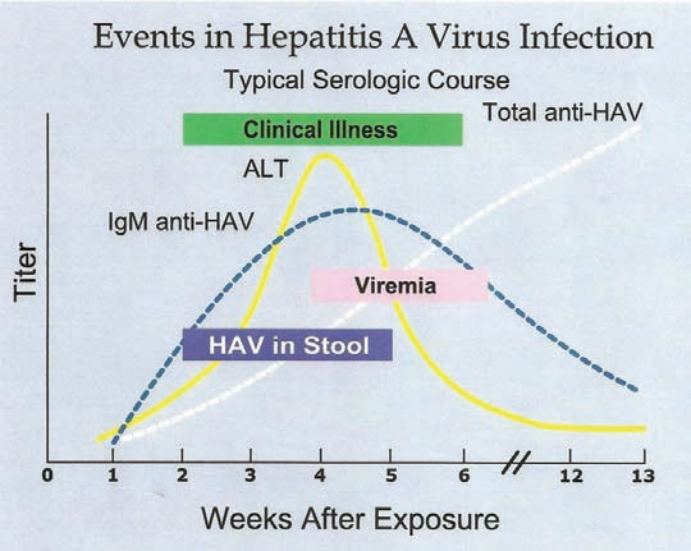
Natural Course of Viral Hepatitis

Since each type of viral hepatitis has its own characteristic natural course, I will briefly describe the natural course of the disease for the three most common of these viral infections.

Viral Hepatitis A

The course of viral hepatitis A is generally self-limited to an acute disorder which results in a complete resolution of the infection and the development of permanent immunity to it.

Figure 1



CDC Training Slide, 2009

Hepatitis A is transmitted by the oral/fecal route (dirty hands play an important role in the transmission of this disease). After the infection is contracted, there is a largely asymptomatic period that lasts around one to two weeks. The virus may be found in the blood and the stool early in the course of the disease, while the patient remains asymptomatic.

This is a period of high infectivity. The liver enzymes (LFTs) start a period of rapid elevation during the first week or so of the disease, followed by clinical symptoms early in the second week. The ALT is particularly affected with very large elevations, up to seven times the normal rate by the fourth week of the disease. The production of antibodies against the infection starts during the asymptomatic prodrome and peaks rapidly. As the serum anti-HAV antibody titer rises (IgG antibody) the disease is controlled. The IgG anti-HAV antibody confers immunity and is protective against the disease. By the fourth week of the course, the titers of IgG anti-HAV antibody have increased to a high enough level to control the disease, causing the virus to be eliminated from the blood and the ALT levels to decrease back to normal. The elimination of the virus from the blood and the decrease in ALT levels occurs gradually. The end result is complete resolution of the infection and permanent immunity against it.

In a very small number of cases, the IgG anti-HAV antibody is either not produced or produced in very small amounts. In these cases the viremia and ALT levels continue increasing until the patient dies within a few more weeks. These fulminating cases are rare but do occur.

From a life insurance point of view, hepatitis A is not a significant issue. Cases found to have an elevated HAAb are immune to this disease either because of vaccination or because of a prior acute infection with this virus. There is no chronic form of hepatitis A.

Viral Hepatitis B

The Hepatitis B virus is a DNA virus, making it unique among the viruses infecting the liver as a primary target organ. This is a large virus because its core contains a large number of proteins required to facilitate the initial transcription of the viral DNA into native viral RNA, and also contains reverse transcriptases for incorporation of the viral DNA into the hosts' cellular DNA.

Because of its complexity, the hepatitis B virus produces a variety of end products other than the virus itself. Perhaps the most important of these additional products is the HBe particle. This is an incomplete, non-infective viral particle with unique antigenic qualities that is produced only during periods of very active viral reproduction, indicating a severe and very active infection that carries a worse prognosis. Both the HBeAg (Hepatitis Be antigen) and the HBeAb (Hepatitis Be Antibody), which confers no protection or immunity, can be detected in the blood of patients actively producing HBe particles.

Hepatitis B can induce the production of protective antibodies capable of conferring permanent immunity to the patient producing them, but this is something that does not happen in all cases. Approximately 5% of all patients with acute hepatitis B go on to develop chronic hepatitis B. The mode of transmission of this disorder is also unique in that it can be transmitted both horizontally and vertically.

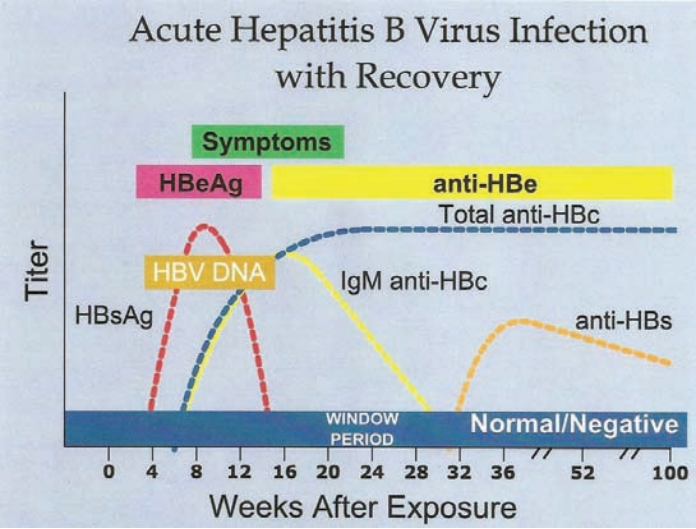
Vertical or mother-to-child transmission occurs almost exclusively in Asia where it is the dominant form of transmission. It produces a chronic and initially asymptomatic (for many years) form of the disease, but may cause the same kinds of long-term outcomes as the horizontally transmitted form of hepatitis B.

Horizontal transmission, through contact with infected blood and body fluids (including sexual transmission), is the dominant form of transmission for hepatitis B elsewhere in the world. It produces an initially acute disorder which may transition into a chronic form of hepatitis B with a severe long-term prognosis.

Acute and Chronic Hepatitis B, Horizontally Transmitted (Common Worldwide)

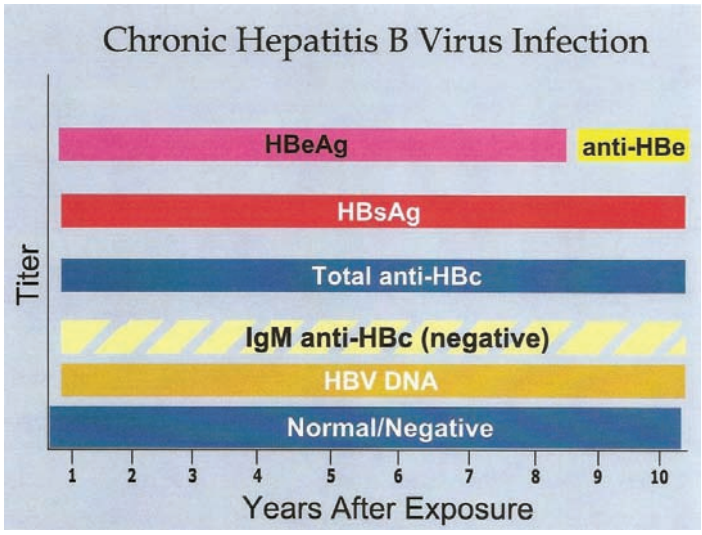
The most common form of hepatitis B seen worldwide, with the exception of Asia, is horizontally transmitted by infected blood and fluids, including sexual contact. It has a definite acute clinical phase, which may be followed in many cases by transition into a chronic phase.

Figure 2



CDC Training Slide, 2009

Figure 3



CDC Training Slide, 2009

After initial contact with the virus there is a long prodrome period of up to 10 weeks with no clinical symptoms. However during this period, patients infected with this virus have HBsAg (Hepatitis B surface antigen), viral DNA and HBeAg (Hepatitis Be antigen) present in their blood from very early in the prodrome period. These patients are highly infective during this period which occurs prior to the onset of antibody production and before any clinical symptoms become evident.

The initial production of both IgM and IgG Hepatitis B core antibodies (HBcAb) against the HBcAg (Hepatitis B core antigen) starts prior to the onset of clinical symptoms and generally succeeds in clearing the virus, the HBsAg and the HBeAg from the blood. However even though these patients may be free of circulating viruses, immunity is not permanent until HBsAb (Hepatitis B surface antibodies) are produced and a protective titer is achieved. It takes eight to 10 months for the production of HBsAb to start. This results in a window of vulnerability to reinfection with hepatitis B. HBeAb (Hepatitis Be antibodies) may be produced much earlier than the HBsAbs but they are not protective and do not confer immunity to the patient.

Approximately 5% of all adult patients who develop acute hepatitis B fail to produce HBsAb and do not develop immunity to the disease. If the hepatitis B infection is contracted during childhood, a much larger percentage of these children, from 30 to 50%, fail to develop HBsAbs and do not develop immunity to the disease. These patients transition into a chronic infection with hepatitis B.

Patients with chronic hepatitis B have variable blood levels of circulating HBsAg, viral DNA and also variable levels of HBcAb which do not confer immunity. They may also have circulating HBeAg, showing an active infection, and/or HBeAbs which provide no immunity to the disease. Of all patients with chronic hepatitis B, 1% per year will succeed in spontaneously clearing the virus and develop immunity. The reasons for this spontaneous clearance of the virus are not known.

Hepatitis B Carriers, Vertically Transmitted (Common in Asia)

Hepatitis B can be transmitted vertically from an infected mother to an uninfected young child either during pregnancy itself or during the lactation period. The level of activity of the hepatitis B infection in the mother is the most important factor determining the risk of transference of the infection to the child. Approximately 90% of all children of mothers with active infection who are positive for both HBeAg and HBeAb will become infected during the perinatal period. Only 10% of all children of mothers infected with less active hepatitis B, who are positive for the HBsAg only, not the Be antigen, become infected this way.

The vertical mode of transmission is common in Asia but nowhere else in the world. Patients with this disorder have variable circulating levels of HBsAg, and viral DNA, but no circulating antibodies to hepatitis B.

Long-Term Chronic Hepatitis B

Long-term chronic hepatitis B has been extensively studied in Asia where it is a major cause of mortality. These studies have determined a possible autoimmune liver injury is associated with the long-term immune reaction to this virus. During the course of chronic hepatitis B there is a period of very active immune reaction against the virus. The level of circulating virus decreases during this period, but the level of liver inflammation increases. Liver enzyme elevations are not directly related to this liver inflammatory reaction although they generally increase with variable ALT levels. The inflammatory reaction is much worse when it is associated with concurrent alcohol intake and, in these cases, the elevation of the liver enzymes and ALT do correlate with the level of liver inflammation.

The degree and duration of the inflammatory injury produced during this period determines the ultimate long-term outcome of the disease, and may cause acute or subacute reactivations of smoldering chronic virus infections. Approximately 2.1% of all chronic hepatitis B patients with these severe inflammatory reactions develop cirrhosis per year. The prognosis for developing cirrhosis is worse in cases with fibrosis documented by a prior biopsy.

Hepatocellular Carcinoma

Hepatocellular carcinoma is very common in Asia and relatively rare in the rest of the world. Its primary cause is long-term chronic hepatitis and 70 to 80% of these cases in Asia are associated with chronic long-term hepatitis B infections, mostly among vertically infected patients. Hepatocellular carcinoma primarily affects males with a 3-to-1 male-to-female ratio. Its incidence increases with a duration of chronic hepatitis lasting more than 40 years, elevations of the ALT and possibly with concurrent diabetes. Hepatocellular carcinoma is refractory to therapy, the only hope for cure is to catch it early enough that surgical excision may be curative. Repeat hepatic ultrasounds and repeat alpha fetoprotein tests are the only available methods to follow these patients clinically and provide early warning to the development of hepatocellular carcinoma while it is surgically treatable.

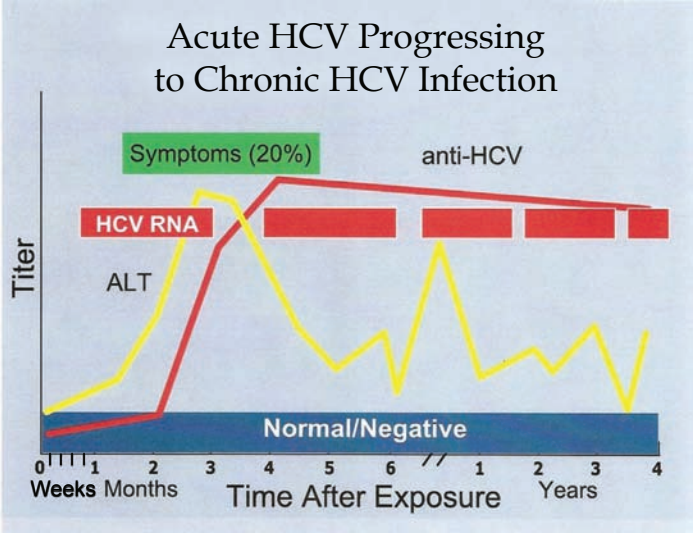
Viral Hepatitis C

The hepatitis C virus is an RNA virus which does not require the complex transcription and insertion routines the hepatitis B virus requires. This is a much smaller and simpler virus and it can infect its target cells and start viral production much faster than the hepatitis B virus. Virus production is quite variable with hepatitis C. There can be periods of active viral infection with no release of viral copies into circulation, and partial copies of the virus may be released, as well as the fully assembled virus itself. The hepatitis C virus is only transmitted by horizontal means, through contact with infected blood or body fluids, including sexual transmission. No vertical mother to child transmission has been documented with the hepatitis C virus.

Acute and Chronic Hepatitis C

In the acute phase of the infection with hepatitis C, there is a very short prodrome. Generally clinical symptoms and viremia are present one week after exposure. By the second week there are significant elevations of the blood ALT level, and production of hepatitis C antibody (HCAb) begins. Peak levels of HCAb are reached by the fourth week after exposure. In 15% of the cases the infection is successfully controlled by the HCAb with a gradual reduction of the blood ALT levels and disappearance of the viremia and the clinical symptoms. These cases do not develop permanent immunity to hepatitis C; reinfection is possible.

Figure 4



CDC Training Slide, 2009

In 85% of all the cases of acute hepatitis C, the production of HCAb does not succeed in controlling the infection, resulting in a chronic infection. Chronic hepatitis C is characterized by variable levels of ALT and with an inconsistent pattern of release of viruses and viral products into circulation. The level of hepatitis C viremia is therefore quite variable and may become undetectable for periods of time while the infection remains active in the liver. Therefore a viral count of "0" in patients with chronic hepatitis C is not indicative of a cure for the underlying disorder until it is confirmed with a repeat negative viral count at least six months later. Likewise, variable elevations of liver enzymes in the blood are not directly related to the degree of activity of the underlying hepatitis C infection, although they may be related to other causes like concurrent alcohol abuse.

Due to the variability in the release into circulation of hepatitis C viruses and other associated viral products, the standard immune screening tests for hepatitis C may yield indeterminate results. In such cases, confirmatory tests are required to establish an infection is present. There are two main kinds of confirmatory tests for hepatitis C in general use. The most common of these, and the one generally used by clinical and insurance labs, is the RIBA test. The other test commonly in use is the NAT test, a PCR-based test for the detection of hepatitis C nucleic acids, which is very sensitive and is used for screening blood donations, but so far has not been adopted by general clinical or insurance labs.

The RIBA test checks for a number of different viral proteins in the blood. A positive confirmatory test requires positive identification of two or more viral proteins. If only one viral protein is present the presence of an active hepatitis C infection is not confirmed by the RIBA test.

Long-Term Chronic Hepatitis C

The most serious long-term outcome of hepatitis C is the development of cirrhosis. However, this is not the most common outcome of chronic hepatitis C. It is well established that 80% of all patients with long-term chronic hepatitis C stabilize their diseases and do not develop cirrhosis. The factors that increase the incidence of cirrhosis among patients with long-term chronic hepatitis C are: a) excessive alcohol intake of more than 50 grams per day; b) long-term chronic infection more than 20 to 30 years in duration; c) initial infection occurring at over 40 years of age; d) presence of steatosis or fibrosis by biopsy; e) concurrent infections with more than one virus; f) male gender; and g) immunosuppression. Neither the ALT level, in the absence of alcohol intake, nor the level of circulating virus is correlated with the development of cirrhosis. End-stage cirrhosis caused by chronic long-term hepatitis C is one of the primary causes of liver transplants in the world, with the exception of Asia.

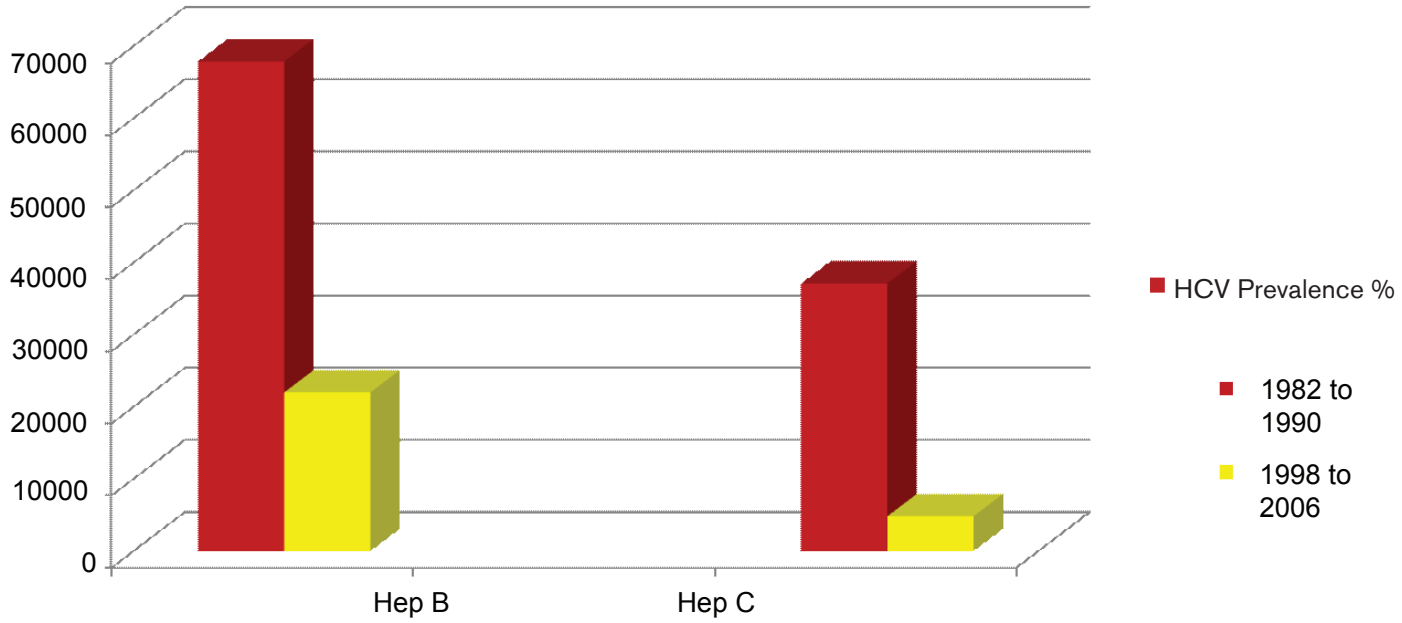
Epidemiology of Viral Hepatitis B and C

The two most important forms of viral hepatitis, in terms of mortality risk and complications, are hepatitis B and hepatitis C. In Asia, the most common form of viral hepatitis is chronic hepatitis B caused by vertical transmission of hepatitis B from mother to child during the perinatal period. In the rest of the world the most common form of transmission is horizontal transmission of hepatitis B and C through contact with infected blood and blood products, primarily during transfusions.

The concept of populations at risk for viral hepatitis makes sense everywhere in the world except in Asia where the primary form of transmission is from mother to child. In the rest of the world, the majority of new cases of hepatitis C are exposed to the virus through contact with infected blood or blood products. Prior to 1990 and the adoption of more stringent methods to screen blood for transfusion, transfusion was the primary route for the transmission of hepatitis C. It is estimated that prior to this date a transfusion entailed a 5 to 10% risk of acute hepatitis C infection. After the new screening for blood donations was adopted in the early 1990s, the incidence of viral hepatitis C occurring after transfusion dropped precipitously.

Figure 5

Average Estimated New Cases of Acute Viral Hepatitis B and C Before and After Blood Screening for Viral Hepatitis, U.S.



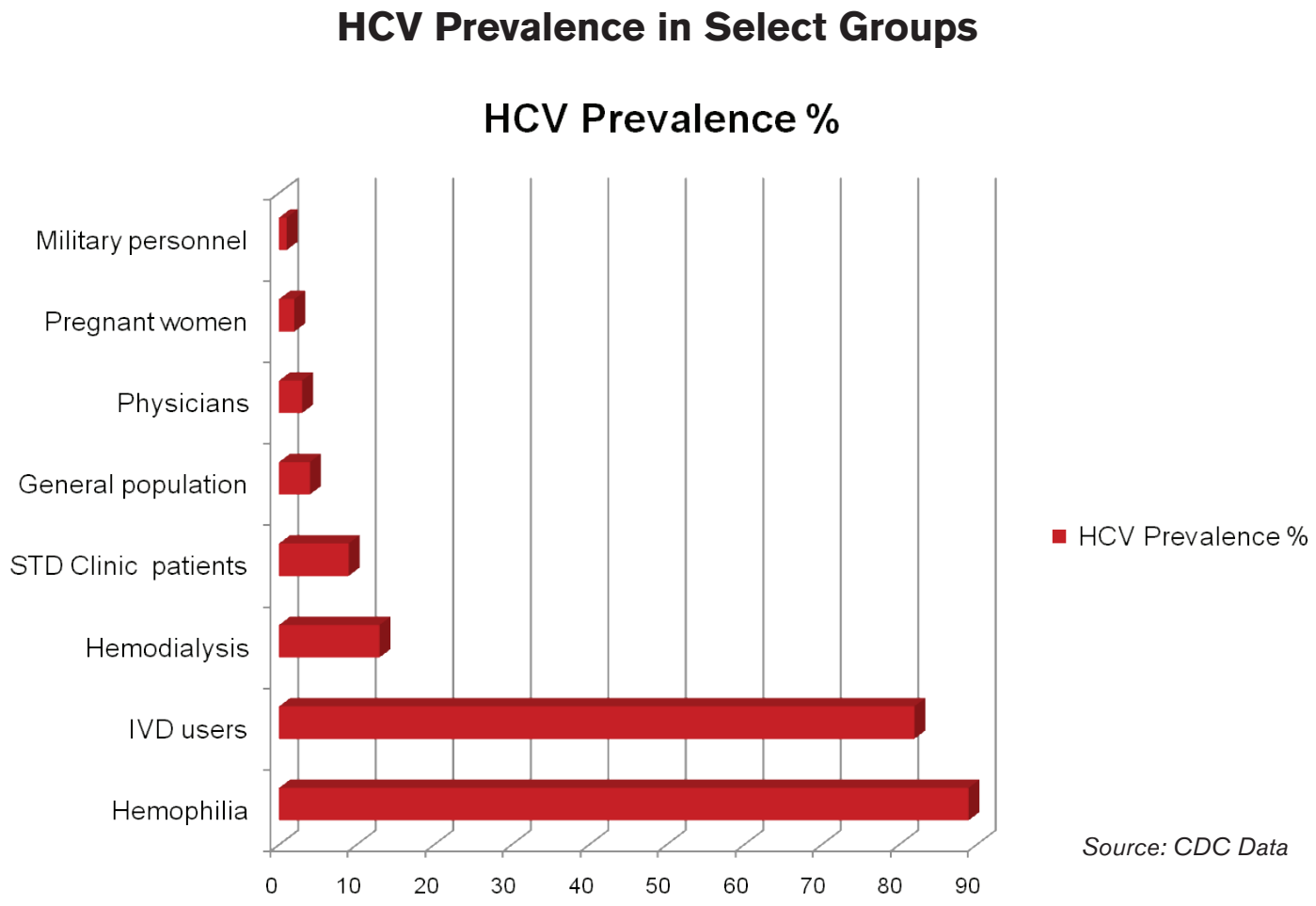
Effective screening of blood bank products has lowered the estimated incidence of new cases of Hepatitis B and C

Source: CDC Data 1980 to 2006

The development of effective vaccines against hepatitis A and B has been another major milestone in the control of viral hepatitis, similar to the effective blood screening for transfusions. The vaccines used have evolved over time and presently there are vaccines which can be safely used with small children. Other than children, many adults subject to occupational exposure to these diseases have been vaccinated.

Studies of hepatitis B spread outside of Asia show that prior to the institution of widespread vaccination programs against hepatitis A and B, approximately 80% of all new infections in the U.S. occurred among adults of all ages, approximately 8% among children and adolescents and approximately 4% among infants in the perinatal period. In 2005, after the adoption of widespread vaccination programs, the highest incidence of new cases of hepatitis B in the U.S. was found among young adults (age 25 to 40). Approximately 79% of these cases admitted high-risk sexual contact or intravenous drug use. The number of new cases among adolescents, children and infants dropped precipitously with vaccination. It is hoped that vaccination programs in Asia will successfully control the rate of vertical transmission of hepatitis B.

Figure 6



Source: CDC Data

The figure showing the U.S. prevalence of hepatitis C in select groups clearly identifies the groups with highest risk for infection in the population at large.

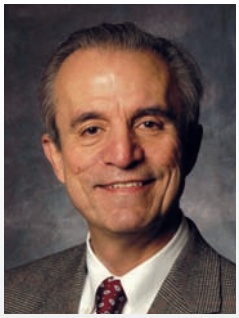
New Developments

Much new information about these diseases has been discovered in the last few years. The following only describes some of the findings which I consider most significant for future follow-up:

1. Mutated strains of both hepatitis B and C have appeared and are abundant in Asia and among special groups of patients with a history of multiple or frequent exposure (i.e. Intravenous drug users). Some of these mutated viral strains convey a much larger risk for the development of early cirrhosis and hepatocellular carcinoma than others. Some strains have been documented to cause a rate of cirrhosis approaching 60% in less than 35 years among infected patients.
2. Multiple infections with a variety of strains of the same virus, or different viruses, all of which may be active at the same time, have been extensively documented. In some studies, the incidence of early cirrhosis and hepatocellular carcinoma is higher among patients with multiple strain or multiple virus active infections.
3. A number of patients with no evidence of active infection with hepatitis B or C (no evidence of viremia or circulating viral particles) who died of end-stage cirrhosis or hepatocellular carcinoma, have been shown to have had viable viral genome material incorporated into the genome of their liver cells. It appears that long-term active, but undetectable by current means, viral hepatitis can and does occur.

Conclusions

Viral hepatitis is a varied group of disorders with widespread distribution and severe long-term outcomes. The diseases present difficulties in terms of identification and determination of severity, and, as such, are inherently difficult to underwrite. The need to require screening of cases of long-term chronic hepatitis B with alpha fetoprotein levels or liver ultrasounds is emphasized. It is hoped this brief summary will be of help in the underwriting of these complex and variable disorders. ■



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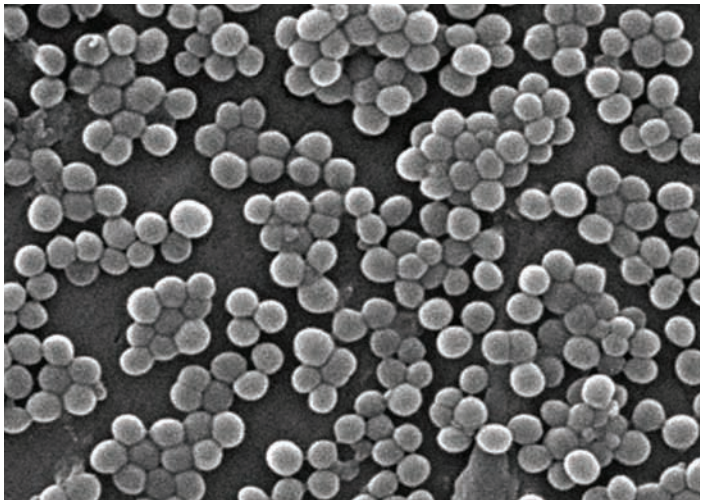
THE METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS EPIDEMIC (MRSA), A BRIEF REPORT

By Dr. Oscar A. Cartaya M.D., M.P.H., M.S., D.B.I.M

The following is a brief report on a relatively new and expanding problem, the spread of Methicillin Resistant Staphylococcus Aureus (MRSA) which has not been given much attention in underwriting circles but which can entail a very significant mortality risk under some conditions.

MSRA is a mutation of the normal S. aureus which, like the normal strains of S. aureus, lives as a harmless colonizer in human skin and nasopharyngeal mucosa. Approximately 30% of the general population carries colonies of these bacteria in their bodies with an unknown percentage of them harboring the methicillin resistant strains (MRSA) of S. aureus. This is one nasty bacterium which is difficult to distinguish clinically from the normal methicillin sensitive strains, and it is capable of producing invasive infections which are difficult to treat adequately and can produce massive necrosis of the infected tissues.

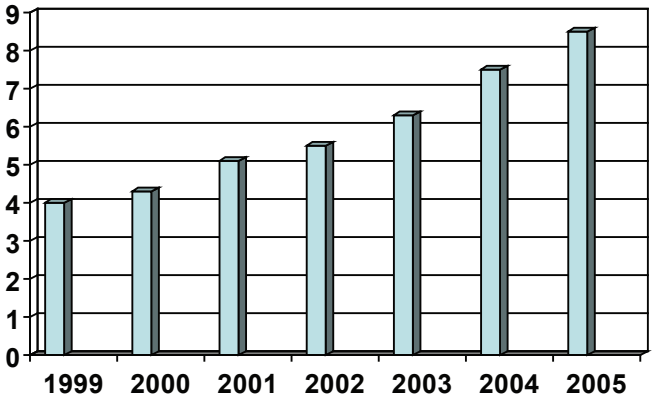


A Staphylococcus aureus MRSA strain colony is morphologically indistinguishable from colonies of a Staphylococcus aureus methicillin sensitive strain.

The incidence of invasive MRSA infections is still relatively low but it has increased steadily and become a leading cause of pneumonia, surgical site infections and cardiovascular infections. The reservoir for these infections is colonized people, patients, relatives of patients and so forth.

There are two strains of MSRA, a so-called hospital-acquired MRSA (HA-MRSA) and a so-called community-acquired MRSA (CA-MRSA). These two strains differ from one another in important ways: their invasiveness into the deep tissues and organs are different and they have different patterns of antibiotic resistance. Of the two, the CA-MRSA is the most invasive but also the most readily treatable strain.

MRSA Related Discharges/1000 Hospitalizations



Source: Klein, EID, 2007

This is a significant problem. In 2008–2009, the Association for Professionals in Infection Control (APIC) estimates 34 per 1,000 of all hospital infections are due to MRSA. This is 8.6 times higher than the estimates reported for 1999 -2000. The mortality is high when these organisms produce invasive infections. The Active Bacterial Core Surveillance/ Early Infection Prevention Network (ABCs/EIPN) 2005 report estimated 94,000 invasive MRSA infections in U.S. hospitals, among which 19,000 died (18%). These estimates were based upon CDC (Centers for Disease Control) data from 2003.

An actual study based upon 5,287 cases of invasive MRSA from July 2005 to December 2005, all of whom were hospitalized, was reported in JAMA in 2007 by Klevens. There were 1,598 deaths among these patients, a mortality rate of 30.2% among the patients in this study.

In conclusion, this is a disorder which is steadily increasing in incidence. It is not readily diagnosed, it is difficult to treat and it is capable of producing invasive necrotizing infections involving deep tissues, the heart and the lungs. Mortality is very high in these invasive cases. This brief report is intended to bring this issue into underwriting awareness. We are seeing cases of this disease and processing claims of insured individuals who have died from this condition. An active invasive infection with MRSA is dangerous and has to be taken into serious consideration during underwriting as the mortality of these infections is high. There is no increase in mortality associated with colonization of the skin or nasopharynx by MRSA. ■

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