Alcohol Alert

National Institute on Alcohol Abuse and Alcoholism

Number 89

Alcohol's Effects on Immunity—Increasing the Risks for Infection and Injury

Many people are aware that excessive drinking[a] can be harmful to the liver and other vital organs; however, there is another, less obvious, body system that is vulnerable to the negative effects of alcohol: the immune system. Because of alcohol's effects on the immune system, people who drink to excess are at increased risk of contracting infectious diseases, may have more complications after surgery, and often take longer to recover from illness, compared with those who drink at lower levels. Disruptions in immune system function also contribute to organ damage associated with alcohol consumption. This *Alcohol Alert* reviews the normal workings of the immune system and explores how alcohol interferes with these functions.

What Is the Immune System?

Our bodies are constantly exposed to a barrage of microbes, including viruses, bacteria, and fungi. Some of these are necessary for our well-being, such as the bacteria that live in the intestine and help with digestion; others can cause illness or have other toxic effects. The immune system is the body's defense against infectious disease, helping to distinguish, for example, between "good" and "bad" bacteria and eliminating harmful organisms (so-called pathogens) from the body. Equally important, however, is the immune system's ability to detect tissue damage and orchestrate the body's response, including removing damaged tissue and assisting in subsequent tissue repair and regeneration. To perform all of these functions, the immune system relies on an elaborate network of highly specialized cells that interact in a tightly orchestrated way.

Some of these defense and damage-response networks are in place at birth; this is called our *innate immunity*. Other parts of the immune system develop throughout life, allowing the body to "learn" and adapt whenever it encounters a new pathogen; this is called our *adaptive immunity*. The innate immune system includes physical barriers, such as the skin, that prevent organisms from entering the body directly; physiological barriers, such as enzymes in the stomach and intestines, that destroy many pathogens and toxins that enter the body with food; and specialized immune cells that work throughout the body to combat infection and disease. The innate immune system mounts the first swift response to pathogens or tissue damage, seeking to attack and destroy invaders or eliminate damaged cells. An example of innate immune system activation is the initial inflammation, often characterized by redness and pain, that occurs in response to an infection or infection-free tissue injury. The adaptive immune system, on the other hand, mounts a longer-lasting response, involving numerous types of immune cells and molecules. It not only protects the body from pathogens that bypass the defenses of the innate immune system, but it "remembers" each particular pathogen it encounters. Therefore, if the pathogen should invade a second time, the body can launch an even speedier and more targeted counterattack.

[a] Definitions of excessive, heavy, and binge drinking may vary among the original research articles cited in this *Alert*. Please refer to original source for details. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) defines low-risk drinking as no more than 3 drinks on any single day and no more than 7 drinks per week for women, and no more than 4 drinks on any single day and no more than 14 drinks per week for men. Drinking above this level increases the risk for alcohol use disorder. NIAAA defines binge drinking as a pattern of drinking that brings blood alcohol concentration levels to 0.08 g/dL. This typically occurs after 4 drinks for women and 5 drinks for men—in about 2 hours. The Substance Abuse and Mental Health Services Administration defines heavy drinking as drinking 5 or more drinks on the same occasion on each of 5 or more days in the past 30 days.

Highly specialized immune cells, including white blood cells, are key players in innate and adaptive immunity, particularly cells called monocytes and macrophages, neutrophils, natural killer (NK) cells, dendritic cells, T cells, and B cells. These cells circulate in the bloodstream and also reside in primary and secondary lymphoid organs, including the thymus, bone marrow, and lymph nodes and spleen, as well as in organs like the liver and brain (see figure). This widespread distribution allows the body to respond to not only general infections but also localized infections and tissue injury. To optimally exert their effects, the immune cells communicate with each other and with various other cells in the body through signaling molecules called cytokines, which trigger specific immune responses. In addition, B cells produce proteins called antibodies or immunoglobulins, which recognize foreign molecules and bind to them, thus marking them for destruction.

Considering the important roles of the immune system, and the many players and interactions that contribute to its proper functioning, it is not surprising that disruptions to the system—for example, those related to alcohol consumption—can adversely affect health.

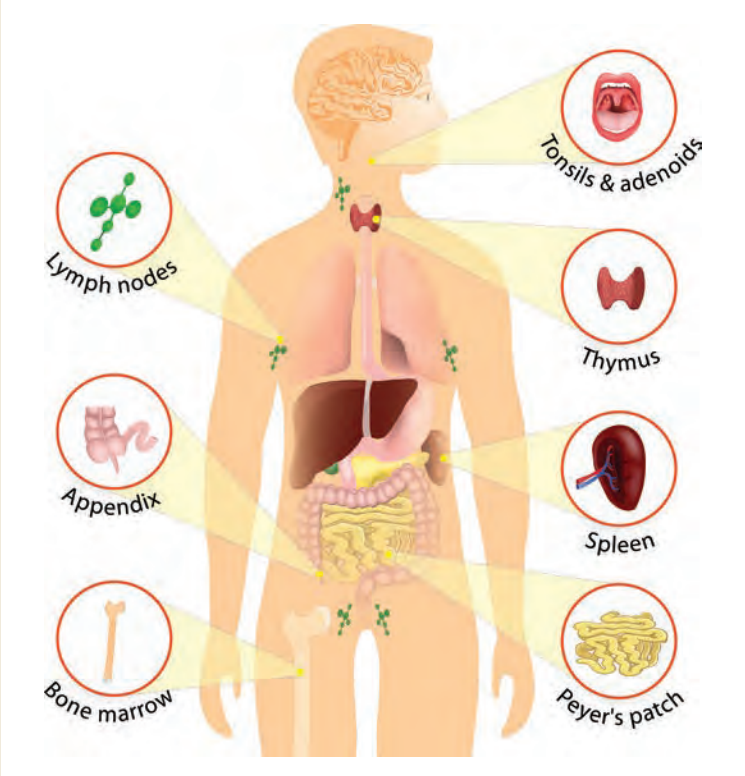

Figure Distribution of immune cells in the body. Immune cells circulate in the bloodstream, reside in the tissues depicted here—which have a dedicated role in immune function—and also reside in organs such as the brain, liver, lungs, and skin.

Alcohol's Effects on the Immune System

Alcohol consumption can alter the number, survival, and function of most immune cells. Although these alterations alone may not be sufficient to adversely affect one's health, if a person is exposed to a second "hit," such as a virus, his or her immune system may be unable to respond properly, increasing the risk of infection. The specific effects of alcohol on the immune system depend largely on how often and how much a person drinks. Even a single episode of binge drinking can have measurable effects on the immune system, from within the first 20 minutes to several hours after alcohol ingestion.[1] Over the long term, alcohol misuse weakens the immune system and increases the risk and severity of viral and bacterial infections, including human immunodeficiency virus (HIV), hepatitis B and C, and lung infections.[1] It can reduce the effectiveness of vaccines and contribute to a host of diseases, including alcoholic liver disease, alcoholic pancreatitis, inflammation in the gastrointestinal tract and brain, and cancer.[1,2]

Alcohol also adversely affects the immune system through its effect on the liver. An important component of the innate immune system, the liver produces a wide variety of antibacterial proteins.[3] If the liver is severely damaged by alcohol, it is less capable of producing these proteins, thereby increasing our susceptibility to bacterial infection. Indeed, bacterial infection is one of the most common complications of severe alcoholic hepatitis and alcoholic cirrhosis.

Consuming alcohol during pregnancy can disrupt development of the fetal immune system. It can increase risk of infection and disease in infants after birth and possibly throughout their lives. One study found that the effect of prenatal alcohol exposure on neonatal infection is most significant if alcohol exposure occurred in the

second trimester of pregnancy, a time when the immune system is developing. The risk is even more significant for babies who are born prematurely. Additional research is needed to determine how maternal drinking affects the fetal immune system and whether these effects can be reversed or reduced.[4]

Alcohol's Effects on the Gastrointestinal (GI) Tract

In addition to its direct effects on the immune system, alcohol can have an indirect impact on immunity through its actions in the stomach and intestines (GI tract). The GI tract is one of the first parts of the body to come into contact with alcohol and, as a result, bears the brunt of alcohol's harmful effects.

The intestine is home to a wide variety of bacteria necessary for proper digestion; however, these bacteria can become problematic if they are not well-controlled and held in careful balance with each other. Chronic alcohol consumption alters the composition of bacteria in our GI tract, collectively known as microbiota. It reduces the numbers of beneficial bacteria and allows an increase in unhealthy bacteria. This imbalance limits the ability of immune cells in the GI tract to distinguish between normal and disease-causing organisms,[5] and it is associated with diseases such as irritable bowel syndrome, food allergies, diabetes, cancer, obesity, and cardiovascular disease.[6]

Chronic alcohol exposure, and indeed even a single episode of binge drinking, can also damage the wall of the intestine, allowing bacterial toxins and other harmful byproducts to leak from the intestine into the bloodstream. Once in the bloodstream, these compounds are transported to vital organs such as the liver, where they can activate inflammation and increase the risk, and even severity, of diseases such as alcoholic liver disease.[6–8] The migration of bacteria from the gut into the bloodstream also can lead to systemic infections, sepsis, and multiple organ failure.[5]

Alcohol's Effects on the Liver

The central function of the liver is metabolizing, or breaking down, nutrients from digested food and detoxifying toxic substances after they pass through the gut. The liver is the chief organ for metabolizing and eliminating alcohol from the body and, as such, it is especially susceptible to damage caused by alcohol and its toxic byproducts. Alcohol-induced liver damage can lead to activation of immune cells within the liver as part of the inflammatory response to tissue injury. In addition, alcohol can harm the liver by promoting the leakage of bacterial toxins from the gut into the bloodstream, as noted above, which also activates the liver's inflammatory response. With chronic, excessive alcohol use, this acute inflammatory response persists to become chronic inflammation, and results in further damage, impaired tissue repair, and the development of increasingly severe forms of liver disease, including hepatitis, fibrosis (i.e., scar tissue formation), and, ultimately, cirrhosis of the liver.[9]

Other Health Consequences

In addition to those described above, a variety of other illnesses have been linked to the effects of alcohol on the immune system. Several of these adverse health consequences are discussed below.

Respiratory Diseases

Alcohol damages numerous components of the lung's defense system, increasing susceptibility to pneumonia, tuberculosis, and other respiratory infections. For example, heavy drinking hampers the ability of innate immune cells to identify and destroy bacteria that enter the airways and can produce lung infection.[10] Heavy drinking also impairs the function of immune cells that recognize and destroy the pathogen that causes tuberculosis.[11] In individuals with dormant tuberculosis infections, alcohol misuse can weaken the immune system, causing the pathogen to become active.[10] Finally, long-term drinking damages the body's first line of defense against respiratory infections—namely, the cells lining the airways that are covered with tiny hairs (i.e., cilia), which trap pathogens and other inhaled particles before they can reach the lungs and cause disease.[10]

The potential consequences of lung infections—or any kind of lung damage—also are more severe in people who drink heavily. As one example, they are at increased risk of a life-threatening condition called acute respiratory distress syndrome (ARDS), which causes widespread inflammation of the lungs and leads to decreased oxygen levels in the blood. ARDS can result from lung infections and, particularly, bacterial pneumonia. It is two to four times more common in people with a history of chronic alcohol misuse.[12]

Cancer

Alcohol has been linked to an increased risk of cancer, including cancers of the liver, mouth and throat (i.e., upper aerodigestive tract), large intestine, and breast. The risk of harm differs depending on the type of cancer, the amount of alcohol consumed, and even genetic factors.[13] For example, heavy drinkers with a genetic mutation leading to a deficiency in aldehyde dehydrogenase 2, an enzyme that metabolizes acetaldehyde, a toxic byproduct of alcohol, are at considerably elevated risk for cancer of the esophagus.[14]

Alcohol's effects on the immune system also may make cancer cells more aggressive. Normally, immune cells from both the innate and the adaptive immune system, and the molecules they produce, help to eliminate cancer cells and control cancer growth and progression. However, alcohol-induced disruption of immune cells may allow the cancer to grow and progress.[13] As a result, cancer patients who drink heavily are more likely to die from cancer-related complications (and to die sooner) than those who drink less.[13]

HIV Infection

The complex interaction between alcohol, immunity, and disease is particularly relevant to HIV infection. HIV attacks the immune system by destroying a type of T cell vital to fighting infections. The destruction of these cells leaves people with HIV vulnerable to other infections, diseases, and complications.[15] Many studies examining the connection between alcohol, HIV, and the immune system have focused on the mucosa—the cell layer that lines various parts of the body, including the lungs, airways, GI tract, and genitalia. These mucosas are the body's initial defense against invading pathogens. Converging evidence indicates that alcohol misuse disrupts mucosa function and, in doing so, increases risk of HIV, accelerates HIV progression, and contributes to other infections and inflammation.[16]

Recovery from Traumatic Injury

About one-third of all patients with wounds such as burns, broken bones, and brain and other tissue injuries have blood alcohol levels above the legal limit at the time of injury.[17] Alcohol intoxication not only increases the risk of such injuries, but it can adversely affect outcomes for these patients. These effects appear to be particularly attributed to altered immune function, which makes patients more vulnerable to subsequent challenges to the immune system, such as surgery or infection. As a result, these patients are more likely to die during the recovery period.[18,19]

Alcohol intoxication is especially harmful for people with burn injuries. Approximately 50 percent of burn patients have detectable blood alcohol levels when they are admitted to the hospital. These patients have more complications, require longer hospital stays, and have greater mortality rates compared with patients who are not intoxicated at the time of injury. Patients with burn injuries are especially susceptible to infection of the lung. Alcohol intoxication at the time of injury further increases the risk of such infections by suppressing the immune system. Similarly, both burn injuries and alcohol disrupt the barrier function of the intestine, allowing bacteria to enter the bloodstream and increasing the risk of infection throughout the body.[20]

Immune Activity in the Brain

Recently collected data indicate that alcohol-induced immune activation contributes to neuropathology and perhaps even alcohol use disorder.[b] Animal studies find that alcohol consumption increases neuronal damage via the activation of immune factors.[21] Studies also have found that mice bred for high alcohol consumption exhibit an increase in the expression of certain genes involved in immune signaling, suggesting a role for immune cells in drinking behavior.[22]

[b] Alcohol use disorder (AUD) is a diagnostic term that refers to clinically and functionally significant health, psychological, social, or legal problems caused by recurrent alcohol use.

Though human research in this area is limited, studies using postmortem human brains have found that immune factors are increased in the brains of people who had alcohol use disorder. These studies have also found that the expression in the brain of certain immune factors is correlated with lifetime alcohol consumption. In addition, immune molecules, such as inflammatory cytokines, produced when bacteria leak from the gut into the bloodstream, can be transported to the brain where they produce a long-lasting inflammatory response.[22] Much more research is needed to determine how neuroinflammation occurs; how it affects brain function at the molecular, cellular, and circuit levels; and how the brain and peripheral immune systems communicate. Nonetheless, this is a promising avenue of research with the potential to enhance our understanding of alcohol use disorder and other alcohol-related conditions.

Practical Implications for Patients Who Drink

Alcohol's effects on the immune system have important implications for treating critically ill patients with a history of alcohol use disorder. Such patients are more likely to require hospitalization, have longer hospital stays, or need treatment in an intensive care unit. They also are more likely to die from their illnesses.[23–26] In addition, these patients are at increased risk of numerous complications, such as persistent fever, pneumonia, blood infections, ARDS, or confusion and disorientation. Finally, they may need higher doses of certain medications to achieve effective treatment.[26] Treating patients who drink excessively for serious medical problems is, therefore, particularly challenging. Physicians need to be aware of a patient's alcohol use to be able to offer the best treatment and to prevent more serious or even fatal complications.

Conclusion

Considerable progress has been made in bringing to light the relationship between alcohol and the immune system. However, the immune system is exceedingly complex, and there still are many gaps in our understanding of just how alcohol affects immunity and, ultimately, health. Scientists are working to better define the ways in which alcohol interacts with and hampers the immune system. The knowledge gained from this research is expected to lead to new ways of preventing and treating alcohol-related illnesses, enabling physicians to bolster weakened immune responses and tailor treatment to the unique needs of patients with alcohol use disorder.

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Alcohol can either activate or suppress the immune system depending on, for example, how much is consumed and how concentrated it is in the various tissues and organs. That dual action predisposes heavy drinkers both to increased infection and to chronic inflammation. This issue of *Alcohol Research: Current Reviews* details how alcohol affects the immune system and how researchers are harnessing this knowledge to help prevent and treat alcohol-related harm.

For more information on the latest advances in alcohol research, visit NIAAA's Web site, **www.niaaa.nih.gov**