Hepatitis A Virus

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Hepatitis A is an acute, self-limiting infection of the liver by hepatitis A virus (HAV), an enterically transmitted, hepatotropic member of the picornavirus family. Although HAV infection may occasionally result in fulminant hepatitis and death, it is not recognized to cause persistent infection or chronic hepatitis, even in severely immunocompromised individuals.

Reports of icteric disease in early Chinese literature and in the writings of Hippocrates may represent hepatitis A, but the disease discussed cannot be distinguished reliably from jaundice due to other causes (1). The earliest documented outbreaks of probable hepatitis A occurred in soldiers in Europe in the 17th and 18th centuries. Hepatitis A has plagued military campaigns throughout history, and many of the earliest terms used to describe the disease, like kriegsikterus and jaunisse des camps, reflect this close association (2).

Studies of hepatitis before and during World War II clearly established the existence of two distinct infectious forms of the disease, which later came to be known as hepatitis A and hepatitis B (3, 4). Experimental transmission studies defined the major features of hepatitis A: a relatively short incubation period (15 to 49 days), a fecal-oral mode of transmission, and long-lasting immunity that could be passively transferred. An animal model of HAV infection in marmosets was established by 1967 (5). The responsible virus was visualized in fecal extracts from adult volunteers in 1973 using immune electron microscopy (6), a finding that also resulted in a crude, but sensitive, test for antibody to HAV (anti-HAV). Viruslike particles approximately 27 nm in diameter were specifically aggregated by convalescent, but not preinfection, human sera (Fig. 1). The identification of HAV and the demonstration that infection could be transmitted to marmosets and tamarins, and, later, to seronegative chimpanzees ushered in a new era of research on hepatitis A that culminated in the propagation of the virus in cell culture (7), molecular cloning and sequencing of the viral genome (8), and the subsequent development and licensure of safe, effective vaccines (9, 10). Although the intensity of research on hepatitis A declined significantly following the licensure of effective vaccines, renewed interest in the virus has arisen because of its unusual alternative extracellular forms, circulating within the infected host in a quasi-enveloped form (eHAV) completely cloaked in host membranes, but shed in feces as a highly stable, naked, nonenveloped virion (11).

VIROLOGY

Classification

Based on the structure of its capsid and the organization and sequence of its positive-strand RNA genome, HAV is classified as the type species of the genus Hepatovirus within the Picornaviridae, a large and diverse family of viruses that includes many other agents of medical and veterinary importance. Although HAV shares many features in common with other members of this family, very limited nucleotide sequence relatedness (12) and several attributes specific to HAV (13) distinguish it from other picornaviruses and warrant its classification in a separate genus. Other viruses classified within the hepatoviruses include HAV strains recovered from nonhuman primates and viruses identified recently in bats, hedgehogs, shrews, and rodents, some of which appear to share antigenic determinants with human HAV (14).

Physical Characteristics of HAV

Genome Organization

The single-stranded, messenger-sense RNA genome of HAV contains a single, long, open reading frame (ORF) flanked by both 5′ and 3′ untranslated RNA segments (UTRs) (Fig. 2). It lacks the 5′ m7G cap structure typical of host mRNAs, and is instead covalently bound at its 5′ end to a virus-encoded protein termed VPg (3B) (15). As with other picornviruses, VPg likely serves as a protein primer for RNA synthesis. The 5′ UTR contains a high degree of secondary and tertiary RNA structure that has been defined by a combination of phylogenetic analyses, functional genetic studies, and direct biophysical and nucleic acid mapping techniques (16). This part of the genome contains both essential RNA replication elements and a highly structured segment that functions as an “internal ribosome entry site” (IRES) directing interactions of the RNA with 40S ribosomal subunits. The IRES drives internal initiation of viral translation in a 5′ cap-independent fashion, bypassing multiple upstream AUG codons (16). Translation may initiate at either of two AUG codons at positions 735–737 and 741–743, although the second of these codons is preferred (17). Although cap independent, HAV translation requires most, if not all, eukaryotic translation initiation factors, and results in a polypeptide of approximately 2,227 amino acids residues.
Electron micrographs of HAV. (A) Immune electron micrograph of HAV particles from human stool reacted with convalescent serum. The particles are heavily coated with and aggregated by antibody. Both “full” and “empty” particles can be seen. (B) An immune electron micrograph showing particles from human stool reacted with a preinfection serum. The 27- to 28-nm particles are nearly devoid of antibody and some fine structure can be seen. (C) Quasi-enveloped eHAV particles (panels a–d) and a nonenveloped HAV virion purified by density gradient centrifugation from supernatant fluids of infected Huh-7 cell cultures. The density of the fractions containing the particles is shown below the images. (A) and (B) Reprinted from Richman DD, Whitley RJ, Hayden FG (ed) Clinical Virology, 3rd ed, with permission. (C) (Reprinted from Clinical Virology, 3rd ed, with permission.)

FIGURE 1

that is proteolytically processed into both structural (P1) and nonstructural (2BC and P3) polypeptides (Fig. 2). Following a translation terminator sequence, the genome ends with a 3’ nontranslated region of 63 nucleotides followed by a poly(A) tail of variable length as is typical of picornavirus genomes.

In addition to critical RNA structures within the 5’ and 3’ UTRs that have regulatory functions in the replication cycle, a large, conserved, complex stem-loop structure within the polyprotein-coding segment of the genome (3D region) functions as a cis-acting replication element (cre) (18). Similar cre elements are found in other picornaviruses, although in different regions of the genome, and function as RNA structures (see below) while also encoding proteins to be translated.

Structural and Nonstructural (Replicase) Proteins

The primary cleavage of the polyprotein occurs cotranslationally between the VP1pX and 2B protein segments of the polyprotein, producing P1 (structural proteins) and P2-3 (nonstructural proteins) precursor polypeptides (Fig. 2). This cleavage is mediated by the only protease encoded by the virus, the 3C protein (3Cpro) (19, 20). 3Cpro, a cysteine protease (21), is responsible for all processing events in the polyprotein with the exception of scission at the VP4-VP2 junction—a late event following RNA packaging into the capsid and that may, in part, be catalyzed by RNA—trimming at the VP1-pX junction, mediated by one or more unknown host proteases (22, 23).

The P1 segment comprises four structural polypeptides in order from the amino terminus, VP4 (also known as 1A), VP2 (1B), VP3 (1C), and VP1pX (1D), named according to picornaviral convention, with VP1 being the largest (Fig. 2). The carboxy-terminal pX extension is found only in quasi-enveloped eHAV particles, and is absent in the mature, nonenveloped virion shed in feces (see below). Thus, the proteins in the mature naked capsid are approximately 23, 222, 246, and 273 amino acids in length, respectively. While pX is often referred to as “2A,” this segment of the polyprotein lacks homology with any other picornaviral 2A proteins (indeed, with any other protein in the database), and does not possess the cis-active protease activity found in the 2A proteins of other picornaviruses. pX functions in capsid assembly and is present in early assembly intermediates (24–26), and is thus best considered a part of the structural protein complement of the virus (i.e., P1 segment). VP4 (1A) is substantially smaller than its homologs in other picornaviruses, but recently has been confirmed to be present in the HAV capsid (27).

Each of the nonstructural proteins derived from the P2-P3 segment of the polyprotein is likely to contribute to assembly of a membrane-bound viral replicase complex that is responsible for synthesis of new RNA genomes. Unlike other Picornaviridae, HAV has no nonstructural 2A protein. 2B and 2C, and probably the unprocessed precursor 2BC, are involved in directing rearrangements of cellular membranes required for replicase assembly (28, 29). The 2B protein is very hydrophobic, and may anchor the replicase complexes to altered intracellular membranes (28). On the other hand, 2C has NTPase activity and contains a helicase motif. The P3 nonstructural proteins include an RNA-dependent RNA polymerase (3Dpol), the cysteine protease (3Cpro), and 3B (VPg), the protein primer for RNA synthesis. VPg is likely to be doubly uridylated in a slide-back reaction templated by the RNA cre and catalyzed by 3Dpol and 3CD (30). It remains covalently linked to the 5’ end of both positive- and negative-strand RNAs, but is probably stripped from the
positive-strand RNA by an unknown VPg unlinkase following viral entry and release of the genome into the cytoplasm. 3A contains a hydrophobic 21 amino acid stretch that is believed to anchor the 3ABC precursor of VPg to cellular membranes. Interestingly, the 3A transmembrane domain targets 3ABC to mitochondrial membranes, where it proteolytically cleaves mitochondrial antiviral signaling protein (MAVS), an important adaptor protein involved in the induction of interferon responses to virus infection (31).

Virion Structure
The viral genome is encapsidated within a stable icosahedral protein shell (the capsid) comprised of 60 copies of each of the four P1 polypeptides: VP1, VP2, VP3, and VP4. Mature virions purified from the feces of infected humans or chimpanzees band at 1.32 to 1.34 g/cm³ in cesium chloride (CsCl) and sediment at approximately 160 S (32). Particles with lower density that band at about 1.27 g/cm³ in CsCl and sediment at 70 to 80 S can often be detected in HAV preparations, and may represent empty capsids devoid of genomic RNA (32, 33) (Fig. 1). Unlike poliovirus and other well-studied picornaviruses, the smallest of the structural proteins, VP4, is not myristoylated at its amino terminus (34). Mutational studies suggest a noncanonical capsid assembly pathway that differs from that of other well-studied picornaviruses, with the 8-kDa carboxy-terminal pX extension on the largest capsid protein, VP1, playing a critical role in assembly of pentamer subunits rather than VP4 as is the case with other picornaviruses (24, 25).

Recent X-ray crystallographic studies of formalin-inactivated virus (27) (Fig. 3) indicate that the surface of the capsid is relatively smooth, devoid of depressions present in other picornaviruses that serve to shield receptor-binding sites from antibodies. The protein chains within the capsid are organized like other viruses in the picornavirus family with the exception of VP2, the amino terminus of which is dramatically repositioned such that it interacts with adjacent pentamer subunits, potentially contributing to the high physical stability of the particle (see below). This “domain swap” recapitulates the capsid structure of insect cripaviruses that are distantly related to the picornaviruses, distinguishing HAV from other mammalian picornaviruses and suggesting an ancient evolutionary relationship (Fig. 3) (27).

Antigenic Composition
HAV strains recovered from humans and from nonhuman primates appear to comprise only a single serotype worldwide (35), a fact that has important implications for the success of vaccines. However, neutralizing murine monoclonal antibodies (MAbs) do not recognize denatured capsid proteins, but only their completely folded native conformations within the capsid. Antisera raised to synthetic peptides or proteins expressed from recombinant DNA show only weak reactivity with native capsids and have very limited virus
Neutralization activity (36), ruling out the development of vaccines based on recombinant DNA technology.

Antigenic variants of HAV resistant to neutralizing MAbs have been selected by repeated passage of cell culture–adapted virus in the presence of these antibodies (37). These neutralization escape variants contain a limited set of substitutions in closely spaced neutralization epitopes in polypeptide loops within VP3 and VP1 (38). The critical neutralization epitopes of HAV are thus conformationally defined structures rather than linear epitopes, and involve residues of VP1 and VP3. The exact structure of these epitopes is now known from X-ray crystallographic studies (27).

Competition studies with various neutralizing MAbs suggest the existence of a single immunodominant site. Remarkably, a combination of only two murine MAbs is capable of efficiently blocking the binding of antibodies present in polyclonal human convalescent sera (38).

Quasi-enveloped eHAV Virions

In addition to the nonenveloped, naked virions described above, HAV has been recognized recently to be released from cells noncytolytically, completely wrapped in host-cell membranes (39) (Fig. 1). The membranes enveloping the capsid in these particles appear to lack any virally encoded protein, distinguishing these “quasi-enveloped” virions (termed “eHAV”) from classic enveloped viruses that possess glycosylated viral peplomers on their surface (11). Nevertheless, these eHAV virions are fully infectious in cell culture, yet completely resistant to neutralizing antibodies targeting the capsid in standard infection focus-reduction assays due to the surrounding membranes. The biogenesis of eHAV appears to involve the recruitment of fully assembled, intracellular capsids by components of the cellular endosomal complex required for sorting (ESCRT) complex, and likely involves the budding of the capsid into multivesicular bodies (MVBs) that subsequently release their contents into the extracellular space at the plasma membrane (39) (Fig. 4). This process provides a mechanism for viral egress from the cell, allowing the virus to cross the plasma membrane without cell lysis, and may have many features in common with the biogenesis of exosomes.

Surprisingly, quasi-enveloped eHAV particles appear to be the only form of virus circulating in blood during acute infection, both in humans and in experimentally infected chimpanzees, whereas virus shed in stool is composed exclusively of naked, nonenveloped virions (39). It is likely that both types of virus are produced within hepatocytes, and that the eHAV membrane is lost during passage through the biliary system due to high concentrations of bile salts in the proximal biliary canaliculus. Interestingly, hepatitis E virus, an unrelated positive-strand RNA virus that also causes acute hepatitis, has evolved very similar alternative extracellular forms (11).

Genetic and Antigenic Diversity

Partial sequencing of the genomes of HAV strains recovered from human or nonhuman primate sources in widely separated geographical areas has revealed only limited genomic diversity (40, 41). Thus, primate-derived virions are closely related genetically, especially when compared with the genetic diversity evident among other picornaviruses. Two major genotypes (I and III) have been described among these strains, as well as two minor genotypes (II and VIII), whose nucleotide sequences differ from each other at 15% to 25% of base positions in the genomic region studied (VP1-2A junction). Three other genotypes (IV, V, and VI) each include a single simian HAV strain (41). Much greater diversity is evident among related viruses in bats, shrews, hedgehogs, and rodents, which show a 32.4% to 47.4% distance from human HAV in their amino acid sequences (14). These novel viruses have yet to be assigned to specific
genotypes, but they are close enough in sequence to human HAV to warrant their assignment to the Hepatovirus genus. A considerable number of distinct HAV strains have been entirely or nearly entirely sequenced (8, 14, 42–44). Multiple, cell culture–adapted variants derived from one human HAV strain (HM175) have also been fully sequenced, revealing genomic regions that undergo change during propagation in cell culture and may result in attenuation of the virus (42, 45–47).

HAV strains recovered from humans demonstrate high-level (90% to 95%) conservation in the amino acid sequences of the viral capsid proteins. Consistent with this finding, viruses belonging to distinct genotypes elicit antibodies with substantial cross-neutralizing activity, indicating that these viruses comprise only a single HAV serotype (35). Although some MAbs are capable of distinguishing unique epitopes that are variably present in strains of HAV isolated from humans or from naturally infected cynomolgus and African green monkeys (44, 48), simian and human strains of HAV demonstrate substantial antigenic cross-reactivity. This close antigenic relatedness may extend even to non-primate hepatoviruses, as some bat sera appear to recognize human HAV antigens (14). Given the distance between sequences encoding structural proteins, however, it seems likely that at least some of these recently identified viruses comprise one or more additional HAV serotypes.

Stability and Resistance to Chemical Agents
In common with type C enteroviruses, the naked, non-enveloped HAV particle is stable at low pH (pH < 3.0) (49, 50). However, the thermal stability of HAV is considerably greater than that of enteroviruses (50, 51). Incubation of the virus for 4 weeks at room temperature results in only a 100-fold decrease in infectivity. Significant loss of infectivity starts to occur with exposure at 60°C for short periods and infectivity is destroyed almost instantaneously by heating above 90°C (52). However, outbreaks of hepatitis A have been reported following ingestion of partially cooked shellfish, suggesting that brief steaming may be insufficient to destroy the virus. In addition, HAV infectivity is highly resistant to drying, and infectious virus has been recovered from acetone-fixed cell sheets. It is also highly resistant to detergents, surviving a 1% concentration of sodium dodecyl sulfate, as well as to such organic solvents as diethyl ether, chloroform, and trichlorotrifluoroethane (50, 53). Solvent-detergent inactivation procedures thus do not reduce the infectivity of HAV, explaining why hepatitis A transmission has occasionally been associated with the administration of

FIGURE 4  Biogenesis of quasi-enveloped eHAV virions (11). Several hypothetical mechanisms may account for the release of quasi-enveloped virions from hepatocytes. The most likely mechanism for eHAV biogenesis involves (a) the recruitment of assembled intracellular HAV capsids to cytoplasmic multivesicular bodies (MVBs) by protein components of the cellular ESCRT (Endosomal Sorting Complex Required for Transport) system such as ALIX, followed by the budding of capsids into MVBs such that they become enclosed in membranes within the MVB. Movement of the MVB to the plasma membrane and fusion of the outer MVB membrane and plasma membrane then delivers eHAV to the extracellular environment. Alternatively, (b) ESCRT-associated proteins might mediate release of eHAV directly at the plasma membrane. A third possibility (c) is that HAV capsids are engulfed in autophagosomes for transport to either MVBs or the plasma membrane. Loss of the eHAV membrane after egress from the cell (d) leads to the production of naked, nonenveloped virions. (Reprinted from reference 11 with permission of the publisher.)
high-purity clotting-factor concentrates that are devoid of antibody (34). These properties of the virus may contribute significantly to its ability to persist in the environment and cause common-source outbreaks.

HAV can be reliably inactivated by autoclaving (121°C for 30 minutes) and by exposure to hypochlorite (chlorine bleach) in concentrations of 1.5 to 2.5 mg/l for 15 minutes (53). Although chlorine is most commonly used to avoid HAV contamination in water, environmental surfaces can also be decontaminated by quaternary ammonium formulation containing 23% hydrochloric acid (toilet-bowl cleaner). Glutaraldehyde (0.50% for 3 minutes), iodine (3 mg/l for 5 minutes) and potassium permanganate (30 mg/l for 5 minutes) probably are also effective. HAV is also inactivated by short incubation (5 minutes at 25°C) in 3% formalin or in diluted formalin for 3 days at 37°C, and by ultraviolet irradiation (55, 56).

**Biological of HAV**

**Host Range**

Serologic studies and direct experimental challenge support the capacity of human HAV strains to infect chimpanzees and other old world primates, including vervet, rhesus, and cynomolgus monkeys, as well as several species of new world primates, including tamarins (Saguinus sp.), marmosets (Callithrix sp.), and squirrel (Saimiri sp.) and owl (Aotus sp.) monkeys. Chimpanzees have extensively been used as a model of human HAV infection (57, 58), as have marmosets (59) and owl monkeys (60). HAV has also been isolated from monkeys in the wild. Some simian strains have significant sequence variation and minor antigenic differences from monkeys in the wild. Guinea pigs are susceptible to HAV infection and are commonly used in the laboratory for demonstrating viral replication (61). However, infection of cultured cells is typically noncytopathic and commonly leads to long-term persistence in the cell cultures, requiring weeks to months to reach detectable titers in cultured cells (64, 65). Nonetheless, a much broader host range for hepatoviruses is indicated by the recent discovery of multiple HAV-like viruses among bats, shrews, hedgehogs, and rodents (14). Whether any are capable of infecting humans or nonhuman primates is not known.

**Growth in Cell Culture**

HAV was first isolated ex vivo in marmoset liver explant cultures and was subsequently propagated in continuous fetal rhesus monkey kidney cells (7, 63). HAV can be propagated in a variety of different types of mammalian cells, including those of primate origin such as BS-C-1, FRhK-4, and MRC-5 cells (64, 65). However, wild-type viral strains from infected patients usually replicate very slowly and to relatively low titers in cultured cells, requiring weeks to months to reach maximal titers. With continued in vitro passage, the virus becomes progressively adapted to growth in cell culture, replicating more rapidly and achieving higher titers (65). Cell cultures of murine, guinea pig, porcine, or dolphin origin can also support HAV growth (66).

In contrast to the invariably transient nature of HAV infections in humans, infection of cultured cells is typically noncytopathic and commonly leads to long-term persistence of the virus in cells. This is consistent with the fact that HAV replication does not induce shutoff of cellular protein or nucleic acid synthesis as observed with poliovirus. However, highly cell culture–adapted variants of HAV that replicate very rapidly can cause cytopathic effects in culture, and can even be adapted to conventional plaque assays (47, 67). Cellular injury appears to arise from the induction of apoptotic pathways leading to programmed cell death (67). Continuous passage of the virus in cell culture may result in a reduction in the ability of the virus to replicate and cause disease in primates (68). Adaptive mutations that permit HAV to replicate efficiently in cell culture include mutations within the IRES that enhance cap-independent viral translation in a cell-type–specific fashion and mutations within 2B that promote viral RNA replication in multiple cell types (69–72).

As with other positive-strand viruses, purified genomic RNA, whether extracted from virions or produced synthetically from cloned cDNA, is replication competent when transfected into permissive cultured cells (73). This characteristic has allowed for reverse molecular genetics studies that have elucidated many aspects of HAV biology. However, recovery of virus from synthetic wild-type RNA (in contrast to HAV RNA with cell-culture–adaptation mutations) is difficult in transfected cell cultures, and usually requires inoculation into the liver of susceptible primates (74).

**Viral Attachment and Cellular Entry**

HAV enters cultured cells via two distinct mechanisms. Quasi-enveloped eHAV particles enter via an acidification-dependent, endosomal pathway that entails very slow uncoating of the viral RNA, probably subsequent to dissolution of the enveloping membranes in a late endosomal/lysosomal compartment (39). Initial attachment is likely mediated through phosphatidyserine receptors, as the uptake of eHAV by plasmacytoid dendritic cells is reduced in the presence of annexin V (75). In contrast, entry of mature, nonenveloped virions occurs rapidly and is not inhibited by agents blocking endosomal acidification. A specific cellular protein, HAVCR1 (also known as TIM-1), a mucin-like glycoprotein, has been suggested to serve as a receptor for the virus (76, 77). HAV binds to the cysteine-rich, globular C-terminal extracellular domain of the protein (78). TIM-family proteins facilitate the entry of many enveloped viruses by mediating interactions with phosphatidyserine on the virion surface, suggesting a possible role in quasi-enveloped eHAV entry (79). However, HAVCR1 is widely distributed in different tissues, and the hepatotropic nature of HAV infection cannot be explained by this interaction. Although the hepatocellular asialoglycoprotein receptor has also been suggested to play a role in viral entry by mediating the uptake of IgA-virus complexes (80), it cannot explain initial infection of the liver before the development of antibodies. X-ray crystallography has revealed that the HAV capsid lacks a receptor interaction site similar to those found in other picornaviruses, and this finding has led to speculation that HAV may have a completely different mechanism of cellular entry (27). More studies are needed to define this aspect of the viral replication cycle.

**Translation and Replication of the HAV Genome**

Following viral entry and release of the genome into the cytoplasm, the RNA undergoes translation fully under direction of the IRES, leading to expression of both structural and nonstructural proteins (Fig. 5). The nonstructural proteins (2BC) direct the reorganization of intracellular membranes into a tubular-vesicular membranous network within which the direct the synthesis of new viral RNAs (28, 29). The HAV IRES requires intact cellular initiation factor eIF-4G to function, which distinguishes it from other picornavirus IRES (81). Several cellular proteins, including polyprotein cleavage and ubiquitin–proteasome protein (PTB), significantly stimulate its ability to direct internal initiation of translation (82). Studies of other picornaviruses suggest that the virion RNA serves as a template for negative-strand RNA synthesis by the RNA-dependent RNA polymerase 3Dpol, thereby
Virion Assembly and Release
Assembly of the HAV capsid differs significantly from the process followed by other picornaviruses. The C-terminal pX extension of VP1 is essential for the PI capsid protein precursor to fold as required for efficient 3Cpro processing and for assembly of pentamer subunits that contain five copies each of VP4-VP2, VP1, and VP1pX (24, 25). Twelve of these pentamers subsequently assemble into a complete capsid, thereby packaging newly synthesized RNA genomes and triggering the cleavage of VP4-2 to VP4 and VP2. This "maturation cleavage" is likely associated with a conformational rearrangement of the capsid proteins that stabilizes the final structure.

Current data suggest that these nascent VP1pX-containing virions are then recruited to MVBs through interactions with ALIX and probably other ESCRT-related proteins, acquiring a membrane as they bud into this compartment (39) (Fig. 4). Fusion of the outer MVB membrane with the plasma membrane then releases membrane-wrapped eHAV virions to the extracellular environment.

Several lines of evidence, including unpublished data from our laboratory, suggest that release occurs across both the apical (canalicular) and basolateral (liver sinusoidal) membranes of polarized hepatocytes (83, 84), with loss of the eHAV membrane mediated by high bile-salt concentrations in the proximal biliary canaliculus. The pX domain of VP1pX is subsequently trimmed off the particle, resulting in fecal shedding of naked HAV virions produced in the liver and secreted via the biliary tract, coupled with a viremia composed of quasi-enveloped eHAV virions. Large numbers of naked virions have been visualized in the bile of infected chimpanzees (85), supporting this scenario. However, an enteric site of replication for fecally shed virions cannot be ruled out.

PATHOGENESIS
Animal Models
Current understanding of the pathogenesis of hepatitis A comes largely from studies of experimentally challenged nonhuman primates. Many of these studies were carried out several decades ago and used currently outdated methods for detecting virus and assessing immune responses. However, recent detailed analyses describe HAV infection in two intravenously inoculated chimpanzees, and a third, cohoused animal that became infected by the natural fecal-oral route (57, 58, 75) (Fig. 6). Infection is self-limited in chimpanzees and other nonhuman primates and is generally similar to nonicteric infections in children rather than more severe presentations of hepatitis A in adults. Following inoculation intravenously or orally, a lengthy incubation period (2 to 5 weeks) is followed by the relatively abrupt onset of liver injury marked by elevations of ALT and inflammatory infiltrates within the liver. In tamarins, the duration of the incubation period (measured to the onset of elevated serum liver enzyme activity) correlates inversely with inoculum size, increasing by approximately 5 days for each log10 reduction in dose (86). Progressively higher amounts of virus are found in serum and shed in feces throughout this phase of the infection (87). Both fecal shedding and the magnitude of the viremia begin to decline abruptly following the elevation of serum alanine aminotransferase (ALT), a measure of liver injury. Virus-specific antibodies first appear at this point in the infection (Fig. 6), which typically occurs several weeks after challenge. Laboratory parameters return slowly to normal over a period of 4–12 weeks, although, for reasons that are not understood, viral genomes persist within the liver in slowly decreasing quantities for months after infection in chimpanzees (57). It is not known whether the presence of this RNA indicates the persistence of infectious virus.

Tissue Tropism
Liver
While there may be extrahepatic sites of replication of HAV (discussed below), pathology for the most part is restricted to the liver. HAV, like many other picornaviruses, is very organ specific, perhaps because of specific hepatocyte receptors or intracellular replication factors. Large amounts of virus are
present within the liver throughout the asymptomatic, prodromal, and acute phases of the infection (Fig. 6). Viral antigen has been identified by immunofluorescent microscopy and immunohistochemistry within hepatocytes and in tissue-resident macrophages (Kupffer cells) of experimentally infected nonhuman primates (88), whereas electron microscopy has revealed viruslike particles enclosed within membrane-limited vesicles in hepatocytes (89) (Fig. 7).

While it is clear that antigen present in hepatocytes is indicative of active replication, antigen found in macrophages may reflect only the scavenger function of these cells.

In chimpanzees, low-grade, focal hepatocellular necrosis is observed in the early stages of the infection in chimpanzees (90), followed by more severe changes as serum ALT activity rises; these changes include increasing focal areas of necrosis in the lobular periphery and then throughout the hepatic parenchyma, coupled with widely scattered Councilman bodies, remnants of apoptotic hepatocytes. Periportal inflammatory cell infiltrates composed of lymphocytes and occasional polymorphonuclear leukocytes are present in the liver of infected chimpanzees and owl monkeys (60) as well as from humans (91) (Fig. 8). Virus particles are abundant in the bile of chimpanzees (85), reflecting secretion of HAV from hepatocytes into the proximal biliary canaliculi—commonly considered to be the source of virus shed in feces. Thus, both the naked virus particles shed in feces as well as quasi-enveloped virus circulating in blood (39) originate from hepatocytes.

Wild-type or low-passage HAV is not cytopathic in cell culture, and liver histopathology does not suggest widespread necrosis or apoptosis of hepatocytes in vivo. The presence of large quantities of virus in hepatocytes before the onset of hepatic inflammation and ALT elevation also argues against a
in renal or central nervous system tissue. A more interesting possibility is the pancreas: acute pancreatitis sometimes accompanies hepatitis A (98).

**Immune**

**Innate Immune Response**

HAV is a surprisingly stealthy virus in chimpanzees, evoking very little type I interferon (IFN-α/β) production and intrahepatic interferon-stimulated gene (ISG) expression despite replicating to high levels within the liver (57) (Fig. 6). This characteristic distinguishes it sharply from hepatitis C virus (HCV), which induces robust transcriptional upregulation of numerous ISGs in the liver. The basis for this difference is not clear. Stable HAV polyprotein-processing intermediates with cysteine protease activity disrupt signaling pathways by cleaving adaptor proteins required for induction of IFN-α/β responses. Thus, 3ABC (Fig. 2) is directed to mitochondrial membranes by a transmembrane domain in 3A, cleaving MAVS (IPS-1), and thereby disrupting signaling from RIG-I-like receptors (31, 99), whereas 3CD (Fig. 2) cleaves TRIF (TICAM-1), which is essential for Toll-like receptor 3 (TLR3) signaling (100). In both cases, the HAV processing intermediates are more active than mature 3Cpro in effecting these cleavages, indicating an exquisite adaptation of HAV to the human innate immune response. The unrelated HCV NS3/4A serine protease similarly degrades both of these adaptor proteins. However, the HAV 3Cpro protease also degrades NEMO (IKKγ) (101), which contributes to NF-κB activation and the induction of type I interferons, whereas NS3/4A does not. HAV also achieves much higher levels of viral protein expression than HCV (57), and this is likely to contribute to its greater capacity to suppress interferon responses in the liver.

Despite the low levels of IFN-α and ISG expressed in HAV-infected chimpanzees, freshly isolated human plasmacytoid dendritic cells (pDCs) are capable of sensing quasi-enveloped eHAV virions released from infected cell cultures, thereby producing IFN-α through a TLR7-dependent mechanism (75). pDCs appear to be recruited to the liver and are found within the sinusoids during the first week of infection in the chimpanzee but, for reasons that are not clear, such cells are no longer detectable within the liver at the onset of hepatic inflammation.

In vitro studies suggest that natural killer cells are capable of recognizing and lysing HAV-infected cells, and thus may contribute to control of the infection (102). Consistent with this phenomenon, microarray analyses of liver tissue from acutely infected chimpanzees are indicative of a strong type II IFN-γ response correlating with the onset of liver injury and elevation of serum ALT (57).

**T Cell Immunity**

The mononuclear inflammatory infiltrates that typify the histopathology of acute hepatitis A (90, 91) have long suggested that adaptive T cell responses may mediate HAV-associated liver injury. Early studies demonstrated that HAV-specific CD8+ cytotoxic T cell clones could be isolated with appropriate cytokine stimulation from the livers of acutely infected humans, whereas CD4+ T cell clones were more likely to be recovered during convalescence (103). The CD8+ T cells produce IFN-γ and are capable of killing HAV-infected fibroblasts in cell culture (103, 104). Granzyme B and perforin mRNA transcripts are also upregulated in acutely infected chimpanzee liver (57). These findings indicate that CD8+ T lymphocytes mediate liver damage and

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**FIGURE 8** Photomicrograph of a liver section from a patient with acute hepatitis A, showing inflammation of the portal and periporal areas by lymphocytes coupled with lobular disarray and hepatocellular ballooning degeneration (cytoplasmic vacuolization). (Hematoxylin and eosin stain; original magnification 40x). (Adapted from Martin A, Lemon SM, Hepatology 2006 with permission of the publisher.)

Major direct cytopathic effect of HAV. Clinical hepatitis coincides with the appearance of cellular and humoral immune responses, and the pathology of hepatitis A is thus likely to result from the immune response to the infection.

**Gastrointestinal Tract**

It is not known how HAV reaches the liver in the initial stages of the infection. Because the virus is acid resistant, it can survive passage through the stomach and thus could initially replicate somewhere lower in the gastrointestinal tract, although this hypothesis remains to be proven. While HAV antigen was identified by immunofluorescence microscopy in isolated cells lining the crypts of both the jejunum and ileum in owl monkeys in which the virus was inoculated via feeding tube (60), a similar search for viral antigen in gut tissue failed to identify any infected cells in a cohort of intravenously infected marmosets (88). Virus has also been identified in saliva from infected chimpanzees, but the significance is uncertain (92). The lack of compelling evidence for a primary site of replication in the gut rules out this possibility, however, given similar difficulties in identifying a gastrointestinal site of replication for noroviruses. An alternative possibility is that HAV might be taken up by specialized M cells in the small intestine, undergo transcytosis, and pass into the lymphatics, as proposed for poliovirus (93).

**Other Extrahepatic Sites of Replication**

Viral antigen has been detected in splenic macrophages and in Kupffer cells, but this finding may not represent active replication in those cells (88). Nonetheless, fluorescent in situ hybridization has revealed appreciable amounts of viral RNA in the spleen of bats infected with a nonprimate hepatovirus, suggesting that the HAV may replicate in this organ (14). Replication in other organs appears less likely. Meningoencephalitis and transverse myelitis have been described in association with acute hepatitis A (94, 95), as has acute renal failure in nonfulminant hepatitis A (96, 97). However, no direct evidence suggests replication of the virus...
possibly contribute to viral control. However, recent studies in infected chimpanzees suggest a more important role for noncytolytic virus control mediated by virus-specific CD4+ helper T cells (58, 105). Direct ex vivo analyses demonstrated that virus-specific CD4+ T cells are multifunctional, and produce multiple cytokines (IFN-γ, TNF-α, IL-2 and IL-21) in response to a variety of HAV-specific peptides (58). This CD4+ T cell response correlates temporally with reductions in viremia, and the decline in HAV genome copy number in the liver during convalescence (Fig. 6). In contrast, direct ex vivo analysis revealed the CD8+ T cell response to be relatively abbreviated, and that virus-specific CD8+ T cells acquire effector functions only after viremia had begun to decline. These findings thus suggest an alternative model of noncytolytic, cytokine-mediated control of the infection (105). T cell responses to HAV infection are thus important for recovery and pathogenesis, but their role in subsequent protection against reinfection is not known.

As discussed above, a member of the T cell immunoglobulin mucin family, HAVCR1 (TIM-1), has been suggested to function as a cellular receptor for HAV (77). This cell surface receptor family is important in T cell regulation, TIM-1 stimulates T cell expansion and cytokine production and is associated with atopic disease (106). An inverse relationship between asthma and childhood exposure to HAV has been suggested but not conclusively demonstrated (107). One hypothesis is that activation of T cells through TIM-1 by HAV or by its natural ligand may affect T cell differentiation and the regulation of Th2-driven allergic inflammatory responses, such that recent reductions in childhood HAV infections may be associated with increases observed in the incidence of atopic diseases (108).

Humoral Immunity
Although the onset of liver damage correlates closely with the appearance of circulating anti-HAV antibodies (Fig. 6), neither antibody-dependent nor complement-mediated cytotoxicity has been demonstrated in hepatitis A (109). While circulating immune complexes containing HAV and HAV-specific antibodies (primarily IgM) have been found during acute infection, immunoglobulin and complement deposits are not found at the sites of liver cell damage (110). Virus-specific antibody responses thus play an uncertain role in the pathogenesis of hepatitis A, but they are likely responsible for solid protection against symptomatic reinfection and for the protection afforded by immunization with formalin-inactivated vaccines (111). Passive immunization with pooled human immune globulins (IGs) results in low levels of circulating antibody that nonetheless provide complete protection against symptomatic infection.

The antibody response to HAV infection is vigorous and long lasting. Both IgM and IgG anti-HAV antibodies are capable of neutralizing HAV infectivity (112, 113); they first appear coincident with the onset of hepatic inflammation and ALT elevation (Fig. 6). Microarray assays show that genes involved in B cell development and the recruitment of B cells to the liver (for example, CXCL13) are transcriptionally upregulated to impressive levels in liver biopsies from infected chimpanzees (57). This transcriptional activation persists for months, and IgG antibodies targeting the viral capsid may comprise as much as 12% to 15% of all IgG present in convalescent serum collected several months after infection. Immunity to HAV persists for life, and second infections associated with hepatic disease are unknown.

Although nonenveloped HAV virions are readily neutralized by antibody in vitro, quasi-enveloped eHAV virions show no reduction in titer when incubated with neutralizing antibodies (39). This is surprising, given the protective nature of anti-HAV and the fact that only eHAV virions are detectable in the blood during acute infection (39). However, while not well understood, eHAV appears to be susceptible to neutralization within an endocytic compartment following uptake into cells. This is evidenced experimentally by the ability of neutralizing antibodies to inhibit viral replication when added to cultures as late as 4 to 6 hours after adsorption and removal of an eHAV inoculum (39). The antibodies appear to traffic to a late endosomal/lysosomal compartment in which the eHAV membrane is slowly degraded, allowing antibodies to interact with the capsid and neutralize infectivity prior to interactions of the capsid with its receptor. Such postentry neutralization is not observed with naked, nonenveloped virions (39). Whether an IgG receptor is involved in trafficking of the antibody is not known.

While serum antibodies are clearly protective against infection, it has been difficult to judge the role of mucosal immunity because antibodies in saliva or feces either are not detected or are present only at very low levels (114). Individuals with agammaglobulinemia are at risk for particularly severe or persistent infections with other picornaviruses, but this risk has not been described with HAV.

**EPIDEMIOLOGY**

**Global Incidence and Prevalence of HAV**

The World Health Organization (WHO) estimates that approximately 1.5 million cases of hepatitis A occur worldwide annually, but the rate of infection is probably ten times higher (115). Although HAV is the most common cause of hepatitis globally, major geographic differences in endemicity exist that are linked to the level of economic development and sanitary conditions.

Three principal patterns of endemicity (high, intermediate, and low) are considered to exist worldwide based on the results of age-specific prevalence of anti-HAV antibodies (Fig. 9). In areas of high endemicity, including underdeveloped regions of Africa, Asia, and South America, HAV is readily transmitted due to poor socioeconomic conditions; the prevalence of anti-HAV reaches 90% in younger adults. Most infections in these areas occur in childhood (before the age of 10 years), many of which are asymptomatic or not recognized as hepatitis. The burden of overt disease is quite low in these areas because the majority of the population has achieved immunity to the disease by adolescence. In areas of intermediate endemicity, only 50% to 60% of adults and 20% to 30% of children have been infected because HAV is not transmitted as readily secondary to improved sanitation. Since there are more adults susceptible to infection, larger outbreaks occur and more persons have symptomatic illness. In areas of low endemicity, such as the United States, Canada, and Western Europe, less than 30% of adults have anti-HAV. When HAV is introduced into such populations, cyclical waves of transmission can occur (116). Important changes have happened in these three classic patterns of global endemicity over the last few decades (Fig. 10). Improvements in sanitation and socioeconomic development in many previously undeveloped regions has resulted in a transition from a high- to intermediate-endemicity pattern. This “epidemiologic transition” has been associated with a paradoxical increase in disease incidence, as it is associated with a decline in the age-specific prevalence of
immunity to HAV, leading to increased susceptibility to infection among older individuals, who are more likely to become symptomatic if infected. Regions of transitional endemicity include China and countries in South America, Central and Southeast Asia, and the Middle East (116).

The median age at seroconversion increased between the years 1990 and 2005 (117). This phenomenon can be expected to result in disease patterns characterized by increased morbidity as cohorts of susceptible older children and adults become infected. There is also greater potential for outbreaks as the susceptible population grows, but relatively high levels of circulating virus persist. Significant outbreaks have occurred in China, including one in 1988 caused by the ingestion of raw clams contaminated with HAV, resulting in nearly 300,000 cases (2). Smaller-scale outbreaks have occurred in China more recently, including one in 2006 involving a large school (118). Korea has also recently experienced a large national outbreak of hepatitis A, probably due to the importation of contaminated shellfish from less-developed regions (119). As a result of such outbreaks and increasing morbidity in older populations, more countries are introducing universal childhood immunization programs, the most notable including South Korea and Argentina (120).

Hepatitis A in the United States

The Prevacine Era

Before licensure of an effective vaccine in 1995, HAV incidence in the United States was primarily cyclic, with peaks occurring every 10 to 15 years. During the 1980s and 1990s, an average of 26,000 hepatitis A cases were reported annually to public health agencies. The outcome of one incidence model, however, predicted an average of 271,000 infections per year between 1980 and 1999, thereby suggesting that only one in ten cases of acute hepatitis A had been reported. More than one-half of those infections, according to the model, were in children aged less than 10 years and likely would have been clinically unrecognizable as hepatitis (121).

Before widespread immunization, approximately one-third of reported cases occurred among children aged less than 15 years, with the highest overall incidence in children.
aged 5 to 14 years (122). Large serosurveys conducted between 1988 and 1994 found that the overall prevalence of anti-HAV was 31.3%, with antibody prevalence increasing markedly with age, ranging from 9.4% among persons aged 6 to 11 years to 74.6% among persons older than 70 years. The age-adjusted prevalence was significantly higher among foreign-compared to U.S.-born persons, and was highest among Mexican Americans and lowest among non-Hispanic whites. In a multivariate analysis, only Mexican-American ethnicity and income below the poverty level were associated with HAV infection among U.S.-born children (123).

Nearly half of all hepatitis A cases in the United States were associated with no identifiable source of infection in the pre-vaccine era (124). Of those cases with an identifiable source, the majority resulted from person-to-person spread of HAV during community-wide outbreaks. Cyclic outbreaks, however, occurred among users of illicit drugs and among men who have sex with men (MSM) (125). Overall, this suggested that nationwide reductions in incidence were more likely to result from routine childhood vaccination than from targeted vaccination of high-risk groups, because children often have unrecognized or asymptomatic infection and play a major role in perpetuating HAV transmission during outbreaks.

Postvaccine Era

The epidemiology of HAV has changed radically since licensure of the hepatitis A vaccine and implementation of a national childhood immunization strategy in the United States. Hepatitis A rates have fallen dramatically and the country has not experienced a nationwide cyclic spike in hepatitis A incidence since 1995 (123). Nevertheless, hepatitis A remains one of the most frequently reported vaccine-preventable diseases in the United States.

Soon after the hepatitis A vaccine was licensed in the United States, the Advisory Committee on Immunization Practices (ACIP) recommended routine vaccination of children aged 2 to 18 years living in communities with the highest rates of infection and disease. An estimated 50% of hepatitis A cases were averted by immunizing children in this age group despite low overall vaccine coverage (10%) (126). Targeting children for immunization resulted in impressive reductions in the incidence of hepatitis A among adults, vividly demonstrating the role young children play in the transmission and propagation of HAV within populations. Although effective regionally, this immunization strategy had only a limited impact on the national incidence of hepatitis A, leading to the expansion of routine immunization to other locations where disease rates were high. By 2003, the incidence of acute hepatitis A had declined overall by 76%, from a rate of 10.7 per 100,000 population during 1990 through 1997 to 2.6 per 100,000 population (127). Due to this precipitous decline, universal vaccination was recommended for all children in the United States aged 12 to 23 months in 2006 (128).

Concurrent with the overall decline in hepatitis A incidence in the United States since the introduction of immunization has been the narrowing of historic differences in rates among racial/ethnic populations and geographical locations. Among Native Americans and Alaska Natives, current rates indicate a 99% decline compared with the pre-vaccine era and are now approximately the same or less than those of other racial/ethnic populations (129). Rates among Hispanic Americans have fallen almost 90%, although the rates remain higher than those for non-Hispanics (130).

The incidence of HAV-related disease reached the lowest recorded rate (0.4 cases per 100,000 population) in 2011. However, the incidence rate started to increase again in 2012 through 2013, reflecting increased numbers of cases among adults aged more than 20 years. A steady increase in hospitalizations due to HAV infection has been noted since 1999 (131). In 2013, a total of 1,781 cases of hepatitis A were reported from 50 states to the Centers for Disease Control and Prevention (CDC), a 14% increase from 2012 (132). Most cases in the United States are associated with exposure during travel, although nationwide outbreaks still occur due to contaminated food. For example, a nationwide foodborne outbreak in 2013 was found to be associated with a frozen fruit product containing contaminated, imported pomegranate arils (133). Approximately 93% of those infected were adults.

The most recent National Health and Nutrition Examination Survey (NHANES), conducted by the CDC, revealed the prevalence of anti-HAV among adults aged more than 20 years to be 24.2% during 2007 through 2012, a significant decline from 29.5% during 1999 through 2006 (132). The lowest age-specific prevalence was among adults aged 5 to 11 years (16.1%) and 17 to 17.6%). Thus, a continuing shift in the age-specific prevalence of anti-HAV is occurring subsequent to the institution of universal childhood immunization. This is resulting in a higher anti-HAV prevalence among children but a lower prevalence among adults due to herd protection. The NHANES survey also revealed that vaccination coverage among adults aged 18 to 49 years was only 12.2% in 2012. Although adults are less likely to acquire infection from children during the vaccine era, they are at greater risk of becoming infected through travel and food imported from endemic areas.

Mortality

The overall fatality rate among cases reported through the CDC surveillance system in the United States typically ranges from 0.3% to 0.6%. Between 2009 and 2013, the hepatitis A–related mortality rate was 0.02 deaths/100,000 population per year, which was consistent with rates over the past few decades. Age-specific mortality rates rise with increasing age, ranging from 0.00 deaths/100,000 population among persons aged 0 to 24 years to 0.08 deaths/100,000 population among persons aged 55 to 74 years in 2013, and 0.07 deaths/100,000 population among persons aged more than 75 years (134).

Transmission

The most important mode of HAV transmission is undoubtedly from person to person via the fecal-oral route. Fecal excretion of the virus is highest during the 2 weeks before and a few days immediately after the onset of symptoms but is likely to continue for many weeks (135). The highest infection rates are seen among family and school contacts, indicating that the infective dose is low and interpersonal spread is efficient. The other major mode of transmission is through contaminated food and water. Many types of food products, including seafood, produce, and meat, have been implicated during outbreaks. Transmission following parenteral exposure, including transfusion of blood products and use of contaminated needles, is also possible but is relatively infrequent due to the brief duration of viremia associated with acute infection.

Of the 1,063 cases in the United States in which risk exposure/behavior was reported in 2013, only 24.5% indicated a possible exposure for hepatitis A during the 2 to 6 weeks before the onset of illness. The most frequently identified risk factor for hepatitis A was linkage to a food-
waterborne outbreak (12.8%). The second most common risk factor was international travel (6.2%), with most cases involving travel to Mexico and Central and South America. Whereas sexual and household contact with another person with hepatitis A have been traditionally among the most frequently identified risk factors, these risk factors were reported for only 5.6% of cases in 2013. MSM and injection drug users accounted for 5.5% and 4.0% of reported cases, respectively (134).

Groups at Increased Risk for Hepatitis A

Travelers
Hepatitis A remains one of the most common vaccine-preventable diseases acquired during international travel. Persons from developed (low-endemicity) countries who travel to developing (intermediate- or high-endemicity) countries are at significant risk for acquiring hepatitis A (136). The risk is higher among travelers visiting areas with poor sanitation and limited access to clean water, although the disease occurs in travelers who report observing strict protective measures and staying in more developed cities or luxury hotels. The incidence rate for nonimmunized travelers is estimated to be 3 cases per 1,000 travelers per month of stay in developing countries. Hepatitis A among Hispanic children who live along the United States–Mexico border has been associated with cross-border travel to Mexico and foodborne exposures during travel (137). Many recommendations and guidelines have been issued in different countries regarding prophylaxis for travelers.

Men Who Have Sex with Men
Numerous outbreaks of hepatitis A have been reported among MSM in the United States, Canada, Europe, and Australia, sometimes in the setting of a larger community-wide outbreak. However, surveys of anti-HAV prevalence among MSM have neither consistently demonstrated a greater propensity for infection compared with a similarly aged population, nor have specific sex practices been consistently identified (138).

Users of Illicit Drugs
Outbreaks among drug users, both injecting and noninjecting, have been reported frequently in the United States and other developed countries since the 1980s (124). In the United States, many outbreaks have involved the use of methamphetamine and transmission by both percutaneous and fecal-oral routes (139). Injection drug users appear to have a higher prevalence of anti-HAV than the general U.S. population (138). Transmission is likely connected to socioeconomic factors, sexual promiscuity, syringe exchange, and contamination of instruments, and to involve both fecal-oral and parenteral routes.

Persons with Clotting-Factor Disorders
Before improvements in viral-inactivation procedures, widespread hepatitis A immunization, and improved donor-screening methods, rare outbreaks of hepatitis A among persons with clotting-factor disorders and hemophilia were reported in Europe and the United States (140)—the result of HAV contamination of high-purity clotting factor concentrates devoid of protective IgGs and prepared from very large donor-plasma pools. However, in recent years, no cases of hepatitis A attributable to administration of blood products have been identified in the United States, and hemophiliacs are not at a higher risk than the general population of acquiring HAV (141).

HAV Transmission in Special Settings

Food-Service Establishments
Food-borne hepatitis A outbreaks are recognized relatively infrequently in the United States. According to CDC surveillance in 2013, about 12.8% of cases in which an exposure was reported could be linked to a food-borne outbreak. This was an increase from previous years because of a nationwide outbreak related to contaminated pomegranate seeds in 2013. The proportion of sporadic cases that might be from food-borne sources is unknown but could be considerable, as approximately 50% of reported cases of hepatitis A still do not have an identified source of infection. HAV contamination of agricultural products can occur at any point during cultivation, harvesting, processing, or distribution (142).

A single HAV-infected food handler can transmit the virus to dozens or even hundreds of persons. However, food handlers are not at a higher risk of hepatitis A because of their occupation, and most infected food handlers do not transmit HAV to consumers or restaurant patrons (142).

Molecular epidemiologic techniques comparing RNA sequences of HAV strains has made possible the identification of previously unrecognized links between cases, as exemplified in a multistate outbreak of HAV subgenotype IB infection among European travelers returning from Egypt in 2012 to 2013. A persistent common source of infection was suspected, as HAV strains isolated from various cases over a period of several weeks were indistinguishable genetically. The 107 cases of hepatitis A infection were eventually linked to strawberries (143). Similar molecular epidemiologic studies have elucidated the origins of HAV strains involved in a recent nationwide outbreak of hepatitis A in South Korea (119).

Child Care Centers
The frequency of outbreaks among children attending day care centers and persons employed at these centers has decreased substantially, as the overall hepatitis A incidence among children has declined since the implementation of vaccination, especially in the United States, since 2006. Because infection among children is typically mild or asymptomatic, outbreaks are often not identified until adult contacts become ill (144).

Schools
In the United States, the appearance of cases of hepatitis A in schools is ordinarily a reflection of disease acquisition and transmission in the community. Secondary transmission to other students is uncommon. However, if multiple cases occur among students, a common source of infection is possible and should be investigated (128).

Health Care Institutions
Nosocomial transmission of HAV is rare, and the CDC recommends adherence to standard precautions. Health care personnel who become infected should avoid patient contact and food handling for 7 days after the onset of jaundice. Patients with typical cases of hepatitis A are not routinely admitted to hospitals, and even when patients are hospitalized, the probability of transmission is low because most are admitted after the onset of jaundice, when the period of maximum infectivity has passed. Outbreaks in hospital settings have been linked to inadequate hand cleaning. Anti-HAV seroprevalence is similar in health care workers and control populations, indicating that health care workers are not at increased risk of acquiring infection (145).
Workers Exposed to Sewage
Among wastewater workers, no work-related instances of HAV transmission have been reported in the United States, and serologic surveys have shown no substantial or consistent increase in the prevalence of anti-HAV. Surveys performed in other countries indicate a possible elevated risk for HAV infection among workers exposed to sewage; however, those analyses did not control for other factors, such as socioeconomic status (146).

Nonhuman Primate Colonies
Persons working with captive nonhuman primates were previously at risk for hepatitis A, but immunization of animal handlers has largely eliminated that risk.

CLINICAL FEATURES
The clinical manifestations of hepatitis A are highly variable, ranging from asymptomatic infection, to mild anicteric hepatitis, acute icteric viral hepatitis, and even fulminant hepatic failure. The risk of clinical disease following HAV infection is determined primarily by the age of the person infected. In children younger than 6 years, 70% of infections are asymptomatic and, if illness does occur, it is typically not associated with jaundice. By contrast, infection during late childhood through adulthood is likely to cause icteric illness in more than 70% of patients. The risk of fulminant hepatitis and death is also much higher in older patients.

Uncomplicated Acute Hepatitis A
Clinical Course
Clinical signs and symptoms of acute hepatitis A are indistinguishable from those caused by other types of hepatitis (see Chapter 5 for differential diagnosis). Thus, while clues from the epidemiologic setting may be present, laboratory tests are required for specific diagnosis. The incubation period is approximately 15 to 50 days, with a mean of about 30 days (Fig. 11). In older children and adults, the illness usually begins with abrupt onset of prodromal symptoms including fatigue, malaise, nausea, vomiting, anorexia, fever, and abdominal pain. Typical symptoms of hepatitis, beginning with darkening of the urine and followed by jaundice and pale or clay-colored stools, will appear after a period of several days to a week. During a large shellfish-associated epidemic in Shanghai in 1988, prodromal symptoms included anorexia (82%), malaise (80%), fever (76%), nausea (69%), and vomiting (47%) among the more severely affected patients who were hospitalized (147). Hyperbilirubinemia was seen in 91%, and 84% were overtly jaundiced (147). Itching, often a sign of cholestasis, occurs in less than 5% of symptomatic patients but may be severe enough to require antipruritics and corticosteroid therapy. The two most common physical findings are jaundice and tender hepatomegaly, which occur in 70% and 80% of symptomatic patients, respectively. Less common clinical findings include splenomegaly (9%), rash, arthralgies, and leukocytosis.

Serum ALT and aspartate aminotransferase (AST) activities are sensitive, but nonspecific, measures of parenchymal liver damage associated with acute HAV infection. ALT elevations, usually higher than AST, may be found even during the prodromal stage. In icteric acute hepatitis A, serum ALT levels are typically less than 2,000 IU/l, but may exceed 20,000 IU/l. While high ALT levels occur in patients with severe hepatitis, the elevation of ALT is not necessarily correlated with the severity of the illness. Alkaline phosphatase levels are usually only mildly elevated in hepatitis A, except when the illness is complicated by cholestasis. Biochemical abnormalities may persist for 2 to 3 months, but usually return to normal by 4 weeks (Fig. 11).

The duration of illness varies. In many patients, the appearance of jaundice is associated with rapid resolution of the prodromal symptoms. After 3 to 4 weeks, most patients feel better, no longer have hepatomegaly, and have normal or near-normal serum levels of ALT and bilirubin. Prolonged jaundice or a relapsing pattern may also occur but ultimate resolution in these cases is universal. Infection with HAV does not cause chronic infection. HAV infection, whether asymptomatic or associated with disease, is associated with the development of a robust immune response, which provides lifelong protection against future reinfection with the virus.

Children
HAV infection in younger children is typically mild; only 30% of children younger than 6 years are asymptomatic. Symptoms, when present, are often nonspecific, and include fever, malaise, anorexia, and nausea. Serum aminotransferase levels can be elevated during the prodromal period and jaundice, when it occurs, usually develops occurs 1 to 2 weeks after symptom onset. Jaundice typically lasts for less than 2 weeks, with aminotransferases returning to normal limits in approximately 2 to 3 months. Acute liver failure is extremely rare in children, occurring in less than 1% of cases.

Hepatitis A in Pregnancy
HAV infection in pregnant women is usually self-limiting and not a threat to the fetus. Although HAV infection does not increase the risk of congenital malformations or spontaneous abortions, there have been rare reports of increased preterm labor and premature rupture of membranes (148).

FIGURE 11 Natural history of hepatitis A. The infection is typically acute in nature, with symptoms and signs of the infection usually occurring within 3 to 5 weeks of exposure. The sequence of events includes shedding of infectious HAV in feces and viremia, followed by increases in serum ALT activity (red line), and the appearance of IgM and IgG anti-HAV antibody responses (the latter typically measured as total anti-HAV antibody). (Adapted from Martin A, Lemon SM, Hepatology 2006 with permission of the publisher.)
Complications and Atypical Presentations

Cholestatic Hepatitis A
Prolonged jaundice is often associated with fever and pruritus and is an indication of cholestatic hepatitis. Peak serum bilirubin levels may reach 12 to 29 mg/dl, and jaundice may continue for up to 18 weeks (149). The cause of prolonged cholestasis is unknown, but is usually reflected histologically by predominantly cholestatic features. The duration of viremia has been found to be longer in patients with cholestatic hepatitis but the virologic and host factors implicated in the pathogenesis are unknown. In a prospective, Korean multicenter study of 595 hepatitis A cases, prolonged cholestasis occurred in 4.2%; preexisting chronic hepatitis B infection, prolonged prothrombin time, and higher total bilirubin levels were associated with increased risk (150). Peak biochemical markers including serum aminotransferases and alkaline phosphatase were not significantly different in patients with prolonged cholestasis (136). Cholestasis ultimately resolves spontaneously with no complications or sequelae. It is important to be aware of this relatively common but atypical feature of hepatitis A and to avoid overly aggressive interventions.

Relapsing Hepatitis A
A relapsing form of hepatitis A has been observed in 3% to 20% of patients. One study reported 12.5% of 297 adults had a relapsing course, of whom 22% had more than one relapse (151). The relapses are usually milder than the initial illness and typically occur after the serum aminotransferases have normalized from the initial episode, and long after the development of anti-HAV. Nonetheless, it seems likely viral replication is ongoing in such cases; HAV has been found in the stool of some patients during relapse (152). The mechanisms underlying relapse are unknown and predisposing factors have not been identified. Similar minor relapses have been observed in experimentally infected chimpanzees, and were not associated with mutations in the viral capsid that might suggest immune escape. The prognosis for relapsing hepatitis is excellent, and all cases ultimately resolve without chronic sequelae.

Fulminant Hepatitis A
Fulminant hepatitis, characterized by rapid onset of liver failure and coma, is rarely associated with HAV infection but is potentially fatal. Fulminant disease is more common in older persons, and recovery from severe disease is less common in patients older than 50 years. The Acute Liver Failure Study Group (ALFSG) study of adults with acute liver failure from 1998 to 2005 found that HAV accounted for 3.1% of patients and only 0.12% of those listed for liver transplantation (139).

The initial clinical presentation is not significantly different from other cases of acute hepatitis A (153). Patients typically have a coagulopathy (prothrombin time >15 seconds or international normalized ratio >1.5) and encephalopathy. The ALFSG evaluated 29 patients with fulminant hepatitis A and developed a prognostic index to predict transplantation or death. The index incorporates four presenting features (serum ALT <2,600 IU/L, creatinine >2.0 mg/dL, intubation, pressors) and was shown to be better than other published models including the laboratory Model for End-Stage Liver Disease score. Laboratory and clinical evidence of deteriorating liver function correlates with a histologic picture of virtually complete destruction of the hepatic parenchyma with only a reticulin framework and portal tracts remaining. Occasionally, small groups of surviving hepatocytes can be seen close to portal tracts, which may be evidence of regeneration (154). As many as 50% of patients with acute, HAV-associated fulminant liver failure may die or require emergency liver transplantation. Spontaneous recovery rates in fulminant hepatitis A range between 30% and 60%, and survivors regain complete liver function. Prognosis is influenced by age, clotting factor levels, stage of coma, and presence of kidney disease. Recovery from fulminant hepatitis is difficult to predict, and the only effective treatment is liver transplantation.

Host factors associated with increased risk of fulminant hepatitis include older age and underlying chronic liver disease, particularly chronic HCV infection. In a study of 163 patients with chronic hepatitis B and 432 patients with chronic hepatitis C, HAV superinfection occurred in 27 patients (135). All 10 of the patients with hepatitis B infection had an uncomplicated course. In contrast, fulminant hepatic failure developed in 7 of the 17 patients with chronic hepatitis C who acquired hepatitis A, and 6 of those patients died (153). There were 47 deaths (0.015%) recorded among the 310,746 cases in the 1988 Shanghai epidemic that primarily involved adolescents and young adults (147). Of the 47 deaths, 25 were due to fulminant hepatic failure and at least half of the affected individuals had underlying liver disease.

Extrahepatic Manifestations
Rarely, in patients with prolonged illness, extrahepatic disease, including optic neuritis, transverse myelitis, aplastic anemia, and thrombocytopenia, may be noted. Although these conditions are possibly manifestations of immune-complex disease, the relationship of these syndromes to the HAV infection is not established (149). Mild to moderate pancreatitis has also been reported in association with acute hepatitis A (98), but its pathogenesis is equally obscure.

LABORATORY DIAGNOSIS
The serologic detection of IgM anti-HAV is the simplest, least expensive, most sensitive, and most specific approach to laboratory diagnosis. Detection of an HAV-specific antibody of the IgM class (primarily against capsid antigen) indicates current or recent infection and is the gold standard for diagnosis of acute hepatitis A. Such an antibody is almost always present at the onset of symptoms, peaks during the acute or early convalescent phase of the disease, and remains positive for approximately 4 to 6 months (112) (Fig. 11). Many methods have been used to detect IgM anti-HAV, but enzyme-linked immunosorbent assay (ELISA) is now the most commonly used. IgM anti-HAV ELISA assays are available commercially and generally do not detect the low levels of IgM that may persist in patients more than 6 months after acute HAV infection (156).

However, persons who are unlikely to have acute viral hepatitis should not be tested for IgM anti-HAV, and the use of IgM anti-HAV as a screening tool or as part of a test panel used in the workup of nonacute liver function abnormalities should be discouraged. Testing in the absence of clinical signs or symptoms of acute HAV infection lowers the predictive value of the IgM anti-HAV test and can result in increased numbers of false-positive tests for acute HAV infection (157). A positive IgM anti-HAV does not necessarily indicate acute infection because individuals can have a prolonged presence of IgM. In one study of 140 persons reported to have a positive IgM test result in 2003, a total of
87 (62%) did not have an illness that met the case definition for hepatitis A or any other type of viral hepatitis (143). IgG anti-HAV appears at the same time as IgM antibodies to HAV but, unlike IgM anti-HAV, remains detectable for decades thereafter (Fig. 11). Commercial assays are not generally available for specific detection of IgG anti-HAV. However, multiple types of assays are available for detection of total anti-HAV antibody, which, in the absence of acute infection, is largely comprised of IgG antibody and indicative of previous or resolved HAV infection. Conversely, the absence of anti-HAV in a sample collected during the acute phase of illness or early convalescence is strong evidence against a diagnosis of HAV infection. However, if the clinical or epidemiologic situation strongly suggests HAV infection, the test should be repeated within a few days to a week to formally exclude the diagnosis.

Liver biopsy is rarely indicated to establish a diagnosis of acute hepatitis. This procedure is associated with discomfort to the patient, and carries a small but finite risk of death. Moreover, tissue morphology is usually not diagnostic.

Detection of virus or viral antigen in the stool is a useful research tool but has no place in routine clinical diagnosis. Since HAV clinical isolates usually replicate very slowly and then to very low titers in cell culture, virus isolation is insensitive, unreliable, and expensive.

Nucleic acid detection techniques are more sensitive than immunoassays for viral antigen to detect HAV in samples of different origin (e.g., clinical specimens, environmental samples, or food). Amplification of viral RNA by reverse transcription-polymerase chain reaction (RT-PCR) is currently the most sensitive and widely used method for detection of HAV RNA (44). Real-time RT-PCR is rapid, sensitive, reproducible, and potentially quantitative. Nucleic acid sequencing of PCR amplimers may confirm their specificity and provide the ultimate means of identifying and characterizing the responsible virus genotype or strain (158). Sequencing of selected genomic regions of HAV is used to determine the genetic relatedness of isolates for epidemiologic investigations (159).

RT-PCR may be used for HAV detection in environmental samples. The same characteristics that facilitate the likelihood of transmission of HAV by contaminated food and water—i.e., the stability of HAV in the environment, especially when associated with organic matter, and its resistance to low pH, drying, and heat—also improve the likelihood of detection in environmental samples. However, HAV detection in food traditionally has not been included as a part of outbreak investigations because of the lengthy incubation period of the disease and the probability that the offending foodstuff usually has been consumed or discarded by the time the outbreak is recognized (160).

PREVENTION

General

Hepatitis A is a vaccine-preventable disease. The WHO recommends hepatitis A vaccination be integrated into the childhood schedule if disease incidence and cost-effectiveness support its use (115). Before vaccines were licensed beginning in 1995, prevention of hepatitis A was primarily aided by adherence to sanitary practices such as hand washing, appropriate heating of foods, and avoidance of food and water from endemic areas. Hand washing is highly effective in preventing transmission, since the virus can survive for up to 4 hours on the hands (161). General hygienic measures are most important in limiting person-to-person spread in the home, school, or work settings. While nosocomial transmission is rare and hospitalized patients require only enteric precautions and private rooms, gloves should be worn when handling anything that is potentially contaminated (162). Chlorination and household bleach (1:100 dilution) are sufficient to inactivate the virus (see above).

The provision of clean water, availability of proper waste disposal, and general improvement in overall living conditions rapidly reduce the incidence of hepatitis A within a population. However, the epidemiologic transition that occurs as a result of these preventive measures leads to a declining hepatitis A seroprevalence that may pose a public health problem; greater numbers of older people may be susceptible to infection and symptomatic illness.

Passive Immunization

Before the licensure of effective hepatitis A vaccines, IG was the sole means of prevention of hepatitis A for people who were either likely to become infected or had recently been exposed. Passive immunization with polyclonal serum IG prior to exposure has been available since the 1940s and has been shown to decrease the incidence of HAV infection by more than 90% (163). IG is a sterile preparation of concentrated antibodies made from pooled human plasma processed by cold ethanol fractionation (164). In the United States, only plasma that has tested negative for hepatitis B surface antigen, antibody to human immunodeficiency virus, and antibody to HCV is used to produce IG. Since 1995, the U.S. Food and Drug Administration (FDA) has required that the process used to make IG include a specific viral inactivation step or that final products test negative for HCV RNA by PCR (128). Despite concern that the decline in the prevalence of anti-HAV in the population might reduce the effectiveness of IG, there is no standard for anti-HAV levels in IG preparations, and at present no evidence of reduced efficacy of IG.

IG provides protection against hepatitis A through passive transfer of antibody. When administered for pre-exposure prophylaxis, 1 dose of 0.02 ml/kg IM confers protection for no more than 3 months, and 1 dose of 0.06 ml/kg IM confers protection for 3–5 months. When administered within 2 weeks after an exposure to HAV (0.02 ml/kg IM), IG is 80%–90% effective in preventing hepatitis A (163). Efficacy is greatest when IG is administered early in the incubation period. When administered later in the incubation period, IG may only attenuate the clinical manifestations of HAV infection (163).

The level of anti-HAV detected in persons one week after the administration of a single intramuscular (IM) 5-cc dose of IG is typically in the range of 50 to 100 mIU/ml (111). By comparison, the titer of anti-HAV detected after recent infection often exceeds 15,000 mIU/ml, and following active immunization with three doses of HAV vaccine, approximately 3,500 mIU/ml. While measurable antibody following IG may disappear rapidly, protection persists for several months (165).

Serious adverse events from IG are rare. Because anaphylaxis has been reported after repeated administration to persons with immunoglobulin A deficiency, those persons should not receive IG. Pregnancy or lactation is not a contraindication to receipt of IG. A thimerosal-free preparation of IG is available and is preferable for use in infants and pregnant women (128). Less-serious reactions can also occur, including pain at the injection site.
Active Immunization

Hepatitis A Vaccines

Several types of hepatitis A vaccine have been developed and evaluated in nonhuman primate models of HAV infection and in human clinical trials. These include formalin-inactivated vaccines (9, 166), live attenuated vaccines (167), and combination HAV and hepatitis B vaccines (168). For the most part, only inactivated HAV vaccines have been evaluated for efficacy in rigorous, prospective, controlled clinical trials, and they comprise the only vaccine type approved for use in the United States (169). However, a live-attenuated HAV vaccine has been used extensively in China since 1992, reportedly with effective results (170). A live-attenuated vaccine (BioVac-A; Wockhardt; Mumbai, India) is also available in India and in other countries (Mevac-A) including Guatemala, Philippines, Bangladesh, Nepal, and Chile.

Havrix (GlaxoSmithKline, Rixensart, Belgium) was the first HAV vaccine licensed for use in the United States in 1995. It is a purified, formalin-inactivated vaccine manufactured from the HM175 virus strain propagated in a human cell line. A second formalin-inactivated vaccine, Vaqta (Merck & Co., Inc., Whitehouse Station, New Jersey), became available in the United States in 1996. It is produced with the CR326 viral strain and has equivalent immunogenicity and tolerance compared to Havrix (171). These two vaccines are indistinguishable in terms of their efficacy. Both have been demonstrated to provide high-level (95% or greater) protection against symptomatic HAV infection in prospective clinical trials of strikingly different design (10, 169). The results of the Vaqta trial even suggested that inactivated HAV vaccine can provide a high level of post-exposure protection against disease (10), a fact confirmed in a later clinical trial (172). The dosing and vaccination schedule approved by the Advisory Committee on Immunization Practices is shown in Table 1.

Twinrix (containing both HAV and HBV antigens; GlaxoSmithKline) was approved by the FDA in 2001. Twinrix is licensed for use in persons aged more than 18 years and contains 720 enzyme-linked immunosorbent assay units (EL.U.) of hepatitis A antigen (half the Havrix adult dose) and 20 mcg of recombinant hepatitis B surface antigen protein (the same as the Engerix-B [GlaxoSmithKline] adult dose). Primary immunization consists of three doses according to the same schedule as that commonly used for single-antigen hepatitis B vaccine (0, 1, and 6 months) (Table 2). After three doses of Twinrix, antibody responses to both antigens are equivalent to responses seen after the single-antigen vaccines are administered separately on standard schedules (173). Clinicians may choose to use an accelerated schedule for Twinrix (i.e., doses at days 0, 7, and 21). The FDA approved an accelerated schedule for Twinrix in 2007; persons who receive a vaccination on an accelerated schedule should also receive a booster dose at 1 year after the start of the series to promote long-term immunity (174).

Vaccine Immunity

Although inactivated hepatitis A vaccine elicits both anti-HAV antibody and virus-specific T-cell responses (175), protection is likely afforded primarily by serum-neutralizing antibodies, based on early studies with passively transferred, pooled human IG (176). Low levels of neutralizing antibody correlate with high-level protection against disease (111).

Indications for Immunization

Indications for hepatitis A immunization have evolved over time, and the current U.S. recommendation, issued by the Advisory Committee on Immunization Practices (ACIP) of the CDC in 2006, is to routinely immunize all children at 1 year of age. Globally, the WHO recommends immunization for children greater than 1 year of age in places with intermediate to low endemicity (115). These recommendations are intended to further reduce hepatitis A morbidity and mortality and make possible the consideration of eventual elimination of HAV transmission. Immunization is also recommended for persons who are at increased risk for infection and for any person wishing to obtain immunity. Children who are not vaccinated by the age of 2 years can be immunized at later ages. Catch-up vaccination programs are strongly encouraged, especially in the context of increasing incidence and outbreaks since 2011.

Persons at increased risk of infection or more severe disease who should be immunized include individuals traveling to or working in countries with high or intermediate rates of hepatitis A (see specific recommendations below in “Pre- versus Postexposure Prophylaxis”), persons with chronic liver disease (especially chronic hepatitis C) or clotting factor disorders, alcoholics, MSM, illicit drug users, individuals with close personal contact with an international adoptee from a country of high or intermediate endemicity during the first 60 days following arrival to the United States, persons working with HAV-infected primates or with HAV in a research laboratory, and individuals with recent exposure (for postexposure prophylaxis). Immunization against HAV infection is safe and effective in persons with chronic liver disease; susceptible people who are either awaiting or have received liver transplants should also be vaccinated (128).

The safety of hepatitis A vaccine during pregnancy has not been determined. However, because the vaccine is produced from inactivated HAV, the theoretical risk to the fetus is low. Nonetheless, immunization is typically not performed during pregnancy unless the risk of exposure to HAV is very high.

### TABLE 1  Recommended regimen: dose and schedule for hepatitis A vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age (yr)</th>
<th>Dose (EL.U.)</th>
<th>Volume (ml)</th>
<th>Two-dose schedule (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Havrix</td>
<td>1–18</td>
<td>720</td>
<td>0.5</td>
<td>0 (6–12)</td>
</tr>
<tr>
<td></td>
<td>&gt;18</td>
<td>1,440</td>
<td>1.0</td>
<td>0 (6–12)</td>
</tr>
<tr>
<td>Vaqta</td>
<td>1–18</td>
<td>25</td>
<td>0.5</td>
<td>0 (6–18)</td>
</tr>
<tr>
<td></td>
<td>&gt;18</td>
<td>50</td>
<td>1.0</td>
<td>0 (6–18)</td>
</tr>
</tbody>
</table>

Abbreviations: EL.U. = enzyme-linked immunosorbent assay units. Mo, months.

### TABLE 2  Licensed dosages of Twinrix

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Dose (hepatitis A/ hepatitis B)</th>
<th>Volume (ml)</th>
<th>No. doses</th>
<th>Schedule (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥18</td>
<td>720 EL.U.</td>
<td>1.0</td>
<td>3</td>
<td>0, 3, 6</td>
</tr>
</tbody>
</table>

Abbreviations: EL.U. = enzyme-linked immunosorbent assay units. Mo, months.

Adapted from reference 128.
Vaccine immunogenicity

After a primary vaccination course, most studies have shown a seroconversion rate approaching 100% in both children and adults (177). Inactivated HAV vaccine produces substantially higher titers of circulating anti-HAV antibody than administration of protective doses of IG. Since long-term persistence of antibody has been demonstrated, HAV booster vaccination is not necessary after the primary series.

Two main groups have shown a diminished response to HAV vaccine: patients with advanced liver disease and those who are immunocompromised. In one study, rates of seroconversion were lower in those with decompensated cirrhosis (66%) compared with those with compensated cirrhosis (98%) (178). Patients with low CD4 counts (< 300 cells/mm³) also experience lower seroconversion rates; persons with advanced human immunodeficiency virus (HIV) infection show seroconversion rates ranging from 52% to 94% (179). Patients who are receiving immunosuppressive medications respond well to a two-dose vaccination series but have suboptimal response to one dose (180).

Diminished vaccine response has been observed in infants with passively acquired antibody as the result of previous maternal HAV infection (128), which is why hepatitis A vaccination is deferred until the infant is 1 year old. In the majority of studies, all infants subsequently had protective levels of antibody, but the final levels were substantially lower than those of infants born to anti-HAV-negative mothers and vaccinated according to the same schedule. Despite lower antibody levels after the primary series, the majority of infants with passively acquired antibody respond to a booster dose 1 to 6 years later (128). Passively acquired antibody declines to undetectable levels in the majority of infants by 1 year of age. After that time, hepatitis A vaccine is highly immunogenic, regardless of maternal anti-HAV status.

In populations with high rates of previous HAV infection, prevaccination testing may be considered to reduce costs by not vaccinating persons who are already immune. However, prior infection does not pose any special risk for vaccination. Postvaccination testing is not indicated because of the high rate of vaccine response. Furthermore, not all testing methods approved for routine diagnostic use in the United States have the sensitivity to detect low (but protective) anti-HAV titers that may be present after vaccination.

### Side Effects and Adverse Events

An estimated 1.3 million persons in Europe and Asia were vaccinated with Havrix before its licensure in 1995 and no serious adverse events were reported (128). Since the institution of routine childhood vaccination in the United States, no serious adverse events have been reported. Among adults, the most frequently reported adverse events occurring less than 3 days after administration were soreness at the injection site (56%), headache (14%), and malaise (7%) (181). Vaccination of a person who is immune because of previous infection does not increase the risk for adverse events.

### Immunization Policies and Vaccine Coverage

Vaccination policies range from being part of a national universal immunization program for children to targeting the vaccine exclusively to high-risk groups. Immunization programs have been very successful in most cases and have reduced the incidence of infection to up to 90%. Countries that have implemented a universal immunization program for children include Argentina, Israel, Italy, Spain, and the United States (118). Targeted policies for travelers have also been effective.

Vaccine coverage in countries that have implemented universal immunization programs has varied. In Argentina, approximately 95% of children were vaccinated in 2006 (182), but in the United States, coverage has ranged from 49.7% to 57.5% between 2010 and 2014 (134). Vaccination coverage in the United States has been slowly increasing each year by approximately 2% since 2010, but there is still room for improvement. In contrast to vaccination coverage rates among children, the rate among adults in the United States is substantially lower (132). In 2013, estimated hepatitis A vaccination coverage was only 12.3% among adults aged 19 to 49 years and 5.4% among adults older than 50 years. Coverage was higher among Asians (16.1%) compared with whites (12.6%) and Hispanics (10.6%). Surprisingly, only 13.3% of adults aged more than 19 years with chronic liver disease were vaccinated.

### Pre- Versus Postexposure Prophylaxis

Postexposure Prophylaxis of Hepatitis A

Active immunization with vaccine and passive immunization with IG have equivalent efficacy when used for

### TABLE 3. Summary of recommendations for prevention of hepatitis A after exposure to hepatitis A virus (HAV) and in departing international travelers

<table>
<thead>
<tr>
<th></th>
<th>Hepatitis A vaccine</th>
<th>Immune globulin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Postexposure prophylaxis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) Healthy persons aged 12 mo to 40 yr at the age-appropriate dose</td>
<td>1) Persons aged &gt;40 yr</td>
<td></td>
</tr>
<tr>
<td>2) Healthy persons aged &gt;40 yr if IG cannot be obtained</td>
<td>2) Children aged &lt;12 mo</td>
<td></td>
</tr>
<tr>
<td><strong>International travel</strong></td>
<td>For most healthy persons, one dose of single antigen before travel</td>
<td>Persons who elect not to receive vaccine, are aged &lt;12 mo, or are allergic to a vaccine component</td>
</tr>
<tr>
<td>Older adults, immunocompromised persons, and persons with chronic liver disease or other chronic medical conditions planning to depart to an area in ≤2 weeks</td>
<td></td>
<td>should receive the initial dose of vaccine and also simultaneously can be administered IG at a separate anatomic site</td>
</tr>
</tbody>
</table>

---

*To countries with high or intermediate endemicity for hepatitis A. IG=immune globulin.*
postexposure prophylaxis (172). Among 1,090 healthy individuals (aged 2 to 40 years) randomly assigned to vaccine or IG within 14 days of exposure, symptomatic HAV infection occurred in a similar proportion of patients in both groups (4.4% versus 3.3%, respectively) (172). Following this study, U.S. guidelines were revised to allow for hepatitis A vaccine to be used after exposure to prevent infection in healthy persons aged 1 to 40 years. Such persons should receive a single dose of hepatitis A vaccine or IG (0.02 ml/kg) as soon as possible, but ideally no later than 2 weeks after exposure (172) (Table 3). Vaccine is preferred over IG in this setting due to long-term protection and ease of administration. However, in children younger than 12 months, or individuals aged more than 40 years, and in immunocompromised persons, persons with chronic liver disease, and persons for whom HAV vaccine is otherwise contraindicated, IG should be given if possible. If immunization against HAV is otherwise warranted, a dose of vaccine should be given simultaneously with IG.

Postexposure prophylaxis should be given to close personal contacts of individuals with serologically confirmed HAV who have not been vaccinated previously, both household and sexual contacts, as well as persons who have recently shared illicit drugs with someone with hepatitis A. Postexposure prophylaxis is also warranted for unvaccinated staff and attendees of child care centers or homes if one or more cases of hepatitis A is recognized in children or employees, or if cases are recognized in two or more households of center attendees. When an outbreak occurs in a day care center, prophylaxis should be considered for members of households that have diarreaped children attending the center. If a food handler is diagnosed with hepatitis A, then prophylaxis should be given to other food handlers at the same location. However, prophylaxis is not indicated when only a single hepatitis A case has been identified in a school, hospital, or office setting.

Prevention of Hepatitis A in International Travelers

In June 2007, the ACIP concluded that hepatitis A vaccine alone provides protection for healthy international travelers aged more than 40 years (Table 3). The first dose of vaccine should be given as soon as travel is considered. However, for optimal immediate protection, IG can be considered in addition to vaccine and should be given to older adults, immunocompromised persons, and individuals with chronic liver disease who are traveling to an endemic area within 2 weeks. Travelers who are allergic to a vaccine component or who are aged less than 12 months should receive a single dose of IG, which provides protection for up to 3 months (Table 3) (128).

TREATMENT

Treatment of typical hepatitis A is supportive; there are no approved antiviral agents that are effective against HAV. Avoiding hepatotoxic medications and abstaining from alcohol is recommended. Hospitalization is rarely needed but occasionally age-appropriate management of nausea and diarrhea, including intravenous hydration, is required. Bed rest has no specific benefit. In contrast to typical acute hepatitis A, in which corticosteroids should never be used, the duration and degree of symptoms associated with cholestatic hepatitis may be reduced by a short course of corticosteroids (149).

Many agents have been studied for the treatment of fulminant hepatitis (e.g., corticosteroids, prostaglandin E, IFN, and ribavirin) with inconclusive results. Liver transplantation is the only potentially successful intervention, although criteria for selecting patients for transplantation have been difficult to establish. Survival is moderately high, even for patients with coma (approximately 66%) and no single factor is predictive of a poor outcome. Overall survival is 55% to 75% among patients undergoing transplantation (153). There is no conclusive evidence that HAV is able to reinfect the transplanted liver.

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