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Review Article

Systematic Evaluation of Guidelines for the Diagnosis and Treatment of Hepatitis E Virus Infection

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Abstract

Background and Aims: The hepatitis E virus (HEV) is a zoonotic disease, and infection with HEV in humans primarily causes acute infections and can progress to chronic manifestation in immunocompromised individuals. Over the past decade, guidelines for diagnosing and treating HEV infection have been developed. This study aimed to systematically assess the quality of current guidelines for diagnosing and treating HEV infection, and we analyzed the differences in guideline quality and primary recommendations and explored possible reasons for these differences. ***Methods:*** Guidelines published between 2013 and 2022 were searched, and studies were identified using selection criteria. The study assessed the quality of the included guidelines using the Appraisal of Guidelines for Research and Evaluation tool, extracted the primary recommendations in the guidelines, determined the highest level of evidence supporting the recommendations, and reclassified the evidence using the Oxford Centre for Evidence-Based Medicine grading system. ***Results:*** Seven guidelines were included in the final analysis. The quality of the guidelines varied widely. The discrepancies may have been caused by the lack of external experts, the failure to consider influencing factors in guideline application, and the lack of consideration of the public's opinion. Analysis of the heterogeneity in primary recommendations revealed differences in algorithms for managing chronic HEV infection, the dosage of ribavirin, and a low level of evidence supporting the primary recommendations. ***Conclusions:*** Guideline quality and primary recommendations vary considerably. Refinement by guideline developers and researchers would facilitate updating and applying guidelines for diagnosing and treating HEV infection.

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Introduction

Hepatitis E virus (HEV) is a small RNA virus with an icosahedral capsid.[1] Worldwide, HEV causes 20 million cases per year, most of which remain asymptomatic; 3.3 million are symptomatic, resulting in approximately 44,000 deaths.[2] Of the eight known genotypes, genotype 1 (HEV1), HEV2, HEV3, and HEV4 are the most common in humans. HEV infection has a wide range of clinical manifestations, including acute and self-limiting hepatitis, chronic liver disease, chronic hepatitis, cirrhosis, and hepatic failure; some patients have extrahepatic manifestations.[3]

In 2012, China developed an HEV vaccine that prevents the spread of HEV. The only first-line drug for patients already infected with HEV is ribavirin (RBV). The primary indication for RBV in hepatitis E is chronic hepatitis E in immunodeficient individuals. However, due to its teratogenicity and hemoglobin-lowering side effects, RBV use is limited, making the treatment of HEV-infected patients challenging. In the past ten years, guidelines for diagnosing and treating HEV infection have been developed.[4–10] The present study analyzed the quality of current guidelines on the diagnosis and treatment of HEV infection using the Appraisal of Guidelines for Research and Evaluation (AGREE II) tool, summarized the primary recommendations of the guidelines, analyzed differences between guideline quality and primary recommendations, and explored possible reasons for these differences.

Methods

Study design

Researchers searched for guidelines on hepatitis E infection from the past ten years and identified them according to selection criteria. Seven guidelines were evaluated and analyzed using the AGREE II tool. The search followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocols.[11]

Search strategy

Guidelines for diagnosing and treating hepatitis E published

between 2013 and 2022 were identified in PubMed, Web of Science, Ovid, ScienceDirect, Embase, China Knowledge, Wanfang, Wipu data, Google, and Baidu. The International Platform for Practice Guidelines Registry (http://www.guidelines-registry.org/) was also searched for a comprehensive collection of guidelines. The search terms included "hepatitis E", "viral hepatitis", "diagnosis", "therapy", "guideline", "statement", "recommendations", and "consensus". The references of selected studies were manually searched.

Selection of guidelines

Inclusion criteria: (1) the target group of the guideline involves people infected with hepatitis E; (2) the guideline involves the diagnosis and treatment of hepatitis E infection; (3) the full text is available online or in a book; (4) the guideline consists of English and Chinese versions. If the guideline had a newer version, the latest version was used.

Exclusion criteria: (1) viral hepatitis-related guidelines without mentioning hepatitis E; (2) duplicate guidelines; (3) evaluation of guidelines; (4) short summaries of guidelines; (5) outdated versions of guidelines; (6) narrative overviews; (7) translations of guidelines. Translations of guidelines may affect the accuracy of guideline evaluations, so only the original versions were used.

Quality assessment of the guide and methodology

To assess the quality of the included guidelines, we used the latest version of the AGREE II tool, a validated guideline research and evaluation tool designed to measure and quantify guideline quality.[12] The AGREE II tool assesses guideline quality through 23 items in six domains: Domain 1 (items 1 to 3): Scope and purpose, which addresses the overall goal of the guideline, the specific clinical question covered by the guideline, and the target population. Domain 2 (items 4 through 6): Participants, involving the perspectives and choices of guideline developers, applicators, and target populations. Domain 3 (items 7 to 14): Rigor of development involving the process of searching and screening of evidence, quality assessment of the evidence cluster, methods of forming recommendations, and updating the guideline. Domain 4 (items 15 to 17): Clarity of expression, clarifying the application of recommendations, and providing appropriate recommendations for different situations. Domain 5 (items 18 to 21): Application, including possible barriers and facilitators to the application process, supporting documents and tools to facilitate the application of the guideline, and the resource implications of applying the guideline. Domain 6 (items 22 to 23): Editorial independence, ensuring that the guideline's recommendations are not influenced by sponsors and that there is no conflict of interest within the group.

Methods: Four reviewers were web-trained by professionals to become proficient in using the AGREE II tool. The four reviewers scored each area on a scale of 1 to 7: a score of 1 indicates strong disagreement, and a score of 7 indicates strong agreement. A score of 1 is given when little or no relevant information is provided. Scores of 2 to 6 are given when the statement does not fully comply with the standard or only partially considers the standard. Higher scores are given when the criteria are more fully met. A score of 7 is given when the statement fully meets all criteria. All items with scoring differences of 3 or more were discussed. Finally, one reviewer summarized all scores for each item and calculated the score for each domain using the following formula:

$$\frac{\text{Score obtained} - \text{Minimum possible score}}{\text{Maximum possible score} - \text{Minimum possible score}} \times 100\%.$$

After reviewing the 23 entries and the combined judgment of the reviewers, the evaluated guidelines were categorized into three categories based on the AGREE II scores: recommended, recommended with modifications, and not recommended. To promote consistency in using the AGREE II tool for evaluating existing guidelines and to provide a level of evidence recommendations for all included guidelines, the following methodology was used: guidelines with an overall score of >60% were recommended, guidelines with an overall score of 30–60% were recommended with modifications and those with an overall score of <30% were not recommended.

Assessment of heterogeneity of guideline clinical entries

Guidelines were scored using the Measurement of Concordance Rating Scale.[13] Critical recommendations for the diagnosis and treatment of HEV infection in the guidelines were extracted based on entries with a score of more than 60%. The highest level of evidence for these recommendations was determined by reviewing the references in the guidelines and searching relevant databases. Evidence was regraded using the Oxford Centre for Evidence-Based Medicine (OCEBM) grading system.[14]

Statistical analysis

Standardized scores for each of the six domains were calculated using statistical analyses, and the median and range for each domain were presented. To test the consistency of the scores of the four assessors, a two-way analysis of variance was used to calculate intragroup correlation coefficients (ICCs). An ICC between 0.01 and 0.20 was considered small agreement, 0.21 and 0.40 fair, 0.41 and 0.60 moderate, 0.61 and 0.80 substantial, and 0.81 and 1.00 very good. Differences where $P<0.05$ were considered statistically significant. The data were analyzed using IBM SPSS version 19.0.

Results

Inclusion guidelines

The search of electronic databases and manual search yielded 498 articles. Endnote excluded 138 duplicates based on article exclusion criteria, 341 articles were excluded by title and abstract, and 22 articles were excluded by full text. Finally, seven guidelines were included, as shown in Figure 1. The studies ranged from 2013 to 2022. Three used the GRADE grading system,[5,7,9] the grading system was a modified version of the Infectious Diseases Society of America criteria,[8] and the other did not indicate the grading system used.[4,6,10] Of these, two were from China,[4,5] one was from the United States,[6] and four were from Europe.[7–10] Six were original versions,[4,5,7–10] and one was an update of the original guideline.[6] One targeted a primary population susceptible to HEV,[4] three targeted people at high risk of HEV and infection,[5,7,8] and three targeted post-organ transplant patients.[6,9,10] One of the guidelines specifically targeted children.[10] Characteristics of the eligible guidelines are detailed in Table 1.[4–10]

Quality assessment of the guidelines

The study used the AGREE II tool to assess the quality of the included guidelines (Table 2).[4–10] Scores for scope, purpose, and clarity of expression were surprisingly consistent, with median scores of 95.8%, and ranges of 91.7–98.6% and 88.9–98.6%, respectively. Scores for the rigor of develop-

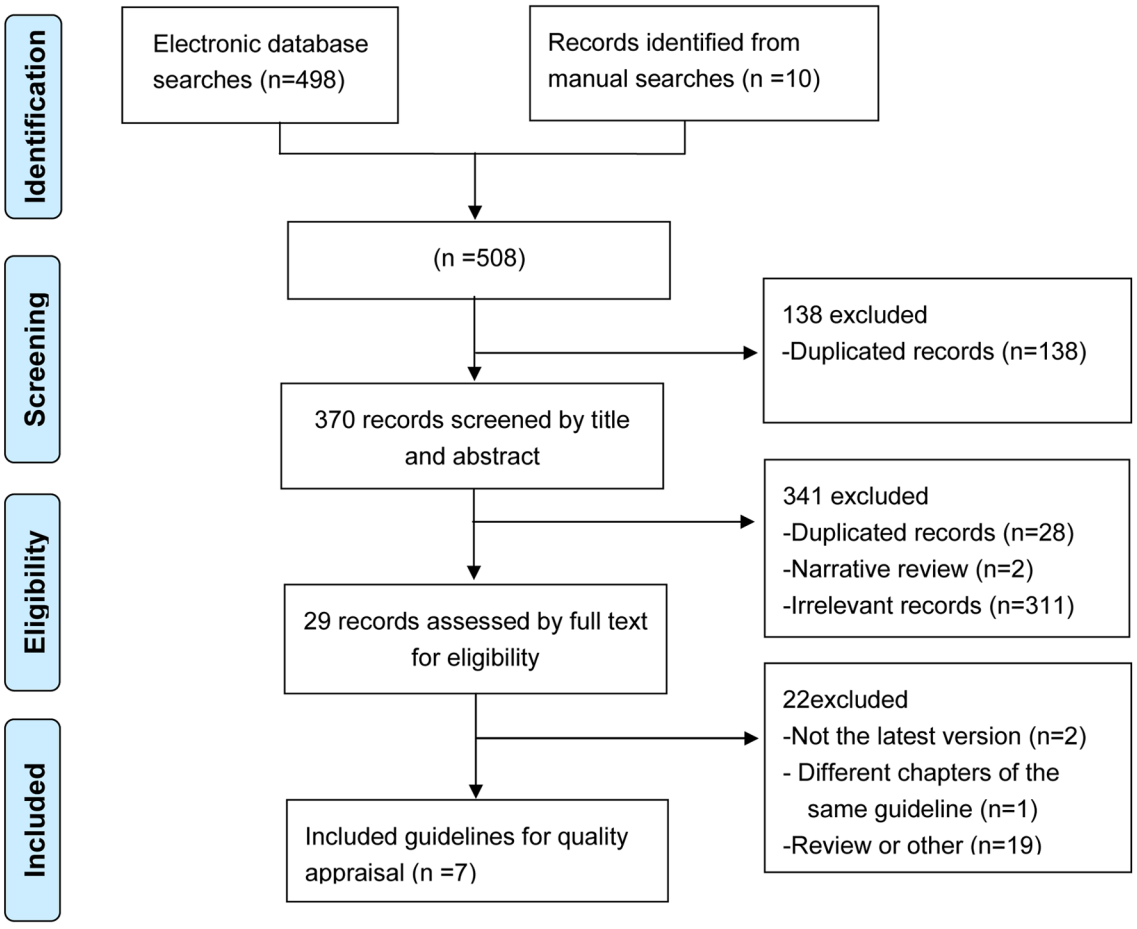

Fig. 1. Study flow diagram.

ment and editorial independence were similar, with median scores of 46.4% (26.0–63.0%) and 50.0% (45.8–97.9%), respectively. Median scores for participant involvement and applicability were 34.7% (range: 26.4–63.9%) and 27.1% (range: 22.9–47.9%), respectively. Detailed evaluation scores for each guideline are presented in Table 2.

Finally, this study provided an initial recommendation based on the scores. Two guidelines had overall evaluation scores greater than 60% and were recommended.[5,9] Five guidelines had overall evaluation scores between 30% and 60% and were recommended for improvement.[4,6–8,10] Four evaluators independently scored the guidelines according to AGREE II, and all four evaluators' ICCs for AGREE II evaluation were greater than 0.8, indicating high consistency in the scores for the same items.

Critical recommended entries and evidence for the diagnosis and treatment of HEV infection

To analyze the variability among the guidelines regarding HEV infection, the study referred to the higher scoring guidelines,[5,9] extracted the critical recommendations for the diagnosis and treatment of HEV infection from the seven included guidelines, identified ten critical recommendations, reviewed the references, and searched the relevant databases to find the highest evidence currently supporting the critical recommendations. The evidence was graded for strength of recommendation and quality of evidence according to the OCEBM grading system, and the included guidelines were compared. The study determined whether the guidelines recommended ten items, including the screening objects, diagnostic methods, and treatment of HEV infection. Detailed recommendation entries, the highest evidence supporting the recommendations, and the evidence grading are presented in Table 3.[4-10,15–24]

Discussion

Generalization of evidence

Most of the recommendations lacked high-quality evidence support. The best evidence to support the primary recommendations was mostly from retrospective case studies or case-control studies. There was a lack of high-quality prospective randomized controlled trials, indicating a need for high-quality studies to support the recommendations.

Quality evaluation of guidelines by AGREE II

The AGREE II scoring system found that the guidelines scored high in scope, purpose, and clarity of presentation. The guidelines almost always identified the health issue on which they focused, clearly stated the recommendations, provided details about the application of the recommendations, and offered different options depending on the situation.

Table 1. Basic characteristics of included guidelines

Guideline ID	Short name	Development organization	Country	Grading system	Topic	Version	Target population	Development method
LanJuan Li, *et al*., 2023[4]	LL	CCSHE, *et al*	China	None	Expert consensus on hospital screening management process of hepatitis E in China	First	susceptible and high-risk populations of HEV	EB
Hui Zhuang, *et al*., 2022[5]	HZ	Chinese Society of Hepatology	China	Grade	Consensus on prevention and treatment of hepatitis E	First	High-risk groups of hepatitis E and infected persons	EB
Helen Te, *et al*., 2019[6]	HT	The American Society of Transplantation Infectious Disease Community	American	None	Viral Hepatitis: Guidelines by the American Society of Transplantation Infectious Disease Community of Practice	updated	organ transplant candidates and recipients	EB
Harry R. Dalton, *et al*., 2018[7]	HD	EASL	European	Grade	EASL Clinical Practice Guidelines on hepatitis E virus infection	First	High-risk groups of hepatitis E and infected persons	EB
Antonio Rivero Juárez, *et al*., 2017[8]	AJ	GEHEP of SEIMC	Spanish	IDSA	Consensus document of the diagnosis, management, and prevention of infection with the hepatitis E virus: Study Group for Viral Hepatitis (GEHEP) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)	First	High-risk groups of hepatitis E and infected persons	EB
Stuart McPherson, *et al*., 2017[9]	SM	BTS	British	Grade	Guidelines for Hepatitis E & Solid Organ Transplantation	First	solid organ transplant recipients	EB
Björn Fischler, *et al*., 2016[10]	BF	ESPGHAN	European	None	Hepatitis E in children: A position paper by the ESPGHAN Hepatology Committee	First	children after solid organ transplantation	EB

GRADE, The Grading of Recommendations Assessment, Development, and Evaluation, OCEBM, The Oxford Centre for Evidence-Based Medicine, IDSA, The Infectious Diseases Society of America, CCSHE, Chinese Consortium for the Study of Hepatitis E, EASL, European Association for the Study of the Liver, GEHEP, The Study Group for Viral Hepatitis, SEIMC, The Spanish Society of Infectious Diseases and Clinical Microbiology, BTS, the British Transplantation Society, ESPGHAN, European Society of Pediatric Gastroenterology Hepatology and Nutrition, EB, evidence-based.

Nevertheless, the guidelines scored low in participant involvement, rigor, applicability, and editorial independence. The median total score for participant involvement was 34.7%. The low score may be because the guidelines did not detail the work of participants in guideline development[8]; however, almost all mentioned the names of the guideline development team members and their work units. Most of the associations that developed the guidelines did not sufficiently consider the choices of patients and the public,[4–8,10] and only the BTS guideline posted the draft on the official website and encouraged clinicians and patients to provide comments. Some guidelines did not indicate to whom they were applicable.[6–10] Guideline developers should consider the needs of patients and the public and specify to whom the guidelines apply.

Three guidelines scored over 60% in the domain of rigor,[4,5,9] while most scored low for several reasons: some did not specify the databases searched for evidence collection,[4–9] did not elaborate on the criteria for inclusion and exclusion of evidence,[4–10] did not clearly describe the evidence grading system used,[4,10] did not describe the recommendation formation process, and had no detailed description of controversial parts.[4,6,8] Some guidelines were not externally reviewed by experts before publication and did not describe whether the guidelines were updated or the periodicity of update.[4,6–10]

Table 2. AGREE II domain score and ICC of the included guidelines

Guideline	Scope and purpose	Stakeholder involvement	Rigor of development	Clarity presentation	Applicability	Editorial independence	Overall assessment
LL[4]	98.6%	62.5%	26.0%	95.8%	47.9%	45.8%	56.31%
HZ[5]	97.2%	63.9%	63.0%	98.6%	25.0%	50.0%	61.71%
HT[6]	95.8%	34.7%	33.3%	98.6%	26.0%	45.8%	49.19%
HD[7]	94.4%	31.9%	52.6%	98.6%	27.1%	77.1%	57.68%
AJ[8]	91.7%	26.4%	39.1%	95.8%	28.1%	97.9%	55.78%
SM[9]	95.8%	61.1%	46.4%	94.4%	30.2%	93.8%	62.29%
BF[10]	94.4%	34.7%	47.9%	88.9%	22.9%	45.8%	50.68%
ICC	0.917	0.989	0.986	0.940	0.994	0.984	–
Median score (range)	95.8% (91.7–98.6%)	34.7% (26.4–63.9%)	46.4% (26.0–63.0%)	95.8% (88.9–98.6%)	27.1% (22.9–47.9%)	50.0% (45.8–97.9%)	–

ICC, intragroup correlation coefficient.

The guidelines had low applicability scores, with all scoring less than 50% and a median total score of 27.1%. This may be because some guidelines did not describe the factors affecting the application of the guidelines.[4–10] These guidelines did not provide documents or tools to facilitate the application of recommendations.[5–10] Did not address the problem of resource inputs into applying the guidelines.[4–10] The guidelines were developed to provide a reference for medical workers, and developers should consider the problems in applying the guidelines with the level of medical resources at all levels of healthcare organizations and provide corresponding recommendations.

The median score for editorial independence of the included guidelines was 50.0%. All guidelines considered the influence of panelists' conflicts of interest on guideline development; however, some did not explicitly state that external sponsorship did not affect the guideline,[4–6,10] which may explain the lower score in this area. External sponsorship may interfere with the primary recommendations to some extent, and guidelines explicitly state that external sponsorship does not affect the guideline outcome to ensure the recommendations are more objective.

The primary recommendations and supporting evidence of HEV infection guideline

Screening objects

Immunocompetent patients with elevated transaminases or extrahepatic manifestations

Most guidelines state that testing for hepatitis E infection should be considered in immunocompetent patients with elevated aminotransferases or extrahepatic manifestations (e.g., neurologic symptoms, acute pancreatitis, thrombocytopenia, and unexplained hemolytic anemia).[4,5,7,8,10] A Swiss multicenter, prospective, observational study analyzed 180 patients (59 with Guillain-Barre syndrome, 51 with neuralgia myasthenia gravis, and 70 with Bell's palsy, along with corresponding matched controls [blood donors]) and found an association between acute HEV infection and neuralgia myasthenia gravis.[15] Another study reported a case of de novo membranoproliferative glomerulonephritis (MPGN) in a renal transplant patient with chronic HEV3 infection. Considering that new-onset cryoglobulinemic MPGN may be associated with HEV infection, it is recommended that screening for HEV should be performed in new-onset cases of MPGN, especially in patients with elevated liver enzyme levels.[25]

Immunocompromised patients with elevated transaminases (solid organ and stem cell transplant recipients and other patients receiving immunosuppressive drugs)

Most guidelines support repeated testing for HEV in immunocompromised patients with elevated aminotransferases, including solid organ and stem cell transplant recipients and other patients receiving immunosuppressive drugs with unexplained aminotransferases.[4,5,9,10] A study reported a case of recurrent hepatitis E infection after allogeneic stem cell transplantation in a patient with acute lymphoblastic leukemia and suggested that screening for HEV RNA in donors appears to be an appropriate tool to avoid parenteral transmission.[16]

Patients with abnormal liver enzymes after receiving blood products and blood donors

Most guidelines recommend HEV screening for patients with abnormal liver enzymes after receiving blood products and for blood donors.[4,5,7–10] HEV is mainly transmitted through the fecal-oral route; however, recent research found that HEV can also be transmitted via blood. A study retrospectively screened 225,000 blood donations collected in southeast England for HEV RNA, and 79 donors carried HEV3, leading to the conclusion that donors could be screened for HEV.[17]

Another study randomly collected 1,302 blood specimens from unpaid blood donors at the Wuhan Blood Center from January to December 2021 and found that elevated alanine aminotransferase levels in asymptomatic donors may be a nonspecific marker of acute HEV infection and transmission. Age was an independent risk factor for anti-HEV IgG positivity in the study population.[26] Since 2012, eight European countries have implemented HEV screening for blood donors[27]; however, guidelines consider that patients infected with HEV after receiving blood products constitute a tiny percentage of cases, and the cost of screening donors for HEV with nucleic acid amplification techniques is high. Routine screening of blood donors for HEV poses a greater economic burden.[7] Given that the prevalence of HEV and the economic situation vary widely in different geographic regions, an adapted HEV screening strategy that considers the local HEV infection rate and the age of blood donors may effectively reduce HEV transmission due to blood donation.

Table 3. Key recommendations and the best evidence for hepatitis E

The key recommendations	The best evidence to support the recommendations at present	Strength of recommendation	Quality of evidence	LL[4]	HZ[5]	HT[6]	HD[7]	AJ[8]	SM[9]	BF[10]
Screening objects										
1. patients with any of the extrahepatic clinical manifestations that have been associated with HEV infection	A Swiss multicenter, prospective, observational, matched case-control study[15]	B	3b	•	•	–	•	•	–	•
2.Immunocompromised patients with elevated transaminases	A case report describes the acute restrictive hepatitis E infection in a patient with acute lymphoblastic leukemia after allogeneic stem cell transplantation[16]	C	4	•	•	–	–	–	•	•
3. Patients with abnormal LFTs after receiving blood products, blood and/or organ donors	A retrospective study of 225,000 blood samples from donors screened for HEV RNA[17]	C	4	•	•	–	•	•	•	•
Diagnosis										
4. Combine serology (detection of antigens, antibodies) and RNA testing to diagnose HEV infection	A case analysis including 470 patients with acute hepatitis[18]	C	4	•	•	•	•	•	•	•
5. HEV RNA detection and HEV antigen detection are recommended for immune-suppressed patients	A case-control study including 226 liver transplant recipients, 129 non-transplanted patients with chronic liver disease, and 108 healthy controls[19]	B	3b	•	•	•	•	•	•	⊕
Therapy										
Acute hepatitis E										
6. Immunocompetent patients usually do not need antiviral therapy and mainly symptomatic supportive treatment	A case report describing the characteristics of infection in three patients with acute hepatitis[21]	C	4	•	•	–	⊕	–	–	⊕
7. RBV treatment for three months in case of severe acute hepatitis E, liver failure, or immune suppression of any cause	A multicenter case series including 21 patients with acute HEV infection[22]	C	4	•	•	–	•	•	•	⊕
Chronic HEV or persistent HEV infection										
8. Reduced immunosuppression is preferred in organ transplant patients; if this measure is not effective or not feasible, switch to RBV monotherapy for three months	A retrospective study of 85 HEV-infected solid organ transplant recipients[20]	C	4	•	•	•	•	•	•	•
9. Monitoring of HEV RNA in plasma or stool, RBV treatment for three months if positive, RBV monotherapy for six months if relapse after drug discontinuation	A European retrospective multicenter study of 255 solid organ transplant recipients[24]	C	4	–	•	•	•	•	•	•
10. If RBV is not tolerated or long-term RBV regimens do not eradicate the virus, INF-α may be considered as an alternative therapy for chronic HEV	A meta-analysis of 44 articles with 582 patients[23]	C	4	•	⊕	•	•	•	•	⊕

•Indicates being recommended definitely; ⊕indicates being mentioned; –indicates being not mentioned.

Diagnosis

Combined serology (detection of antigens, antibodies) and RNA testing to diagnose HEV infection

The guidelines universally recommend a combination of serology (detection of antigens and antibodies) and RNA testing to diagnose HEV infection. A study that evaluated the diagnostic performance of 5 anti-HEV IgM assays found that specificity was >99% while sensitivity ranged from 24% to 72%.[28] Consequently, it is challenging to use as a confirmatory diagnosis of HEV infection. In certain countries and regions, nucleic acid testing has not been widely adopted due to healthcare limitations, leading to the primary use of antibody testing for diagnosis. Guidelines suggest that in immunocompetent patients with suspected acute infection, HEV IgM and HEV IgG should be tested first. If both tests return negative results, HEV RNA should be quantified in serum.[10] A study including 470 patients with acute HEV infection found that the ORF3 assay detected 17 patients who were not identified by either the antibody test or the ORF1 test. Similarly, the ORF1 test identified seven positive individuals who were not diagnosed by either the IgM antibody or the ORF3 test.[18] Despite all guidelines recommending testing for HEV-specific antibodies, antigens, and RNA, they do not specify which assays should be utilized to maximize precision and specificity. Studies have shown that different assays vary in sensitivity for different genotypes of HEV infection.

To compare the diagnostic accuracy of serum HEV Ag and HEV RNA, a study analyzed serum samples from 202 patients with suspected acute viral hepatitis. The results showed that the sensitivity of the HEV antigen assay was 90.5%.[29] The HEV antigen detection cycle correlated with HEV RNA, leading to the conclusion that HEV Ag is a more promising serum marker for recognizing active genotype 4 HEV infection compared to anti-HEV-IgM and HEV-RNA. Urine-based antigen detection might be superior to detecting anti-HEV antibodies or viral RNA in diagnosing suspected HEV infection and monitoring persistent infection.[30] HEV Ag is specifically absorbed by renal cells and then excreted into the urine, where the Ag concentration is more than ten-fold higher, resulting in higher diagnostic sensitivity for urine Ag than for serum Ag.[31] HEV Ag, with a positive predictive value of 100% and a diagnostic accuracy of 57%, could be particularly useful in settings where HEV RNA is not available.[32]

Chinese experts found that the level of pORF2S antigen in urine can reach 80 times that in serum antigen.[31] Accordingly, the world's first urine test kit for hepatitis E was developed, improving the accessibility and diagnostic efficiency of hepatitis E. However, diagnosing hepatitis E still faces challenges. Antigen indicators can detect HEV infection early, and the cycles of antigen and nucleic acid detection overlap significantly. The emergence of antibodies interferes with antigen detection, and there is an undetected period of about one week, which affects test sensitivity.[28] Notably, HEV Ag remained detectable for >100 days after HEV RNA clearance in ribavirin-treated patients with chronic HEV.[33]

HEV RNA testing and HEV antigen testing are recommended for immunosuppressed patients

Most guidelines recommend testing for HEV RNA and HEV antigen in immunosuppressed patients rather than HEV antibody testing.[4–9] This is because antibody testing in immunosuppressed populations is considered an unreliable marker of infection. The laboratory diagnosis of acute or persistent HEV in immunosuppressed individuals must be based on testing for the virus rather than HEV antigen testing.[9] A study involving 226 liver transplant recipients, 129 patients with chronic liver disease, and 108 healthy controls, tested for antibodies to HEV as well as HEV RNA.[19] The study found that one patient became HEV RNA positive 44 days after transplantation and remained anti-HEV negative for at least four months. This suggests that the diagnosis of acute and chronic HEV infections must rely on testing for HEV RNA. However, this recommendation requires further support from high-level prospective studies. Chronic HEV infection is typically asymptomatic or presents with only mild elevation of liver transaminases. It is not easily detected by patients and has a higher likelihood of cirrhosis as the disease progresses[20]; therefore, early recognition of chronic HEV infection and intervention can improve outcomes.

Acute HEV treatment

Immunocompetent patients usually do not need antiviral therapy but mainly symptomatic supportive care

Most guidelines mention that immunocompetent patients usually do not require antiviral therapy and are primarily treated with symptomatic supportive therapy.[4,5,7,10] A case report describes three patients from Pakistan with acute hepatitis characterized by an acute, self-limiting process.[21] Several studies showed that patients with acute HEV infection activate an *in vivo* immune response that inhibits HEV replication, and studies found that HEV-infected CD56+ cell counts are significantly higher than those of patients with HAV, HBV, or HCV infection.[34]

In cases of severe acute hepatitis E, liver failure, or immunosuppression of any cause, RBV treatment for three months

Most guidelines recommend treatment of RBV for three months in cases of severe acute hepatitis E, liver failure, or immunosuppression of any cause.[4,5,7–9] However, there is a lack of high-quality randomized controlled experimental studies to support this recommendation. A multicenter retrospective study of 21 patients diagnosed with acute HEV infection (nine of whom had severe hepatitis and four were on immunosuppressive therapy) were treated with RBV at a dose of 600–800 mg/day for up to three months. All patients cleared HEV and returned to normal liver enzyme levels.[22] Acute hepatitis E treatment has no specific drug other than RBV, although a case report describes successful treatment of severe hepatitis E with steroids, most guidelines do not recommend steroids for the treatment of acute hepatitis E due to insufficient evidence of efficacy.[35]

A survey conducted in Qujing, Yunnan Province, China, among pregnant women (n = 19,762) showed an HEV seropositivity rate of 11.6%, indicating a high prevalence of HEV among Chinese pregnant women.[36] In Africa, the situation is not encouraging, with a pooled seroprevalence of 29.13% (95% confidence interval 14.63–43.63) among pregnant women.[23] Patients infected with HEV during pregnancy may rapidly progress to acute liver failure, maternal mortality, and fetal death, especially in late pregnancy.[37] The mechanism by which HEV infection in pregnant women leads to severe liver injury is unknown but may be related to elevated serum levels of oestradiol, which promotes hepatitis E virus replication.[38]

Challenges remain in the treatment of HEV infection in pregnant women. Currently, there is no established treatment for hepatitis E in pregnant women, which is symptomatic supportive care.[39] Ribavirin is not recommended for pregnant women infected with HEV due to its teratogenic risk.[40] However, in patients with acute HEV infection due to genotype 1 or 2, ribavirin treatment during the third trimes-

ter of pregnancy may be considered due to the high mortality of untreated HEV in mothers and vertically infected infants.[7] A Chinese vaccine has shown protection against hepatitis E in the general population and appears to be safe during pregnancy, although its safety and efficacy in many pregnant women remain to be determined.[37]

The initial detection of Orthohepevirus C (HEV-C) occurred in rats from Germany and Vietnam.[41] HEVs isolated from rats, the natural host of HEVs, are classified as HEV-C, while HEVs infecting humans are classified as Orthohepevirus A. RHEV and HEV-A are two highly divergent viruses, their genomes only share 50–60% genomic identity.[42] Studies considered HEV-C incapable of infecting humans due to significant differences. However, the first case of human infection by rat HEV was reported in Hong Kong, with a second case reported in Canada.[43,44] Asia is the continent with the highest incidence of infected animals, accounting for a total of 295 documented instances. China has the highest number of reported cases within the Asian region.[45] Currently, studies utilized enzyme immunoassay methods for the antigenic diagnosis of rat type r-1 HEV and type b HEV.[46] The most reliable method to determine orthohepevirus C infection is to detect viral genomic RNA by RT-PCR, including nested broad-spectrum RT-PCR.[46,47] The first case of human infection by rat HEV was detected by RT-PCR in serum, feces, saliva, and liver tissue in human infection, and feces contained the highest RNA load.[43] This discovery has significant implications for the epidemiology, clinical aspects, laboratory diagnosis, and prevention of HEV infection in humans.[41]

Treatment of chronic HEV or persistent HEV infection

Reduced immunosuppression is preferred in organ transplant patients in which it is not safe or effective, then switch to RBV monotherapy for three months

Chronic HEV infection denotes HEV replication persisting for six months.[48] All guidelines recommended reduced immunosuppression as the primary approach for organ transplant patients with chronic HEV infection. If this proves ineffective or unfeasible, switching to RBV monotherapy for three months is advised. A study revealed that among patients with chronic hepatitis, 18 (32.1%) achieved viral clearance after reducing the dose of immunosuppressive therapy, and no HEV reactivation was observed after HEV clearance.[20] However, a meta-analysis noted acute renal transplant rejection occurring in one patient 13 months after dose reduction. Therefore, the treating physician should evaluate the physical condition of organ transplant patients, weigh the advantages and disadvantages, and carefully adjust the dose.[49]

Immunocompromised individuals (including solid organ transplant recipients, hematologic patients undergoing chemotherapy, and HIV-infected patients) infected with HEV are susceptible to developing chronic hepatitis due to their inability to rely on autoimmunity for short-term virus clearance.[9] HIV infection is predominantly prevalent in southwestern China, particularly in Yunnan Province. A significant anti-HEV seroprevalence has been observed in a large HIV cohort from Yunnan Province, with age, gender, CD4 cell count, WHO stage, marital status, and total cholesterol levels identified as risk factors associated with HEV co-infection in HIV-infected individuals.[50] Chronic HEV infection in HIV-infected patients occurs predominantly in those with CD4+ T-cell counts <200/mm^3.[7] Significant rates of IgG seroreversions and IgM intercalations in this population limit the use of antibodies for diagnosing HEV infection, highlighting the importance of detecting HEV RNA in serum.[10] Antiviral therapy should be considered early in patients with nonpharmacologic causes of immunosuppression, such as HIV infection.[8] Polyethylene glycolated interferon-a (INF-α), ribavirin, or a combination of both is effective in treating HEV infection in patients with hematologic disorders and HIV infection.[5,7]

Monitoring of HEV RNA in plasma or feces, three months of RBV treatment for those who are positive, and six months of monotherapy for those who relapse after stopping RBV

Most guidelines recommend regular monitoring of HEV RNA in plasma or feces for three months of RBV treatment for those who are positive, and six months of RBV monotherapy for those who relapse after stopping the drug.[5–10] A multicenter retrospective study involving 92 adult solid organ transplant patients and four hematopoietic stem cell transplant patients with chronic HEV, treated with RBV monotherapy, showed that 96 patients received RBV monotherapy for three months, and 63.5% of the patients showed a sustained virologic response (SVR), with a range of RBV treatment between 1.8 and 2.3 mg/L.[51]

Another study of 90 pediatric renal transplant recipients found active HEV replication in the serum and feces of four (4.4%) patients, of whom three achieved a SVR after 2–3 months of treatment, with one patient relapsing but eventually achieving SVR after a second three-month treatment period.[52] Therefore, the use of RBV may be considered for both adults and children with HEV infections.

If RBV is not tolerated or a long-term RBV regimen does not eradicate the virus, INF-α may be considered as an alternative treatment for chronic HEV

Most guidelines recommend considering INF-α for patients with chronic HEV infection who cannot tolerate RBV or whose virus cannot be eradicated with a prolonged RBV regimen.[4,6–9] A meta-analysis found that 13 patients given INF-α had an SVR of 85%.[49] Another study found that 24 weeks of INF-α therapy in a 45-year-old HIV-infected patient resulted in undetectable HEV RNA from weeks 4 to 27 after treatment cessation.[53] INF-α does not achieve the same level of viral clearance as RBV. INF-α is recommended only when RBV is ineffective or unavailable, and it is not recommended as the initial treatment for chronically HEV-infected patients.

Issues to be addressed in the diagnosis and treatment of HEV infection

Some durations in the management algorithm for chronic HEV treatment vary slightly, and standardized criteria are lacking

Guidelines recommend assessing liver and kidney function, as well as anti-HEV levels at baseline, four weeks into treatment, at the end of treatment, and 12 weeks after treatment.[4] The guideline suggests testing for HEV RNA in serum at four weeks of RBV treatment; if negative, continue RBV treatment for 12 weeks; if positive, extend RBV treatment to 24 weeks.[8] It recommends detecting HEV RNA in serum on the seventh day, one month, two months, and three months after RBV treatment, along with monthly monitoring for fecal HEV RNA. If HEV RNA is not detected in plasma and feces three months after RBV treatment, discontinuation of the drug is advised. If HEV RNA is detected in plasma and feces at any of these times, RBV should be continued until six months or until two fecal tests, one month apart, are negative for HEV RNA.[9] The guideline also suggests monthly monitoring of HEV RNA during treatment and for three months after discontinuation.[10] Close monitoring of viral load in patients with chronic HEV and adjustment of

the treatment regimen according to viral clearance may reduce the likelihood of progression to cirrhosis due to prolonged disease.

Diagnosis of HEV infection is controversial, and specific nucleic acid testing sample types and methods are not specified

One study found that after three months of RBV treatment, all patients had negative plasma HEV RNA; however, at the end of treatment, five patients still excreted fecal HEV RNA, and all these patients relapsed.[54] Thus, the presence of HEV in the feces, even after clearance from the blood, suggests ongoing HEV infection. This study suggests that measuring fecal HEV RNA and evaluating blood HEV RNA during treatment can help determine the appropriate duration of treatment. The study found that ORF3 (Polymerase Chain Reaction analysis) detected viral RNA in 32 patients but not in ORF1 (Polymerase Chain Reaction analysis); ORF1 detected viral RNA in 11 patients but not in ORF3.[18] It was concluded that the parallel use of the two broad-spectrum polymerase chain reaction methods significantly improves the performance of molecular diagnosis of HEV. Considering the sensitivity and specificity of each test, in combination with the time window of detection for different samples, can effectively reduce the occurrence of missed diagnoses in HEV patients.

There is no uniformity in the optimal dose and duration of RBV therapy in patients with HEV infection

For chronic HEV infection, the guideline recommends RBV 600 mg/d monotherapy for three months[5,8]; the guideline suggests adjusting the RBV dose according to creatinine clearance estimated by the Cockcroft-Gault equation and prolonging the dosage if the effect is poor.[9] The guidelines suggest that if HEV RNA is not cleared within three months of immunosuppression reduction, RBV (15 mg/kg/d) should be considered for three months with close monitoring of anemia and renal function[10]; some guidelines do not accurately specify a recommended dose of RBV.[4,6,7] The study found that a median of three months of RBV monotherapy resulted in 63.5% of patients experiencing viral clearance and that the therapeutic range for RBV treatment of chronic HEV infection in transplant recipients ranged from 1.8 - 2.3 mg/L.[51]

The diagnostic and therapeutic options for the different genotypes of the hepatitis E virus should be clearly indicated

None of the included guidelines mention the most appropriate diagnosis and treatment for the different genotypes of HEV infection. HEV 1 and HEV 2 are restricted to humans, whereas HEV 3 and HEV 4 infect humans and many animal species. HEV 1 and 2 are predominantly found in outbreaks or epidemics in developing countries with poor sanitation and underdeveloped economies.[24,55] HEV 3 is primarily found in developed countries.[56,57] Genotype 4 is predominantly present in Asian countries such as China and Japan, it has also been identified in Europe.[58] Pigs still predominate, with subtypes 4a, 4b, 4d, and 4h being the most common.[59]

The presence of HEV Ag in acute and chronic genotype 4 hepatitis E is in good agreement with HEV RNA, making HEV Ag a more promising serum marker for recognizing active genotype 4 hepatitis E infection than anti-HEV IgM and HEV RNA.[29] A Study reports for the first time that hepatitis E virus genotype 4 causes chronic infection in a non-solid organ recipient. The individual rapidly developed liver cirrhosis induced by GT4 (subtype 4a) chronic HE and was rescued by a regimen of ribavirin treatment.[60]

Patients with hepatitis E GT4 have a higher risk of developing acute (chronic) liver failure, and pleural fluid, respiratory infections, decreased gamma-glutamyl transferase, elevated lactate dehydrogenase, and raised alpha-fetoprotein are independent predictors of acute and chronic liver failure in hepatitis E patients.[61] Presenting renal injury and lower triglyceride were independent factors associated with 28-day mortality.[61] HEV infection can lead to chronicity and rapid progression to liver fibrosis and cirrhosis in immunocompromised organ transplant recipients. A study that successfully established chronic HEV infection in immunocompromised rabbits found that vaccination completed before immunosuppression conferred full protection against both HEV3 and HEV4 infections, but vaccination during immunosuppression was only partially protective, and the efficacy did not improve with increased or additional vaccine doses.[62] The Hepatitis E vaccine may improve the prognosis of immunosuppressed patients with HEV virus infection, and more research is needed to support it. Studies are needed to clarify the epidemiological characteristics of HEV in different countries and geographic regions and to discover the most appropriate diagnostic modalities and therapeutic options for different genotypes of HEV.

Novel drugs need to be developed to treat HEV infection

RBV has adverse effects, and a study found that RBV caused a decrease in Hb regardless of the RBV dose and that the decrease in Hb was more substantial as the plasma concentration of RBV increased. RBV has teratogenic effects and is contraindicated for use in pregnant women.[51] INF-α can be used as an alternative therapy when RBV is ineffective or unavailable, but INF-α treatment causes auto rejection and is only used for the treatment of chronic HEV infection in patients with liver transplantation or HIV and is not available for most organ transplant recipients.[7] A study that screened a best-in-class drug repurposing library consisting of 262 drugs/compounds identified vidofludimus calcium and pyrazofurin as novel anti-HEV entities, and clinical studies are still needed to evaluate the effect of these two drugs for treating chronic hepatitis E.[63] At the same time, research is needed to discover novel drugs to treat HEV infection.

Recommendations for the development and updating of guidelines for HEV infection

The study provided references for developers of guidelines and related researchers on HEV infection. It emphasized considering the opinions of patients and the public in guideline development. Developers should identify the target audience for the guidelines and update the process accordingly. Researchers should employ a comprehensive search strategy to gather relevant guidelines, specifying criteria for evidence selection and evaluating evidence quality. Guideline developers should consider factors influencing guideline application and resource allocation, addressing any potential impact of external sponsorship on guideline outcomes.

Guidelines should be externally reviewed before publication. Since the quality of the evidence supporting the primary recommendations is low, researchers need to conduct high-quality prospective studies to support the recommendations. Sensitivities of different tests for different genotypes of HEV infections vary, necessitating a worldwide study to clarify the prevalence of HEV in different regions and identify the most appropriate tests for different genotypes of HEV infection.

The RBV dosage should be clearly stated in the guidelines to aid readers. Additionally, researchers need to develop new drugs for pregnant women and organ transplant patients. Some studies suggest that antigen testing is superior to nu-

cleic acid and antibody testing for diagnosing HEV infection. They also stated that nucleic acid testing can replace antibody testing entirely. However, the diagnosis of HEV infection remains controversial. Therefore, guideline developers should focus on the diagnostic methods for HEV infection, as well as on diagnosis and treatment options for special populations (e.g., HIV-infected individuals and intravenous drug users).

Strengths and limitations

This study has several strengths and limitations. Strengths include (1) Comprehensive searching of guidelines from the previous ten years using a robust search strategy; (2)Utilization of the AGREE II tool for assessing and analyzing guidelines, with two-way analysis of variance employed to calculate ICCs, thus mitigating the impact of subjective factors on scores; (3) Summarization of primary recommendations from included guidelines, followed by regrading of evidence using OCEBM to investigate heterogeneity and underlying reasons for primary recommendations. However, there are limitations to consider: (1) The limited number of guidelines meeting the selection criteria may result in primary recommendations that lack comprehensiveness; (2) The AGREE II tool, while focusing on guideline quality, does not evaluate the clinical impact of recommendations.

Conclusion

The quality of inclusion guidelines regarding the diagnosis and treatment of HEV infection varied widely. Discrepancies may have arisen due to the lack of review by external experts, insufficiently strict inclusion and exclusion criteria, and oversight of factors influencing guideline application. Several issues need to be resolved regarding the diagnosis and treatment of HEV infection. There is no uniform standard for the optimal dosage and duration of RBV treatment for HEV-infected patients. and the use of RBV and INF-a is limited due to adverse drug reactions. It is recommended that high-risk groups be vaccinated against HEV and that researchers develop new medications to treat HEV infections. The quality of evidence currently supporting the primary recommendations is low. Guideline developers and researchers are expected to address these issues gradually to enhance the application of guidelines for diagnosing and treating HEV infection.

HEV, hepatitis E virus; LFTs, liver function tests; RNA, Ribonucleic Acid; RBV, ribavirin; INF-α, interferon-alpha.

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Conflict of interest

The authors have no conflict of interest related to this publication.

Author contributions

Research direction determination (YMT); literature search (TG); literature quality evaluation (TG, CYZ, YQD, XFY); data summarization and draft writing (TG); revision (YMT, WMB). All authors contributed significantly to this study and approved the final manuscript.

Data sharing statement

The data used to support our findings are available from the corresponding author at tangyingmei_med@kmmu.edu.cn upon request.

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