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REVIEW

Gastrointestinal and Hepatic Manifestations of Ebola Virus Infection

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Abstract
Aim Although Ebola virus infection (EVI) clinically presents with common, prominent, gastroenterologic manifestations, this subject has not been previously reviewed. This work critically and comprehensively reviews this subject.
Methods This study is a comprehensive literature review generated by computerized search of literature, supplemented by review of monographs and textbooks in pathology, gastroenterology, infectious diseases, and virology.
Results Common gastrointestinal manifestations include diarrhea—70 %, nausea and vomiting—60 %, and abdominal pain—45 %. The diarrhea and nausea and vomiting frequently produce profound, life-threatening hypovolemia requiring intravenous administration of crystalloid solutions, and frequently produce electrolyte disorders requiring electrolyte supplementation. Although gastrointestinal hemorrhage was commonly reported in early epidemics, its frequency has decreased to 10 % with prevention of disseminated intravascular coagulation. Hyperamylasemia is commonly reported, but the frequency of pancreatitis is unknown. The mean serum AST and ALT levels are each about 200/UL, with an unusual pattern for viral hepatitis of AST > ALT. The serum alkaline phosphatase averages about 160 IU/L, whereas the total bilirubin averages about 0.8 mg/dL. Risks of contracting infection during endoscopy performed on infected patients are unknown, but may be significant, as indicated by hundreds of healthcare workers contracting EVI during epidemics before instituting strict infectious control measures and anecdotal evidence of one endoscopist contracting EVI from performing endoscopy on an infected patient.
Conclusions Physicians must be vigilant for gastroenterologic manifestations of EVI for appropriate diagnosis and therapy. This work should stimulate clinicopathologic studies to improve the current understanding of the gastroenterologic pathophysiology. Endoscopy is currently not standardly recommended to evaluate diarrhea, nausea and vomiting, or abdominal pain associated with EVI due to potential risks, but may be considered for endoscopic therapy for active, life-threatening, GI hemorrhage.

Keywords Ebola virus · Marburg virus · Viral infections · Gastrointestinal infections · Infectious diarrhea · Abdominal pain · Hepatitis · Pancreatitis · Gastrointestinal hemorrhage

Introduction

Gastrointestinal (GI) symptoms are among the earliest, most common, and life-threatening clinical manifestations of Ebola virus infection (EVI) [1]. Despite the current Ebola epidemic, the critical clinical significance of its GI manifestations, and the rapidly accumulating data on such manifestations, a comprehensive literature search revealed

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no review on its GI manifestations. This work aims to fill this void in the literature by critically and comprehensively reviewing recent data on GI manifestations, pathophysiology, and treatment. This review may help facilitate early diagnosis, appropriate management, and prevention of EVI, as well as stimulate research by identifying gaps in the current knowledge of its GI manifestations.

Methods

Literature review was performed by computerized PubMed and MEDLINE searches using key terms "Ebola" and ("liver" or "hepatitis" or "hepatic," or "diarrhea" or "gastrointestinal" or "colon" or "small intestine," or "amylase" or "pancreas" or "pancreatic" or "hyperamylasemia" or "lipase," or "abdominal pain" or "nausea and vomiting," or "endoscopy"); by computerized PubMed and MEDLINE searches using key terms "Ebola" and "review article" for publications during the past 5 years; and by examination of standard textbooks and specialized monographs in gastroenterology, pancreatology, virology, and pathology. Approximately 350 identified articles were screened, and all articles discussing the subject matter of this review were thoroughly reviewed. Other articles were thoroughly reviewed and incorporated into this review if deemed relevant and assigned a high priority based on timeliness, study techniques, study size, and data quality.

Epidemiology

Ebola virus was discovered in 1976 during an epidemic in Zaire (now Democratic Republic of Congo, DRC) and was named Ebola after the Ebola River, a tributary of the Zaire (or Congo) River, near where this epidemic began [2]. Between 1976 and 2013, Ebola caused 1716 cases among 24 outbreaks [3]. The current major epidemic was initially reported in March 2014, when the Ministry of Health in Guinea identified a fatal infection of unknown etiology characterized by pyrexia, vomiting, and profound diarrhea [4, 5], followed by several other cases identified in the Guéckédou and Macenta districts of Guinea [4]. Researchers believe the outbreak began in December 2013 or earlier [6]. The infection spread to the neighboring countries of Liberia in April 2014 and Sierra Leone in May 2014 [5]. An infected patient traveling from Liberia to Lagos spread this infection to Nigeria in July 2014, while an infected patient traveling from Guinea to Dakar spread this infection to Senegal in August 2014 [7]. The infection transmission rate has declined in Guinea, Liberia, and Sierra Leone, and no new cases have been recently detected in Senegal or Nigeria [5]. The infection spread internationally when four cases were diagnosed in the USA and one case was diagnosed in Spain. The World Health Organization (WHO) declared the current epidemic an "international public health emergency" in August 2014 [5]. As of January 2015, 20,747 likely cases and 8235 fatalities have been reported during the current epidemic, primarily among 6 countries including Guinea, Liberia, Sierra Leone, Mali, Senegal, and Nigeria [7]. These tallies likely represent underestimates because of exclusion of patients cared for at home. This epidemic has significantly affected the economies of these African countries [8].

A much smaller outbreak of EVI was reported in the DRC in August 2014, which likely caused 66 cases, including 49 fatalities [7]. This outbreak was believed to be caused by a woman butchering an infected wild animal at home. Genetic analysis has revealed that this DRC outbreak was caused by a different viral strain than that causing the simultaneous epidemic in West Africa [7].

Virology

Ebola is a filamentous, single-stranded, RNA (ribonucleic acid) virus. The Marburg virus is closely related virologically and presents similarly clinically, but demonstrates some epidemiological differences [9]. Both viruses together comprise the Filoviridae family, which is derived from the Latin word "filum" for their filamentous structure [10]. Three of the five known Ebola virus species (Zaire Ebola virus, Sudan Ebola virus, and Bundibugyo Ebola virus) have caused major epidemics in sub-Saharan Africa and constitute, along with a single species of Marburg virus, a major healthcare concern in sub-Saharan Africa [10]. The Zaire Ebola virus has caused most of the reported infections and deaths since 1976. One patient, an ethnologist, contracted another species of Ebola virus, Tai Forest Ebola virus, while performing a necropsy on an infected chimpanzee [11]. The fifth Ebola virus species, Reston Ebola virus, occurs in the Philippines, infecting monkeys and other primates, but not humans [12]. The current West African epidemic is from the same viral species of Zaire Ebola virus that produced the epidemic in the DRC in 1976, but the strains differ from one another, having diverged from a common ancestor [4, 13, 14].

Transmission

The natural reservoir of Ebola virus is likely fruit bats, but is possibly rodents [10, 15]. The virus has been isolated from asymptomatic infections in three species of fruit bats [15]. Primates, including humans, act as end hosts. The virus is transmitted to humans by direct contact with flesh,

blood, or bodily secretions of infected wild animals through activities like hunting, butchering, or eating their raw meat [16]. The virus subsequently spreads among humans through direct physical contact with bodily secretions, blood, or skin of infected patients [17]. Primates can also be infected in the laboratory by inoculation of droplets containing Ebola virus directly into their mouth or eyes [18]. Diarrhea, vomiting, and hemorrhage are frequent clinical manifestations of EVI and supply contagious fluids for person-to-person transmission. High viral loads, occurring during late infection, increase the transmission risk [17]. There is no clinical evidence of airborne viral transmission to humans [17], but airborne transmission has occurred in laboratory animals. The infection can be contracted by embalming or ritually washing corpses of EVI victims in preparation for funerals, as has occurred during the current epidemic. In humans, the virus efficiently replicates in monocytes, macrophages, Kupffer cells, dendritic cells, endothelial cells, hepatocytes, fibroblasts, and adrenal gland cells [19].

Clinical Manifestations

The incubation period ranges from 2 to 21 days, with a mean of 8–10 days [20]. Signs and symptoms usually progress from a non-specific viral prodrome to gastrointestinal, cutaneous, and hemorrhagic manifestations and to multiorgan failure and shock in the terminal stage, unless recovery supervenes. The viral prodrome consists of flu-like symptoms of fatigue, low-grade pyrexia, weakness, anorexia, headache, sore throat, myalgias, and arthralgias [21].

Early Clinical Manifestations

Infected patients are generally <45 years old, consistent with the generally young age distribution of the population in affected African countries [22]. Men and women are approximately equally infected [22]. Pyrexia is the most common clinical symptom/sign, occurring in 89–98 % of cases [22–24]. The onset of pyrexia may be abrupt or proceeded by low-grade pyrexia. It is a predictor of mortality, with higher mean daily temperatures correlated with mortality [22]. Weakness, fatigue, and headache are other prominent, early symptoms (Table 1) [22, 23, 25, 26]. Pulse generally rises by 10 beats/min for every 1 °F rise in temperature, for bacterial or viral infections. Pulse-temperature deficit (or dissociation) occurs when a rise in temperature is uncorrelated with a rise in pulse [27]. Pulse-temperature deficit frequently occurs in EVI, as also occurs in typhoid fever, yellow fever, dengue fever, malaria, and leptospirosis [22, 27]. The underlying mechanism for this phenomenon is unknown [28]. Patients generally present with relatively normal systolic and diastolic blood pressures, unless exhibiting severe hypovolemia [22]. Patients frequently present with mild tachypnea and have a mean oxygen saturation of about 96 % [22]. Patients sometimes exhibit facial or neck edema [22]. A non-pruritic, maculopapular rash may occur toward the end of the first week, may spread from the trunk to the entire body except for the face, and desquamate [23]. All these manifestations typically last for a week or less. After this stage, either convalescence occurs or late manifestations develop, usually leading to expiration.

As with most viral infections, leukopenia, lymphopenia, and neutropenia are common [29]. With advanced/terminal

Table 1 Common symptoms on presentation with Ebola virus infection

Symptom	Frequency (%)
A. Frequency of general/constitutional symptoms	
Pyrexia	84–98
Fatigue/weakness	65–79
Headache	57–96

Symptom	Epidemic in Zaire in 1976 [24] ($N = 228$)	Epidemic in Gabon in 1994–1997 [37] ($N = 15$)	Epidemic in DRC in 1995 [26] ($N = 219$)	Epidemic in Sierra Leone in 2014 [22] ($N = 36$)	Epidemic in Guinea in 2014 [25] ($N = 37$)
B. Frequency of gastrointestinal manifestations in Ebola virus infection among epidemics in five African countries					
Diarrhea	79 %	87 %	74 %	61 %	62 %
Vomiting	65 %	73 %	70 %	NA	7 %
Abdominal pain	NA	7 %	56 %	46 %	NA
GI hemorrhage	43–66 %	NA	NA	NA	9 %

A is based on: [22, 24–26]

DRC Democratic Republic of Congo, *GI* gastrointestinal, *N* number, *NA* not available

disease, the patient can develop leukocytosis and neutrophilia from sepsis. Patients often exhibit moderate thrombocytopenia, with platelet counts ranging from 50,000 to 100,000/ml [29]. Hypovolemia from progressive disease may cause proteinuria, renal insufficiency, and elevated serum blood urea nitrogen and creatinine levels [22]. Patients commonly present with multiple electrolyte abnormalities, especially hypokalemia, hypocalcemia, and hyponatremia, often present with mild hypoalbuminemia, and may develop metabolic acidosis [22].

Late Manifestations

Advanced disease is often heralded by disseminated intravascular coagulation (DIC), with prolonged prothrombin and partial thromboplastin times, and elevated fibrin degradation products. Bleeding usually occurs during late infection, most commonly manifesting as hematemesis, melena, or bloody stools; sometimes manifesting as cutaneous bleeding with petechiae, purpura, ecchymoses, or hematomas; occasionally manifesting as bleeding from the gums or needle puncture sites; and rarely manifesting as epistaxis or hematuria [17, 23]. These manifestations likely arise from DIC.

Severe tachypnea occurs terminally, secondary to respiratory alkalosis from primary metabolic acidosis, and represents a poor prognostic indicator [17, 23, 30]. Hiccups frequently occur with advanced disease and also indicate a poor prognosis [17, 23]. Potential etiologies for hiccups include diaphragmatic or phrenic nerve irritation from phrenic neuritis, pancreatitis, pericarditis, esophageal irritation, gastric irritation, and metabolic disorders [23, 31]. Psychoses, aggressive behavior, confusion, and anxiety can also occur [32]. The central nervous system has never been examined microscopically in EVI patients [33], but a study in non-human primates demonstrated viral meningoencephalitis by light microscopy and Ebola viral antigens by immunohistochemistry [34]. Anuria, multisystem organ failure, and shock are terminal events with expiration usually within several days thereafter [9].

Diagnosis

Physicians should have a heightened suspicion of EVI in patients with pyrexia or other consistent symptoms and signs who have recently travelled to an epidemic region, such as West or Central Africa, or were exposed to a patient with suspected infection. The differential diagnosis also includes malaria, Lassa fever, typhoid fever, meningococcal meningitis, and influenza. Potentially exposed patients should be placed under infectious disease precautions and tested for EVI by RT-PCR (reverse transcription polymerase chain reaction). This test is usually very sensitive and highly specific when performed >72 h after onset of symptoms [35]. Detecting viral proteins by ELISA (enzyme-linked immunosorbent assay) is also very accurate. IgM (immunoglobulin M) antibodies to Ebola virus are also detectable at >3 days after infection [36]. Viral isolation is useful for epidemiological or clinical research, but is generally not practical in real-time clinical situations, especially in countries with limited health resources.

In the USA, local and state health departments should be informed of patients undergoing evaluation for EVI. The United States Centers for Disease Control has promulgated recommendations for evaluation, infectious disease control, and management of patients exposed to Ebola virus [29].

GI and Hepatic Manifestations

Prominent early GI symptoms include diarrhea, abdominal pain, and nausea and vomiting (Table 1) [22, 24–26, 37]. Patients may sometimes present with sore throat and marked odynophagia or occasionally with a globus phenomenon [9, 23]. GI hemorrhage is often associated with DIC, a late manifestation of EVI.

Diarrhea

Diarrhea is the most common GI manifestation (Table 1) [22, 24–26, 37]. The diarrhea is typically watery and often voluminous, as occurred in the current outbreak in Liberia [35]. Stool output of up to 8000 ml/day has been reported [38]. Occasionally, the diarrhea can be grossly bloody, can consist of watery, black liquid from melena diluted with water, or can be a reddish-brown suspension with less than 5-mm aggregates [37]. Volume loss from GI sources, including diarrhea, nausea and vomiting, or GI bleeding, can be profound, leading to hypovolemic shock in inadequately resuscitated patients [30]. The hypovolemia is exacerbated by EVI of adrenal glands: Viral RNA is evident in adrenocortical cells, with congestion and necrosis of infected cells [39]. Loss of physiologic adrenocortical regulation of blood pressure can contribute to refractory hypotension in infected patients. Cytokines and other proinflammatory mediators may also contribute to the diarrhea and other GI symptoms [40]. The profound diarrhea can cause severe electrolyte abnormalities, including hypokalemia or hypocalcemia, and can cause acute prerenal kidney injury. For example, one infected patient in Guinea had a creatinine = 13.9 mg/dL and blood urea nitrogen = 140 mg/dL, whereas another infected patient had a creatinine = 4.9 mg/dL and blood urea nitrogen = 73 mg/dL [25]. Hypoperfusion from hypovolemia can cause

metabolic acidosis with an elevated serum lactate level [25]. These laboratory abnormalities often rapidly improve after vigorous administration of intravenous crystalloid fluids and correction of electrolyte disorders [25]. Diarrhea is correlated with mortality [22, 24].

Histopathological findings include mild, mononuclear cell infiltration in the lamina propria of gastric, small intestinal, and colonic mucosa, with viral antigens present in these cells, as demonstrated by immunohistochemistry [33]. Stool studies for fecal leukocytes, ova and parasites, stool osmolarity, or lactoferrin levels have not been reported in infected patients with diarrhea. The diarrhea is most likely related to viral infection of GI mucosa.

Hyperamylasemia

Among 112 patients with EVI in Sudan, all 55 patients with fatal outcomes had hyperamylasemia, with amylase levels ranging from 100 to 300 U/L, whereas 57 surviving infected patients and 11 uninfected hospitalized control patients almost never exhibited hyperamylasemia [41]. However, this difference occurred at 6–8 days after onset of clinical manifestations of Ebola infection and not earlier; it may therefore reflect hyperamylasemia from advanced/terminal infection. Serum lipase levels and radiologic imaging of the pancreas were not determined in this study. Pancreatitis is diagnosed as a clinical syndrome consisting of at least 2 of the following three findings: (1) typical symptoms of abdominal pain or nausea and vomiting, (2) hyperlipasemia or hyperamylasemia, and (3) radiologic imaging demonstrating pancreatic or peripancreatic inflammation and injury. During the 1976 outbreak in Zaire, one patient complained of severe epigastric pain radiating to the back, relieved by leaning forward, and profound vomiting on two consecutive days associated with hyperamylasemia [24]. Geisbert et al. [39] did not detect Ebola virus in pancreatic islet cells of infected non-human primates, but Larsen et al. [34] detected viral antigens by immunohistochemistry and demonstrated focal necrosis in the endocrine and exocrine pancreas. Future studies, correlating GI symptoms with serum lipase levels and radiographic abnormalities on pancreatic imaging, are required to determine the incidence of pancreatitis in EVI patients.

Abdominal Pain

The frequency of abdominal pain among epidemics is reported in Table 1 [22, 24–26, 37]. The etiology is likely multifactorial, including, aside from pancreatitis, potentially: First, EVI of intestinal mucosa, as detected by immunohistochemistry (see "Diarrhea" section), may cause abdominal pain [42]. Moreover, laboratory macaques with EVI develop pathologic abnormalities including congestion and hemorrhage of enteric mucosa and serosa, and congestion of adrenal glands, spleen, and liver [34, 39]. Whether these abnormalities contribute to abdominal pain is currently unknown. Second, bloody stools, a manifestation of enteroinvasive infections, might contribute to abdominal pain [23]. Third, early (<48 h) infection of abdominal lymph nodes, including mesenteric lymph nodes, can cause abdominal pain. Pathologic findings in mesenteric lymph nodes include immunopositive mononuclear cells; extravasation of erythrocytes in subcapsular, cortical, and medullary sinuses; erythrophagocytosis; and hemosiderosis with multiple foci of congestion [39]. Also intestinal hypoperfusion from septic shock may cause abdominal pain.

Nausea and Vomiting

Nausea and vomiting is common (Table 1) [22, 24–26, 37]. The etiology is unknown, but may include: First, pancreatitis, as aforementioned, can cause nausea and vomiting; second, gastric mucosal viral infection, as evidenced by mild mononuclear inflammation in gastric mucosa and viral antigens detected by immunohistochemistry [33]. Third, elevation of serum aminotransferase levels (see "Hepatic manifestations") is associated with vomiting. Fourth, abnormal gastric motor function has been found in some cases of viral gastroenteritis [43], including postinfectious gastroparesis [44], which may contribute to vomiting. For example, a patient transferred to Hamburg, Germany, for treatment of EVI during the current epidemic had a large volume of gastric residuals [38]. Fifth, intestinal pseudo-obstruction can cause vomiting. For example, abdominal ultrasonography performed on an infected patient transferred from Sierra Leone to Hamburg, Germany, revealed edema of the gastric, small intestinal, and large intestinal walls and distended bowel loops, without evident intestinal obstruction, findings consistent with pseudo-obstruction [38].

GI Hemorrhage

EVI was initially called Ebola hemorrhagic fever because hemorrhage, especially GI hemorrhage, was initially so common with infection. For example, during the 1995 epidemic in Kikwit, DRC, EVI was initially clinically misdiagnosed as bacillary dysentery because of very frequent GI hemorrhage [26]. Signs of hemorrhage, primarily from the GI tract, occurred in 52 % of 37 patients reported in the 2001 outbreak in Gabon and DRC [45]. The term Ebola hemorrhagic fever has recently been abandoned, however, because the hemorrhage, including GI hemorrhage, is less common than previously reported. For example, only about 10 % of patients in the current epidemic

experienced GI hemorrhage [29]. Moreover, GI or other hemorrhage is often a late manifestation and is associated with DIC, as demonstrated by multiple data. First, prolonged prothrombin time, prolonged partial thromboplastin time, and presence of fibrin degradation products support the diagnosis of DIC [10]. Second, D-dimer levels, a nonspecific monitor of DIC, were elevated among 123 infected patients during the Sudan Ebola virus outbreak in 2000 [41]. Third, in vitro studies have revealed overexpression of tissue factors that promote DIC in virally infected monocytes and macrophages [10, 46]. Fourth, animal models with EVI exhibit a rapid decline in protein C levels, consistent with widespread activation of the coagulation system leading to overconsumption and decreased levels of protein C during DIC [46, 47]. Fifth, elevated levels of thrombomodulin, an anticoagulant that activates protein C, are detected in infected patients with hemorrhagic manifestations or fatal outcomes [48]. GI hemorrhage or bloody diarrhea is still occasionally reported as an early presentation [25].

Other potential contributing factors to the GI hemorrhage include: first, thrombocytopenia (platelet count typically 50,000–100,000/μL) [10]; second, viral infection of hepatocytes can cause focal hepatic necrosis [49], impair hepatic synthesis of clotting factors, and therefore promote hemorrhage [10]. Hepatic failure is, however, unusual with Ebola infection, except in terminal cases. Third, electron microscopy demonstrates viral inclusions within endothelial cells, suggesting that vascular endothelial cell injury could contribute to the hemorrhage [33]. Fourth, Geisbert et al. [39] demonstrated marked congestion of duodenum and cecum in infected non-human primates, whereas Feldmann et al. [10] demonstrated a gastroduodenal lesion and hemorrhage in the ileum in an infected patient. Endoscopic findings have not been reported in EVI patients.

The hematocrit is typically only moderately decreased in patients with GI hemorrrhage. For example, the mean hematocrit was 31.2 ± 3.4 in patients with GI bleeding in the current epidemic in Guinea [25]. However, the hematocrit nadir and hematocrit decline may not fully reflect the degree of GI bleeding because of hemoconcentration from volume depletion from concomitant diarrhea or nausea and vomiting. Contrariwise, very rapid volume repletion may produce an abrupt hematocrit decline from hemodilution without GI bleeding. Ferritin, an acute-phase reactant, is elevated in patients with hemorrhagic manifestations, severe viremia, and fatal prognosis [48]. GI hemorrhage is not statistically correlated with mortality [48].

Hepatic Manifestations

Significant elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) frequently occur, with mean levels of 200–300 U/L (Table 2) [22, 37]. Values of liver function tests for other types of viral hepatitis are presented in Table 3 [52–64]. The mean AST and ALT levels are highest in hepatitis B and yellow fever, intermediate in EVI, and lowest in Dengue fever and hepatitis C. Highly elevated aminotransferase values with EVI may partly reflect severe systemic illness rather than hepatotropic injury. In EVI, the mean alkaline phosphatase value is about 160 U/L and total bilirubin is about 0.8 mg/dL (Table 2). The mean total bilirubin level is much higher

Table 2 Values of serum liver function parameters in two different Ebola virus epidemics

Serum parameter of liver function	Fatal cases: mean ± SD (median)	Nonfatal cases: mean ± SD (median)
A. In 39 fatal cases versus 17 non-fatal cases in an epidemic in Sierra Leone in 2014		
AST (normal 10–37 U/L)	793 ± 121 U/L (599 U/L)	229 ± 71 U/L (118 U/L)
ALT (normal 9–47 U/L)	257 ± 62 U/L (149 U/L)	92 ± 20 U/L (51 U/L)
Alkaline phosphatase (normal: 30–110 U/L)	265 ± 49 U/L (160 U/L)	124 ± 15 U/L (125 U/L)
Total bilirubin (normal 0.3–1.2 mg/dL)	0.91 ± .09 mg/dL (0.7 mg/dL)	0.78 ± .06 mg/dL (0.76 mg/dL)
Serum parameter of liver function		Mean ± SD
B. In 39 cases of Ebola virus infection in an epidemic in Gabon in 1994–1997		
AST (normal 10–37 U/L)		190.1 ± 65.9 U/L
ALT (normal 9–47 U/L)		261.5 ± 420.5 U/L
Alkaline phosphatase (normal 30–110 U/L)		189.5 ± 181.8 U/L
Total bilirubin (normal 0.3–1.2 mg/dL)		1.37 ± 0.68 mg/dL
Direct bilirubin (normal 0–0.3 mg/dL)		0.67 ± 0.60 mg/dL
Gamma glutamyl transferase (normal 8–39 U/L)		73.6 ± 83.7 U/L

Source: [22, 37]

AST aspartate aminotransferase, *ALT* alanine aminotransferase

Table 3 Mean serum AST and ALT levels in various acute viral hepatic infections

Viral infection	Mean AST (normal 10–37 U/L)	Mean ALT (normal 9–47 U/L)	Total bilirubin (normal 0.3–1.2 mg/dL)	Comments
Dengue fever				
Study 1 ($N = 60$)	76 U/L	37 U/L	NA	Virus preferentially attacks midzonal hepatic region. Hepatic failure rarely occurs
Study 2 ($N = 1582$)	93 U/L	86 U/L	NA	
Yellow fever	2766 U/L	660 U/L	5–10 mg/dL (direct bilirubin)	Virus preferentially attacks midzonal hepatic region. Sometimes causes fulminant hepatitis
Hepatitis B	1296 U/L	2109 U/L	9.3 mg/dL	Exhibits ballooning degeneration and necrosis of hepatocytes
Hepatitis C	73 U/L	308 U/L	5.2 mg/dL	Acute cases rarely symptomatic. Early infection shows cholestasis, while later chronic infection shows non-specific hepatic inflammation

Based on: [52–64]

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *N* number of patients

with hepatitis B, hepatitis C, and yellow fever infection than with EVI.

With EVI, the AST > ALT, an unusual pattern for most types of viral hepatitis [22]. However, one study showed similar mean AST and ALT levels in patients with EVI [37]. Hepatitis B and hepatitis C demonstrate the usual pattern of ALT > AST. An AST/ALT ratio >2 is highly suggestive of alcoholic liver disease, though a ratio >1 can rarely occur in chronic hepatitis and post-necrotic cirrhosis [50, 51]. Potential explanations for the AST > ALT with EVI include: First, the AST level may rise from injury to cells containing AST at extrahepatic sites, including kidney, erythrocytes, pancreas, and muscle [41]. Second, alcoholics develop AST > ALT from depletion of pyridoxal 5′-phosphate [65] and mitochondrial injury leading to elevation of mitochondrial aspartate [66]. Whether these mechanisms occur in EVI is unknown. For example, whether EVI produces depletion of pyridoxal 5′-phosphate or mitochondrial injury is unknown.

Persistently elevated liver function tests, particularly AST, indicate a poor prognosis, whereas normalization of liver function tests indicates convalescence and a good prognosis [22]. Among 123 patients during the Sudan Ebola virus epidemic in Uganda in 2000, AST was significantly more elevated in fatal cases (mean ≈ 900 U/L) than in non-fatal cases (mean ≈ 150 U/L). Elevated ALT levels do not correlate with a poor prognosis [41]. Alkaline phosphatase was elevated in some fatal cases (approximate level 100–300 U/L), but was not significantly higher than that in non-fatal cases or uninfected hospitalized controls. Total bilirubin was generally within normal limits in fatal cases [41]. The serum albumin level 6–8 days after the start of EVI ranged from approximately 2–3 g/dL in fatal cases and was significantly lower than that in non-fatal cases. This hypoalbuminemia could reflect hepatic injury; malnutrition from decreased oral intake, diarrhea, or nausea and vomiting; or catabolism from severe systemic disease [41]. Hepatic failure is rare [22].

Histologic hepatic abnormalities include focal-to-widespread hepatic necrosis with nuclear fragmentation, periportal mononuclear cell infiltration, and Kupffer cell hypertrophy. Ultrastructural analysis demonstrated eosinophilic viral inclusions, consisting of viral nucleocapsids, in hepatocytes and Kupffer cells. These inclusions occur more frequently with Zaire Ebola virus [33, 39, 49]. Bile duct inflammation is absent [10, 39], a histologic finding that correlates with the absence of serum bilirubin elevation and only mild alkaline phosphatase elevation during EVI. The lack of cholestasis or histologically severe inflammation distinguishes EVI from the viral hepatitides [67]. Gastrointestinal, hepatic, and pancreatic manifestations of EVI are summarized in Table 4.

Viral Persistence

The virus does not appear to cause chronic hepatitis. Among 19 convalescent patients from the 1995 outbreak in DRC followed for 3 months after hospital discharge, some developed arthralgia, myalgia, orchitis, parotitis, headache, or uveitis; but none developed signs or laboratory abnormalities suggestive of chronic liver disease [23, 68]. In a study among 220 villages in Gabon, IgG antibodies against Ebola virus were detected in 15.3 % of the population, but seropositive patients did not manifest chronic liver disease [69]. Evaluation of liver function tests and possibly liver

Table 4 Summary of gastrointestinal, hepatic, and pancreatic manifestations of Ebola virus infection

Symptom frequency	Characterization	Clinical consequences	Treatment	Suspected or hypothesized pathophysiology
Diarrhea				
Extremely common: 61–79 % frequency among epidemics	Most commonly watery and profuse	Hypovolemia, prerenal azotemia, electrolyte disturbances (e.g., hypokalemia, hypocalcemia), and nutritional depletion	Monitor volume status Treat hypovolemia with aggressive fluid resuscitation with IV crystalloid solutions Aggressively correct electrolyte disorders. Antibiotic therapy for suspected, superimposed, bacterial infections	Evidence of viral inclusions in intestinal mucosa
Nausea and vomiting				
Very common: about 65 % frequency	May contribute significantly to hypovolemia and malnutrition	Consequences similar to that for diarrhea, except that inability to eat per os may cause severe nutritional depletion with consequently attenuated defense against viral infection and poor healing after tissue injury from EVI	Diagnose cause of nausea and vomiting, especially by checking serum lipase levels and excluding mechanical GI obstruction, as clinically indicated. Treat underlying cause of nausea and vomiting if diagnosed, e.g., pancreatitis Administer nothing per os if vomiting is severe Administer oral or intravenous antiemetics, such as promethazine Treat hypovolemia with aggressive fluid resuscitation with IV crystalloid solutions Aggressively correct electrolyte disorders	Possibly multifactorial: pancreatitis, EVI of stomach, pseudo-obstruction
Abdominal pain				
Average frequency = 45 % among epidemics	Often associated with diarrhea or nausea and vomiting	Contributes to patient morbidity Clinical consequences depend upon specific etiology of abdominal pain which is often unidentified clinically	General supportive therapy, e.g., proton pump inhibitors. Avoids narcotics Workup for specific etiologies (e.g., perform abdominal CT scan) Treat specific etiology of abdominal pain if identified (e.g., acute pancreatitis)	Etiology largely unknown. EVI of intestinal mucosa? EVI of mesenteric lymph nodes? Pancreatitis? Etiology may be multifactorial
Gastrointestinal bleeding				
Very common in earlier epidemics Recently found to be less frequent	Typically causes mild bleeding, with mean nadir hemoglobin about 9 gm/dL	Now believed to be associated with DIC occurring as a late manifestation of EVI	Prevent advanced EVI with aggressive, supportive therapy Aggressive prevention and therapy of DIC	Late GI hemorrhage most likely arising primarily from DIC
Abnormal LFTs				
AST and ALT level typically about 200–300 U/L, with AST > ALT	High AST and ALT may reflect advanced infection with disseminated viral infection of liver	Highly elevated AST and ALT levels are strongly associated with mortality	Prevent advanced EVI with appropriate supportive measures Very high mortality once serum AST and ALT levels become highly elevated	Likely due to EVI of hepatocytes

Table 4 continued

Symptom frequency	Characterization	Clinical consequences	Treatment	Suspected or hypothesized pathophysiology
Hyperamylasemia				
Very common: hyperamylasemia (level 100–300 IU/L) in one large study of patients with fatal EVI [41]	Etiology unknown? Is this sometimes due to acute pancreatitis?	Unknown. Could the hyperamylasemia be associated with abdominal pain and nausea and vomiting that very frequently occurs with EVI and therefore arises from pancreatitis?	Supportive therapy to treat hypovolemia, electrolyte disorders, and malnutrition from nausea and vomiting Prevention of nausea and vomiting with antiemetics	Acute pancreatitis? Need to check lipase levels which are more specific than amylase level for pancreatitis and correlate laboratory abnormality with the presence of symptoms of abdominal pain and nausea and vomiting to diagnose pancreatitis. Also need to perform radiologic imaging of pancreas
Other				
Weight loss/nutritional deficiency	Potential laboratory manifestations: leukopenia, lymphopenia, and hypoalbuminemia	Catabolic state potentially resulting in attenuated immunologic defense against EVI and poor healing after tissue injury from EVI	Supportive therapy. Consider aggressive nutritional therapy to reverse tissue catabolism, including possibly hyperalimentation when nutritional deficiency is severe and prolonged	Fluid, protein, and electrolyte loss from vomiting and diarrhea. Decreased per oral intake because of anorexia and vomiting

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *EVI* Ebola virus infection, *IV* intravenous, *DIC* disseminated intravascular coagulation, *LFTs* liver function tests

biopsy in convalescent patients would be necessary to demonstrate chronic hepatitis or cirrhosis after acute EVI.

Transmission Prevention

EVI is highly contagious [70]. The basic reproduction number (i.e., the expected number of secondary cases produced by an infected individual) [71] is 1.50–2.53 for the current epidemic [70]. The high risk of transmission without strict infectious control measures is emphasized by the hundreds of doctors and nurses who contracted and died from EVI during the early phase of the 2014 epidemic in West Africa. Blood and other bodily fluids including feces, vomit, sweat, saliva, and urine are considered infectious. Diarrhea, vomiting, and GI hemorrhage, therefore, increase the risk of transmission. Risk of transmission from fomites or secretions from convalescent patients is low [72].

The WHO has promulgated recommendations for infection prevention and control [73]. Strict sanitary measures, like hand hygiene and personal protective equipment (PPE) for healthcare workers, are critical to control infection and prevent transmission. PPE includes gloves, impermeable gown, impermeable boots, mask, and eye protection. PPE should be worn upon entry to the isolation room, prior to patient contact. Standard precautions for all healthcare workers include hand hygiene, by rubbing the hands with dilute alcohol wipes or washing the hands with soap and running water, prior to donning gloves, after contact with potentially contaminated surfaces, items, or equipment and after removal of PPE.

Environmental cleaning and waste disposal are crucial as feces and vomitus are potentially infectious. Janitors cleaning contaminated rooms should use heavy duty, rubber gloves. Contaminated surfaces should be promptly cleaned and disinfected with standard hospital disinfectant, such as 0.5 % chlorine solution. Potentially exposed surfaces should be cleaned at least once daily with soap and water. Linen soiled with feces or vomit should be placed in leak proof bags and transported to laundry, soaked in 0.05 % chlorine for 30 min, and washed in detergent and water.

Precautions for GI Endoscopy

Diagnosis and treatment of GI manifestations are limited by the significant risk of transmission during invasive procedures as evident during multiple epidemics. For example, laparotomy performed at Kikwit General Hospital, DRC, on a laboratory technician in April 1995 for suspected abdominal perforation from typhoid revealed no perforation, but the patient developed worsening abdominal pain postoperatively. Repeat laparotomy revealed diffuse abdominal bleeding, and the patient

expired 2 days later. Several days later, surgeons and nurses participating in the surgery developed EVI as confirmed by diagnostic serology [26]. Similarly, a physician developed signs and symptoms of EVI after performing endoscopy on an infected patient during the 1996 epidemic in Gabon. The diagnosis was not serologically confirmed because the doctor left to Johannesburg for treatment, but the nurse who took care of the sick doctor also became ill and died in November 1996 [37]. The decline in nosocomial transmission after education and training about protective equipment [26] reinforces the importance of barrier protection for healthcare workers to prevent transmission, by establishing a physical barrier with patient isolation and protective equipment worn by healthcare workers [74].

The American College of Surgeons recommends a protocol for surgery performed on suspected or confirmed cases that should pertain to GI endoscopy [75]. In addition to standard precautions, operating room personnel should wear an impervious surgical gown, leg coverings with plastic film lining the entire fabric, surgical helmet or long plastic face shield, fluid-resistant surgical mask or N95 mask, double layer of gloves, and cape style impervious hoods. During endoscopic procedures, the GI tract should be deflated by aspirating air and fluid before opening ports to avoid back-spray of potentially contaminated material. Elective endoscopy should be deferred or avoided in cases of suspected or confirmed infections. Open surgery should be substituted for endoscopic surgery whenever possible. Emergency endoscopic procedures should be considered as necessary, e.g., therapeutic endoscopy for active upper GI bleeding. Endoscopy, however, is generally contraindicated in the presence of a severe coagulopathy, especially from DIC. Endoscopy guidelines remain tentative, however, because of minimal data.

Treatment

Patients with EVI should be treated in specially designated hospitals equipped with isolation rooms and employing specially trained physicians and nurses wherever possible. Supportive therapy remains the mainstay of treatment, in the absence of specific antiviral therapy and vaccines. Treatment of GI symptoms and their complications can be lifesaving. First, oral antiemetics and antidiarrheal therapy early in infection can prevent profound fluid loss, dehydration, and shock and decrease transmission through control of diarrhea and vomiting [35]. Promethazine is a commonly prescribed antiemetic [76]. Second, fluid resuscitation is critical to prevent prerenal azotemia, acute tubular necrosis, and hypovolemic shock. In the current epidemic in Liberia, hypovolemic patients who could take care of themselves were encouraged to drink oral rehydration solutions due to limited healthcare resources, but patients who were unable to take care of themselves were administered intravenous crystalloid, such as normal saline, Ringer's lactate, or half-normal saline with 5 % dextrose and potassium chloride [35, 77]. Fluid losses should ideally be strictly monitored to guide fluid replacement therapy. Serum BUN and creatinine levels and urinary sodium levels may help assess the fluid status. Central venous pressure monitoring and a Foley catheter can help guide fluid repletion. Central venous catheters permit aggressive intravenous rehydration, as documented in patients treated in the USA and Hamburg, Germany [38, 77]. Invasive blood pressure monitoring and continuous pulse oximetry may be necessary for critically ill patients. Third, correction of electrolyte abnormalities is vital, as sudden deaths, most likely from cardiac arrhythmias, have occurred [35]. Point-of-care machines can be used for instantaneous laboratory testing in countries which lack adequate central laboratory facilities because of inadequate financial resources [25]. Hypokalemia commonly occurs [38], most likely from gastrointestinal loss and inadequate intake. Aggressive replacement is critical; up to 8–10 mmol of intravenous potassium chloride has been administered [38]. Hypocalcemia also frequently occurs, and supplementation with oral or intravenous calcium is necessary [77]. Among patients infected with Sudan Ebola virus, calcium levels were significantly lower in fatal cases, with levels <5 mg/dL 6–8 days after onset [41]. Fourth, dyspepsia or epigastric pain is frequently treated with aluminum hydroxide, cimetidine, ranitidine, or omeprazole [76]. Fifth, nutritional supplementation is essential. In a resource-limited environment, nutrition is limited to intravenous fluids and electrolytes [35]. But if resources are available, parenteral nutrition or, if tolerated, enteral feeding with formula can be administered [38]. Sixth, antibiotics, such as amoxicillin, ciprofloxacin, cotrimoxazole, or cefixime, are often empirically administered for suspected gastrointestinal infections [76]. For example, a patient was administered menopenem for gram-negative septicemia secondary to peritonitis [38]. Empiric antibiotic therapy should provide adequate coverage for gram-negative pathogens, in the absence of a definitively identified pathogen. Seventh, endoscopic interventions to control GI hemorrhage have not been documented with this disease. Whole blood or packed erythrocytes are transfused as required for GI hemorrhage [77]. Platelets and fresh frozen plasma can be transfused to correct coagulopathies [46, 48]. Resolution of gastrointestinal symptoms for 3 days and a negative RNA PCR were the discharge criteria for hospitalized patients in Liberia during the 2014 epidemic [35].

Table 5 Important current unknowns about gastrointestinal, hepatic, and pancreatic manifestations of Ebola virus infection

Clinical presentation	Limitations of current literature	Consequent deficiencies in current knowledge
Diarrhea	No systematic, quantitative stool studies of stool electrolytes, stool volume, etc. No endoscopic studies of colonic findings. Minimal pathologic data	Pathophysiology of the diarrhea poorly characterized
Hyperamylasemia	One large study showed that hyperamylasemia frequently occurs in patients with fatal outcomes, but no data on important question of whether these patients clinically had pancreatitis	Incidence of pancreatitis in EVI not known. Theoretically, pancreatitis could underlie the frequent presentation of patients with EVI with abdominal pain and nausea and vomiting
Abdominal pain	Noted as a frequent symptom, but etiology rarely reported. Lack of radiologic studies to diagnose causes of abdominal pain	Pathology, pathophysiology, and etiology of abdominal pain with EVI largely unknown
Nausea and vomiting	Noted as a frequent symptom but etiology rarely reported	Pathology, pathophysiology, and etiology of nausea and vomiting with EVI largely unknown
Gastrointestinal hemorrhage	Only one reported case of endoscopy performed in a patient with EVI	Minimal data on etiology of gastrointestinal hemorrhage. Minimal endoscopic or pathologic studies. The hemorrhage may result from DIC
		Only one case reporting risks of performing endoscopy on EVI patients
Hepatic injury	Several studies of patterns of liver function tests in EVI, but minimal data on pathology and imaging findings of liver in EVI	Minimal pathologic data correlating pattern of liver function test values and liver injury. Little data on pathophysiology of liver injury in EVI (although virus known to invade hepatocytes and Kupffer cells)
Malnutrition	Malnutrition from EVI clinically appreciated but largely unstudied	Almost no data on this subject despite its clinical importance in promoting recovery from EVI

EVI Ebola virus infection

Outcome

Mortality ranges from 45 to 90 % for Zaire Ebola virus, the most virulent species [78]. Mortality is significantly higher in patients >45 years old [22, 25]. Mortality is similar for males versus females [22, 25]. In a study of 37 patients, mortality was not significantly higher in patients with coexistent chronic medical conditions including hypertension, human immunodeficiency virus infection, renal insufficiency, tuberculosis, or diabetes [25].

Study Limitations

This review is subject to limitations. First, it is limited by a lack of prospective, systematic, clinicopathological studies that create a profound void in the current understanding of the pathophysiology of GI manifestations, especially in the correlation between clinical GI presentation and pathological findings. Most published studies are retrospective and were performed in difficult circumstances in hospitals with limited financial resources and lacking sophisticated medical technology. For example, only one case has been reported of endoscopy for GI hemorrhage in the setting of EVI [37]. This severely limits knowledge about the site and etiology of bleeding GI lesions. Furthermore, there is only one single report about safety of performing endoscopy on EVI patients [37]. This deficiency limits the reliability of currently proposed clinical recommendations. Thus, recommendations regarding endoscopy in EVI patients are limited to clinical common sense and expert opinion in the absence of clinical data.

This weakness, however, also constitutes a strength. This review demonstrates major current deficiencies in clinicopathologic data on GI manifestations, as enumerated in Table 5, which should stimulate further gastroenterologic studies. Another limitation is that the authors have expertise in gastroenterology and hepatology, but are not infectious disease specialists. The authors, however, limited this weakness by focusing on GI and hepatic manifestations rather than the virology of EVI.

Future Trends

ZMapp, a combination of humanized monoclonal antibodies against the Ebola virus surface glycoprotein, successfully reversed advanced infection in 100 % of infected rhesus macaques in one experimental study [79]. Of seven patients who received this drug emergently during the current epidemic, five survived and two died [77]. The US government has contracted with Mapp Biopharmaceutical,

a Californian pharmaceutical company, to accelerate its development [80]. The company will produce a limited quantity of this drug for clinical trials, to assess efficacy and safety. Blood transfusions from convalescent donors who survived EVI have been administered in past and current epidemics [77, 81], but their efficacy is currently undetermined, pending an ongoing clinical trial. Seven of 8 patients transfused with convalescent sera in 1995 survived, but this promising result was confounded by better quality of care administered to these patients [81]. Recombinant human activated protein C and postexposure prophylaxis with recombinant nematode anticoagulant protein C2 have improved survival in non-human primates [82, 83]. Ribavirin has shown no efficacy for Ebola and Marburg virus, even though it was beneficial in Crimean Congo hemorrhagic fever [84]. TKM-Ebola, an antiviral compound that binds and blocks short sequences of Ebola viral messenger RNA, was found to be effective in laboratory mice and primates experimentally infected with Ebola, but was placed on partial hold during a phase I clinical trial by the United States Food and Drug Administration (FDA) in 2014 because of concerns regarding side effects of flu-like symptoms and hypotension [38]. Doctors without Borders, a humanitarian physician organization, has initiated open, uncontrolled, clinical trials of two drugs in collaboration with pharmaceutical companies, including favipiravir, a nucleoside analogue that inhibits replication of numerous RNA viruses including influenza virus and prevents death in laboratory mice experimentally infected with Zaire Ebola virus [85], and brincidofovir, an acyclic nucleotide analogue with efficacy against Ebola virus in vitro and against DNA viral infections [26, 86].

There is no effective vaccine presently available for humans. A vesicular stomatitis virus-based vaccine expressing Ebola viral glycoprotein has shown efficacy in animal studies [87, 88], but has been inadequately tested in humans.

Conflict of interest This paper does not discuss any confidential pharmaceutical data reviewed by Dr. Cappell as a consultant for the United States Food and Drug Administration (FDA) Advisory Committee on Gastrointestinal Drugs.

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