

[ CASE REPORT ]

## A Superinfection of *Salmonella typhi* and Hepatitis E Virus Causes Biphasic Acute Hepatitis

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### Abstract:

A 47-year-old Japanese man was referred to our hospital because of a sustained high fever with diarrhea 12 days after a flight from India. Liver enzymes were elevated with rose spots, hepatosplenomegaly, relative bradycardia, and acute cholecystitis. A liver biopsy depicted the dense infiltration of lymphocytes and Kupffer cells in sinusoids and the granulomatous formation in the parenchyma. The liver damage was initially resolved with the administration of ceftriaxone for 16 days but flared up 1 week later. Laboratory tests yielded positive reactions for *Salmonella typhi* and hepatitis E virus RNA. The pathophysiological presentations of concurrent typhoid and type E hepatitis are discussed.

**Key words:** typhoid hepatitis, hepatitis E, coinfection, ALT/LDH ratio, acute cholecystitis

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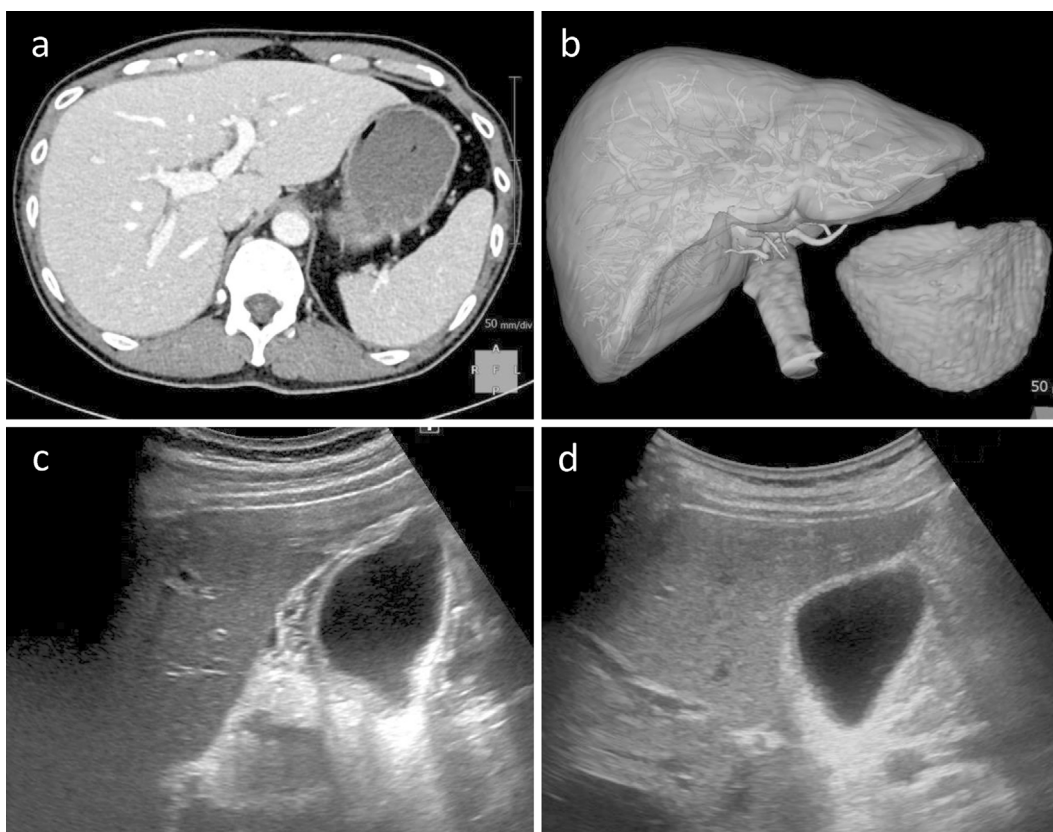
### Introduction

Typhoid fever is an acute generalized infection caused by the bacterium *Salmonella enterica* serovar Typhi (*S. typhi*). The global estimates of the disease burden are approximately 20 million typhoid fever cases and 200,000 deaths annually (1). In the last two decades, a high incidence of typhoid fever has been detected in South and Southeast Asia (2). Humans are the only known reservoir of infection of *S. typhi*, and transmission is by the feco-oral route through the consumption of contaminated water or food. Gallbladder infection during the acute illness persists, resulting in a chronic carrier state (3). The incubation period of typhoid fever can range from 1 to 2 weeks (4), and untreated illness often lasts several weeks and occasionally months. The most common life-threatening complications are intestinal hemorrhaging, intestinal perforation, and encephalopathy with hemodynamic shock (5). Other less common complications include typhoid hepatitis, empyema, osteomyelitis, and psychosis. Hepatomegaly and a moderate elevation of transaminase levels are common findings, being

observed in 21-60% of cases of typhoid fever (6, 7). However, severe hepatic derangement simulating acute viral hepatitis is very rare.

Hepatitis E virus (HEV) is a leading cause of acute viral hepatitis in developing countries, where fecal contamination of drinking water is a major route of transmission; in contrast, zoonotic transmission, mainly through the consumption of uncooked or undercooked meat, is a major route in industrialized countries with a much lower disease burden (8). A global study estimated that HEV accounts for approximately 20.1 million infections, 3.4 million symptomatic cases, 70,000 deaths, and 3,000 stillbirths annually (9, 10). HEV is an RNA virus belonging to the Hepeviridae family, and the majority of viruses with human tropism are classified into four genotypes/a single serotype that is sensitive to heat, chlorination and ultraviolet light (11). It was reported that acute hepatitis E in India is caused exclusively by genotype 1 (12), whereas genotype 2 is dominant in Central America, Mexico, and Africa, and genotypes 3 and/or 4 have been isolated from domestic infections in Japan (13). The incubation period ranges from 2 to 8 weeks, with a mean of 40 days (14). It is known that certain populations are at greater

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**Figure 1.** Image findings on the 1st and 2nd admissions. **a:** Computed tomography using contrast medium (CT) revealed hepatosplenomegaly. **b:** Three-dimensional liver and spleen images were reconstructed based on voxel data obtained by the aforementioned CT study (a) with the aid of the Synapse Vincent software program (FUJIFILM, Tokyo, Japan). The liver and spleen volumes were calculated to be 2,095 mL and 269 mL, respectively, without major vessels of the portal and hepatic veins. **c, d:** Ultrasonography on the 1st admission (c) revealed distinct thickening of the gallbladder wall, which was completely resolved by the 2nd admission (d).

risk of severe disease due to HEV infection. During pregnancy, HEV is transmitted from the mother to the fetus, which results in a poor fetal outcome (15). Transfusion transmission of HEV occurs and is well documented; however, its contribution to the overall disease burden is limited (16).

Although the area of spread and route are common characteristics shared by typhoid fever and HEV infection, clinico-pathological evaluations have rarely been reported for the superinfection of typhoid hepatitis and acute hepatitis E. We herein report the characteristic features of such superinfection in a Japanese man who traveled to India. Clues for diagnosing this superinfection are discussed.

### Case Report

A 47-year-old Japanese man was referred to our hospital with a high fever lasting for the past month and diarrhea. He had left Japan for an 18-day business trip to India 1 month earlier and suffered from a sustained fever and watery diarrhea 10 to 20 times a day since the second day after his arrival at India. He noticed dark urine and nonpruritic, erythematous papules 14 and 24 days after his initial symp-

toms, respectively. Although he took diosmectite and several local remedies during the stay and levofloxacin after returning to Japan for four days each, these medications did not work. His medical history was unremarkable. He did not regularly commit to drinking alcohol or taking any medicine, even over-the-counter agents.

On day 30 from his initial symptoms, his body temperature was 38 to over 39°C, and his pulse rate was 70 to 80 beats per minute. His conjunctiva did not show a change in color suggesting anemia or jaundice. No lymph nodes were palpable from the surface of his body, but 1-4-mm round, nonpruritic, erythematous papules were seen on his chest, abdomen, and the ends of his elbows. Because of severe tenderness at the right hypochondrium, the liver was not palpable, but the spleen was readily palpable. There were no signs of peripheral edema.

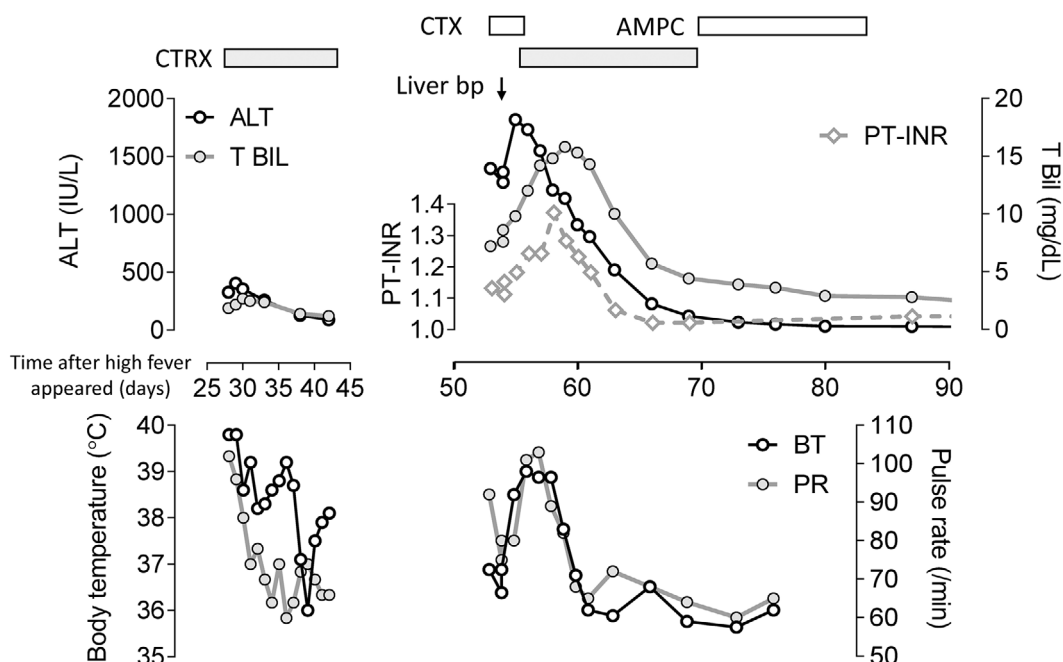
Computed tomography using contrast medium revealed hepatosplenomegaly (Fig. 1a) with 2,095 mL and 269 mL liver and spleen volumes (Fig. 1b), respectively, without perfusion disturbance of the liver. Murphy's sign was positive, and abdominal ultrasonography revealed marked edematous thickening of the gallbladder wall (Fig. 1c).

The results of his regular laboratory panel on admission

**Table. Laboratory Findings on Admission.**

WBC	55 ×10 <sup>2</sup> /mL	Na	127 mEq/L	ANA	40>
neut	85.1 %	K	3.9 mEq/L	AMA	20>
lymph	11.6 %	CL	94 mEq/L	HBsAg	0.3 COI
mono	3.1 %			anti-HCV	0.1 COI
eos	0 %	TP	5.7 g/dL	HA-IgM	0.08
baso	0.2 %	ALB	3.1 g/dL	EBV-IgG	40
RBC	446 ×10 <sup>4</sup> /mL	AST	480 IU/L	EBV-IgM	10>
Hb	12.5 g/dL	ALT	326 IU/L	EBV-EBNA	80
Ht	36.4 %	ALP	1,225 IU/L	CMV-IgG	0.2
Plt	13.7 ×10 <sup>4</sup> /mL	LDH	736 IU/L	CMV-IgM	0.39
		GTP	231 IU/L	HIV1/2	0.4 COI
BUN	11.9 mg/dL	T-BIL	1.9 mg/dL	HEV-IgA	(-)
Crt	0.9 mg/dL	D-BIL	1.3 mg/dL	HEV-RNA	3.5 LC/mL
ESR1	26 mm	PT-INR	1.09	<i>S Typhi</i>	(+) O9

Crt: creatinine, ESR1: erythrocyte sedimentation rate at 1 hour, COI: cutoff index, HIV1/2: antigen and antibody of human immunodeficiency virus genotype 1 and 2 measured by chemiluminescent immunoassay, *S. typhi*: *Salmonella enterica* serovar Typhi, O9: serotype of *S. typhi*

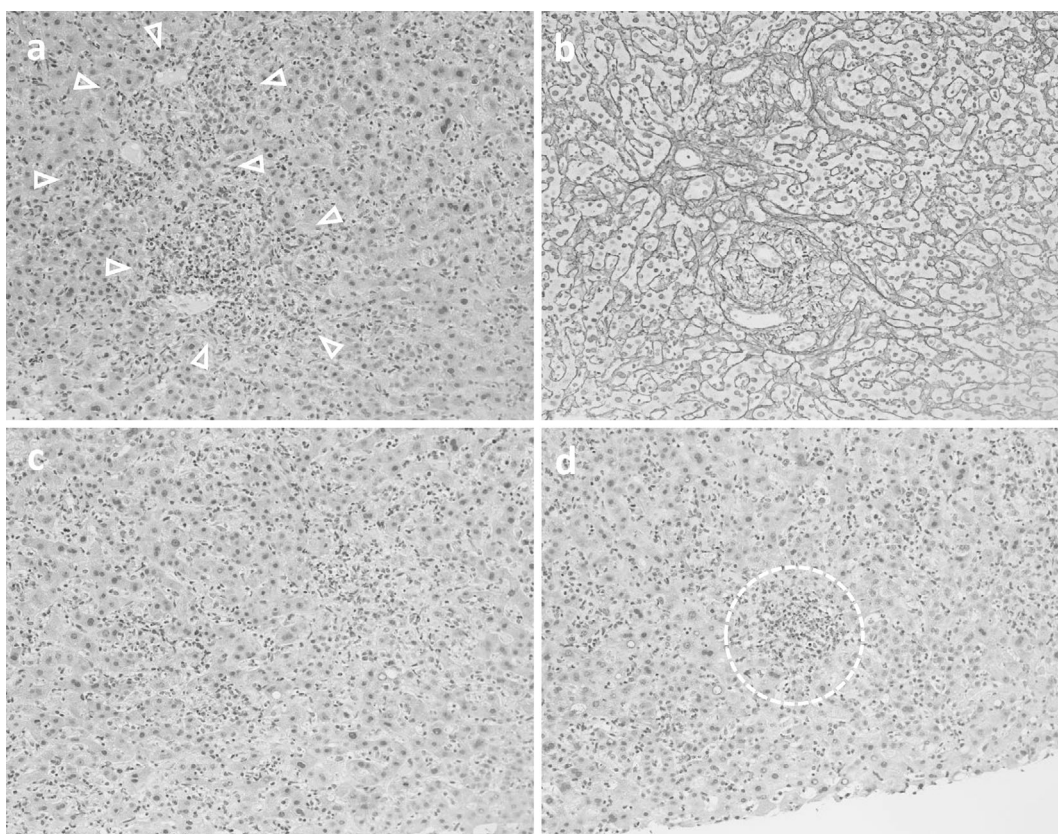


**Figure 2.** The clinical course. ALT: alanine aminotransferase, T Bil: total bilirubin, PT-INR: prothrombin time-international normalized ratio, BT: body temperature, PR: pulse rate, CTRX: ceftriaxone, CTX: cefotaxime, AMPC: amoxicillin, bp: biopsy

are summarized in Table. Abnormal findings included a mild increase in neutrophils (85.1% out of 5,500/mL leukocytes), hyponatremia (127 mEq/L), hypoalbuminemia (3.1 g/dL), increases in hepatobiliary enzymes (alanine aminotransferase (ALT, 326 IU/L); alkaline phosphatase (ALP, 1,225 IU/L) and lactate dehydrogenase (LDH, 736 IU/L), faint jaundice (1.9 mg/dL total bilirubin (T Bil) with 1.3 mg/dL direct bilirubin), and mild elongation of prothrombin time (1.09 of PT-INR). Regarding liver cell damage, there were no positive reactions suggesting naïve infection of common hepatotropic pathogens such as hepatitis A virus, hepatitis B virus, hepatitis C virus, Epstein-Barr virus, or cytomegalovirus. In

terms of autoimmune reactions, anti-nuclear antibody or anti-mitochondrial antibody was negative.

The administration of 1 g of ceftriaxone (CTRX) every 24 h was initiated soon after admission; however, the ALT and T Bil levels increased to 404 IU/L and 2.7 mg/dL on the 29th and 30th days, respectively, with a body temperature of over 39°C (Fig. 2). After the dose of CTRX was doubled on the third day of admission when *S. typhi* sensitive to CTRX was detected in blood and stool cultures, liver cell damage and diarrhea gradually improved over 2 weeks to 88 IU/L for ALT. ALP peaked at 1,850 IU/L 10 days after admission. Because his symptoms were clearly improved except



**Figure 3.** Microscopic observations of the liver on the 2nd admission. A liver biopsy specimen was obtained from segment 8. Hematoxylin and Eosin staining (a, c, d) and silver staining (b) of the adjacent section to (a). The open triangles (a) and dotted circle (d) reveal the portal area and granuloma-like collections, respectively. Original magnification  $\times 200$ .

for a fever of up to  $38^{\circ}\text{C}$ , his admission was terminated on the 16th day. Although IgA-type anti-HEV antibody was negative, a positive reaction for both genotypes 1 and 2 of HEV-RNA in his blood sample on admission was reported after discharge.

In the following days, jaundice gradually manifested together with a low-grade fever and nausea. Although the diarrhea and skin lesions disappeared, the patient was hospitalized again on the 53rd day since his initial symptoms appeared due to marked elevations of ALT (1,394 IU/L), ALP (1,940 IU/L), and T Bil (7.2 g/dL) and elongation of PT-INR (1.13). The elevation of LDH was limited to 577 IU/L. At his second admission, his body temperature was  $37.2^{\circ}\text{C}$ , and his pulse rate was 92 beats per minute. Abdominal ultrasonography showed no obvious thickening of the gallbladder wall (Fig. 1d).

To avoid additional load on the liver metabolism, the administration of cefotaxime was initiated with a dose of 1 g every 12 hours after the second admission. Liver biopsy specimens obtained under ultrasound guidance 54 days after his initial symptoms showed mild infiltration of small, round-shaped cells at the portal area without fibrous elongation (Fig. 3a, b). There was marked hyperplasia of mononuclear phagocytes and lymphocytoid cells in the sinusoids (Fig. 3c) with granuloma-like collections of mononuclear cells (Fig. 3d). Because ALT was elevated to 1,817 IU/L

with the further deterioration of the functional liver reserve (T Bil, 12 mg/dL; PT-INR, 1.18) on day 55, cefotaxime was replaced by CTRX at the dose that had been effective at the first admission on day 56, when the body temperature was  $39.2^{\circ}\text{C}$  and the pulse rate was 101 beats per minute with 1,731 IU/L ALT. Although PT-INR and T Bil peaked at 1.37 and 15.8 mg/dL later on days 58 and 59, respectively, the ALT level continuously decreased, and CTRX was stopped on day 69, followed by the initiation of the oral administration of 500 mg of amoxicillin 4 times a day.

On day 78, the patient was discharged with a T Bil of 3.6 mg/dL, PT-INR of 1.02, and ALT of 44 IU/L. In the outpatient clinic, his liver enzymes and hepatic reserve normalized, and a negative reaction for *S. typhi* in stool was confirmed 3 times. On day 166, laparoscopic cholecystectomy was completed to avoid the risk of carrying *S. typhi* latently and developing biliary malignancy in the future.

## Discussion

Due to globalization and modern modes of transportation of both people and goods, distance and time that serve as natural defenses against infectious diseases offer progressively less protection. Because the pandemic area and infectious route of contaminated water are shared, typhoid fever and hepatitis E have a higher risk of coinfection, especially

for people who travel from nonendemic areas. We herein report a case of biphasic liver damage due to typhoid and type E hepatitis.

The liver biopsy specimen obtained on the second admission revealed histological findings characteristic of both typhoid hepatitis and viral hepatitis (17). It is uncommon in cases of viral hepatitis for jaundice to peak with a high fever. Therefore, both pathogens might have played on systemic and liver involvement with different specificities at different time points in his clinical course. However, we may reasonably assume that the liver damage observed at the first admission had mainly been caused by *S. typhi*, rather than HEV, which is considered to have been the main causative agent for the severe form of liver damage leading to the second admission. At the first admission, in addition to a sustained fever and diarrhea, several typical manifestations of typhoid fever were observed, including hepatosplenomegaly, rose spot, relative bradycardia, and acute cholecystitis. The ALT/LDH ratio [(ALT value/upper normal range of ALT)/(LDH value/upper normal range of LDH)], which was reported to be less than 4 in cases of typhoid hepatitis (17), was 2.3. On the other hand, at the second admission, rose spots, relative bradycardia, and acute cholecystitis were not observed, and the ALT/LDH ratio was 12.8. Furthermore, the HEV detected in his sera was a mixture of genotypes 1 and 2, suggesting that he had contracted the infection in India, where a non-domestic genotype 2 has been more frequently observed due to increasing globalization. Because the nested reverse transcription-polymerase chain reaction assay amplifies common sequences for all four genotypes and because only one serotype has been identified for all four genotypes, the negative reaction of anti-HEV IgA antibodies may not have been due to phylogenetic differences. The incubation time suggests that the period in which his sera were evaluated may have fallen within the window-phase for the detection of anti-HEV antibodies. In addition, HEV-RNA has been reported to be undetectable for 7 to 40 days, with an average period of 21.4 days after the onset (18). The presence of a phase showing positivity and negativity for HEV-RNA and anti-HEV antibodies, respectively, further supports the notion that *S. typhi* and HEV were the main causative agent for the initial and subsequent hepatitis, respectively.

In terms of the diagnosis and treatment of typhoid fever and acute hepatitis E, laboratory confirmation of typhoid fever by blood culture has a limited sensitivity of approximately 50% (2). CTRX has been widely used and was effective in our case; however, since 2010 there have been increasing reports of extended spectrum cephalosporin-resistant strains of *S. typhi* in Asia and Africa requiring oral azithromycin and intravenous meropenem (19). Because chronic biliary carriers of *S. typhi* have an elevated risk of hepatobiliary cancers (20), cholecystectomy was conducted in our case once his general condition was fully recovered. It was reported that Vi-tetanus toxoid conjugate vaccines can induce effective immunity for *S. typhi* in more than 80% of

immunologically naive adult volunteers (21-23). Typhoid vaccination may be offered to travelers to destinations where the risk of typhoid fever is high.

Although recent HEV infection can be diagnosed by detecting immunological reactions against HEV, there is currently no consensus across laboratories because the sensitivity and specificity vary widely (24, 25). Therefore, detection of HEV-RNA by reverse transcription polymerase chain reaction is favorable, particularly for the immunocompromised. Generally, hepatitis E is an acute illness; however, chronic illness has been reported in solid organ transplant recipients receiving immunosuppressive medication and has been successfully treated by the withdrawal or reduction of the immunosuppressive drugs and the administration of ribavirin and/or interferon (26). Immunization with hepatitis E vaccine reportedly induced antibodies against HEV and provided protection against hepatitis E for up to 4.5 years (27). The vaccine was licensed in China in December 2011.

Hepatic involvement in typhoid fever was initially reported by William Osler in 1899 and is common in the mild form (28). The average ALT and T Bil values at the peak in 27 cases with typhoid hepatitis were reported to be  $296 \pm 38$  IU/L and  $2.9 \pm 0.6$  mg/dL, respectively (17), values that are similar to those at the first admission in our present case. In contrast, certain populations are known to be at a greater risk than others of severe diseases due to HEV infection. These include persons with preexisting liver diseases (29). The severe liver damage observed at the second admission of our case is consistent with this assumption, as the patient was already suffering from typhoid hepatitis.

The mechanism underlying viral-bacterial synergistic interactions has been most intensively explored in cases of influenza virus and pneumococcus coinfection. The acquired immune responses to these viruses and bacteria are quite different, but there is considerable overlap in the innate immune responses to the two pathogens. In the common process, pro- and anti-inflammatory reactions are balanced under a single infection; however, a synergistic infection may sabotage the successful elimination of the pathogens and amplify the inflammatory damage (30). Furthermore, it was reported that bacterium-derived proteases have the potential to cleave the nascent glycoproteins requiring virus replication and increase the viral load (31).

Although hepatitis E viruses share a common mode of transmission and endemic area with *S. typhi*, unfortunately, HEV infection is not routinely evaluated in cases of typhoid fever. It may be best to screen for HEV in all cases of typhoid fever, especially among travelers from nonendemic areas. This coinfection will lead to a biphasic clinical course and severe form of acute hepatitis.

**The authors state that they have no Conflict of Interest (COI).**

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