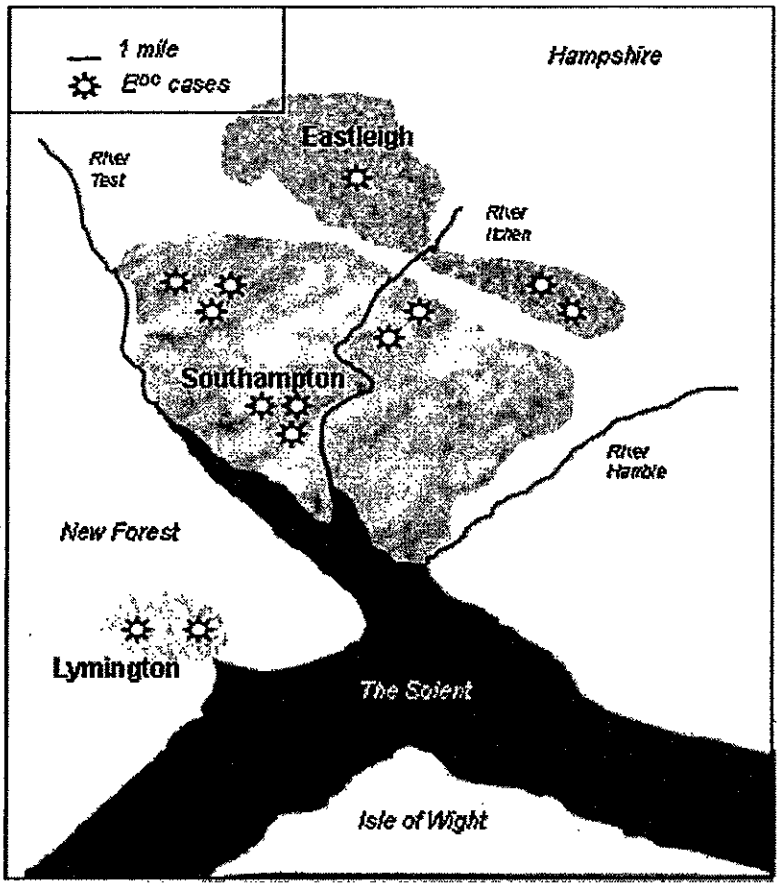

Fig. 1. South Hampshire. Proportion of people above state pension age (65 years for men and 60 years for women) according to 2001 population census data: Southampton 16.5%, Bastleigh 17.1%, Lymington New Forest 25.6%, England and Wales 18.4%).

fever, and anorexia before presenting to their general practitioner. Ten of 13 patients (77%) complained of jaundice and dark urine, suggestive of liver disease, whilst 3 (23%) had abdominal pain. Seven patients were referred to hospital and four (31%) were admitted. ALT levels varied between 300 and 6,777 IU/L (normal range of 10–40 IU/L). Liver synthetic function, as determined by international normalized ratio (INR) estimation, was impaired in two individuals (a third patient with raised INR was on concomitant warfarin therapy since the implantation of a prosthetic heart valve). The severity of the illnesses may have been contributed to by the co-morbidities that are prevalent in the elderly population. Four individuals had type II diabetes mellitus, three had hypertension, and one drank alcohol to levels above the UK Department of Health recommendations (www.dh.gov.uk/en/policyandguidance/healthandsocialcaretopics/alcoholmisus; version of 7.06.2007). Twelve out of 13 patients made a complete recovery after about 2 weeks, but one patient died 2 months after the acute illness from right lower lobe pneumonia. This death was most likely unrelated to his HEV infection.

In summary, by the use of a novel-testing algorithm, 15 cases of acute hepatitis E, of which 13 were not travel associated, have been identified in a 13-month period. By comparison, during the same period only two cases of acute hepatitis A and five cases of acute hepatitis B were identified, leading to the inference that hepatitis E^{IDC} is significantly under diagnosed.

DISCUSSION

In a 13-month period acute hepatitis E^{IDC} has been identified in 13 individuals resident in three towns of coastal Hampshire, UK, with a total population of about 340,000 inhabitants (Fig. 1). In the eight cases diagnosed during the viraemic phase of the disease, HEV genotype 3 was detected (Table I). This genotype, commonly circulating in pigs [Banks et al., 2004; Teo, 2006], has also been recognized in the other cases of hepatitis E^{IDC} reported in UK, summarized in Table II. A possible risk factor for acquiring hepatitis E^{IDC} was identified in two patients who ate shellfish [Mechnik et al., 2001; Koizumi et al., 2004; Ijaz et al., 2005] during the 2 months preceding the illness.

The majority of these patients were elderly males (85%, Table I). It is not clear if genotype 3 is attenuated in pathogenicity, thus causing preferentially overt disease in more susceptible hosts like elderly individuals, or if older people, particularly males, have a greater risk of exposure to HEV due to behavioral or environmental risk factors. This peculiar and puzzling

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TABLE I. Patients' Clinical Details and Laboratory Results of Hepatitis E^{IDC} Cases as Obtained From the First Serum Sample Tested

	Age (years)	Sex	Peak ALT[a] (IU/L)	INR	Bilirubin[b] (μmol/L)	Jaundice	Comorbid condition(s)	Hospital admission	HEV IgG	HEV IgM	HEV genotype
1	68	F	6,210	1.6	75	Yes	NIDDM and hypertension	Yes	+	+	3
2	61	M	951	1.1	28	No	None	No	+	+	3
3	71	M	1,037	1	10	No	NIDDM	No	+	+	ND
4	75	M	2,733	1	123	Yes	Bladder carcinoma, pharyngeal pouch	No	+	+	3
5	82	M	6,777	2.6	154	Yes	AF, IBS, THR	Yes	−	+	3
6	85	M	656	1	172	Yes	Aortic stenosis, hypertension	Yes	+	+	ND
7	76	M	1,705	>8[c]	320	Yes	AVR, CABG	Yes	+	+	3
8	80	F	945	1	94	Yes	Hypertension	No	+	+	3
9	47	M	630	1	28	No	None	No	+	+	ND
10	69	M	959	1.1	115	Yes	NIDDM, CABG, hypertension, hypercholesterolemia	No	+	−	3
11	83	M	3,554	1.2	115	Yes	NIDDM	No	+	+	3
12	56	M	300	NP[b]	68	Yes	Non-alcoholic fatty liver	No	+	+	NP
13	56	M	551	NP[b]	228	Yes	IHD	No	+	+	NP

NIDDM, non-insulin dependent diabetes mellitus; AF, atrial fibrillation; IBS, irritable bowel syndrome; THR, total hip replacement; AVR, aortic valve replacement; CABG, coronary artery by-pass graft; IHD, ischemic heart disease; INR, international normalized ratio; ND, not detected; NP, not performed.
[a]ALT normal value 10–40 IU/L.
[b]Bilirubin normal value 0–20 μmol/L.
[c]On warfarin since 1998.

TABLE II. Published Cases of Acute Hepatitis E^{IDC} in England and Wales

	Location	Period	Number of cases	Age (years)	Sex
Cases detected in single Centers	Southampton, Hampshire [McCrudden et al., 2000]	1999	4	41, 44, 70, 71	1 Male, 3 females
	Truro, Cornwall [Levine et al., 2000]	1999	1	61	Male
	Hull, East Yorkshire [Jary, 2005]	2005	1	54	Male
	Birmingham, Midlands [Sadler et al., 2006]	2005 (5-month period)	8[a]	Median age 60	4 Males, 3 females
	Cornwall and South-West Devon [Dalton et al., 2007]	March 1999–September 2005	21[b]	Median age 67	15 Males, 6 females
Cumulative data of England and Wales	National survey [Ijaz et al., 2005]	1997–2003	17[c]	Median age 70	13 Males, 4 females
	National survey [Lewis et al., 2006]	January–June 2005	24[d]	Median age 59	20 Males, 4 females

[a]2/8 Patients were RT-PCR positive, one patient with genotype 3 while the other with genotype 1 (the latter had been in recent contact with a jaundiced individual returning from Pakistan).
[b]HEV genotype 3 detected in 16/21 (76%) cases.
[c]HEV genotype 3 detected in 11/17 (65%) patients.
[d]10/25 (40%) cases were HEV RT-PCR positive, of which 9 were genotype 3.

demographic feature was previously documented in a nation-wide UK study [Ijaz et al., 2005] of 17 hepatitis E^{IDC} cases diagnosed between 1997 and 2003 in individuals, 14 of whom (82%) lived in coastal and estuarine areas, as are the ones found in our study in the South Hampshire region. Ijaz et al. [2005] pointed out the confounding effect of older age on the place of residence. This bias might not be relevant to this study where the elderly patients affected by acute hepatitis E belonged to a population which, on average, appears younger compared to that in the rest of England and Wales (www.statistics.gov.uk/census2001, Fig. 1).

Although documented in other European countries, Asia, and USA [van der Poel et al., 2001; Clemente-Casares et al., 2003; Widdowson et al., 2003; Buti et al., 2004; Amon et al., 2006; Peron et al., 2006], hepatitis E^{IDC} is still considered an uncommon disease. A recent report by Lewis et al. [2006] suggests that hepatitis E^{IDC} in UK is under diagnosed. However, implementation of routine serology for hepatitis E is hampered by the fact that currently available antibody assays, based on HEV genotypes 1 and 2, lack sensitivity [Lin et al., 2000; Myint et al., 2006]. This has been attributed to several factors of which the main one is likely to be that the currently available recombinant HEV proteins used in the assay systems may not include all relevant immunogenic B cell epitopes encoded within the HEV genome [Wang et al., 2001; Zhang et al., 2003; Zhou et al., 2004]. Additionally, the genetic diversity between HEV genotypes [Lu et al., 2006] warrants the inclusion of each HEV genotype in future diagnostic kits.

In spite of their limitations, currently available antibody assays have been capable of detecting a significant number of hepatitis E^{IDC} cases, leading to the recognition of this emerging disease. This consideration guided the decision to routinely include hepatitis E testing in our laboratory. Cases with a significantly deranged ALT value were tested, in order to target acute hepatitis of clinical importance. By adherence to this algorithm, a pick up rate of 9.3% was obtained.

In a situation of suboptimal performance of currently available antibody assays, RT-PCR represents a useful complementary diagnostic tool [Jothikumar et al., 2006]. Although the duration of viraemia is variable (from few days to few weeks) (1, 10) a serum sample collected at the peak of ALT values has a high chance to be RT-PCR positive thus clarifying cases of acute hepatitis E with atypical serological profiles, as found in two of our patients (Table II), including HEV seronegative cases [Lin et al., 2000; Mansuy et al., 2004].

The incidence of hepatitis E^{IDC} in our center exceeded the frequency of acute hepatitis A (two cases) and hepatitis B (five cases). In UK, where high standards of sanitation and vaccination programs have significantly reduced exposure to hepatitis A and B viruses, hepatitis E^{IDC} may emerge as a major cause of acute viral hepatitis [Lewis et al., 2006]. The high frequency observed in our uncontrolled series may in part be a reflection of a better ascertainment of hepatitis E^{IDC}, which had previously remained undiagnosed, as well as a true increase in incidence in recent time.

In conclusion, it is considered that these findings support the case for more widespread HEV testing according to clearly defined criteria and we propose an effective algorithm for this purpose. This is crucial not only for surveillance purposes and to clarify the epidemiology of HEV in UK, but also for the appropriate management of affected patients. In cases of acute hepatitis, where initial history and viral marker results are negative, autoimmune hepatitis, and idiosyncratic drug reactions are important to consider in the differential diagnosis, with implications for management and prognosis. Thus, in the absence of HEV testing, patients with unexplained raised transaminases may unnecessarily progress to liver biopsy, empirical trial of steroids, or withdrawal of presumed offending drugs. Consideration of HEV infection in individuals without travel-associated risk factors for acute hepatitis may have a major impact on clinical management.

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一般的名称	①乾燥抗HBs人免疫グロブリン ②ポリエチレングリコール処理抗HBs人免疫グロブリン	研究報告の公表状況	The New England Journal of Medicine 2008; 358: 811-817	公表国 フランス
販売名 （企業名）	①ヘブスブリン（ベネシス） ②静注用ヘブスブリン－IH（ベネシス）			

研究報告の概要

HEVは急性肝炎の原因となる病原体であって、慢性肝炎に進展することはないと考えられている。我々は、HEV急性肝炎の14症例を確認したが、3名の患者は肝臓、9名の患者は腎臓、2名は腎臓と膵臓を移植されていた。患者は全員、血清HEV RNAが陽性であった。8名の患者が慢性肝炎になり、確認はアミノトランスフェラーゼ値上昇の持続、血清HEV RNA、慢性肝炎の組織学的特徴によって行われた。移植から診断までの時間は極めて短く、リンパ球数並びにCD2、CD3及びCD4 T細胞の数は、慢性肝炎に進展した患者では著しく低かった。

使用上の注意記載状況・その他参考事項等

代表として静注用ヘブスブリン－IH の記載を示す。
2. 重要な基本的注意
(1) 本剤の原材料となる血液については、HBs抗原、抗HCV抗体、抗HIV-1抗体、抗HIV-2抗体陰性で、かつALT（GPT）値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV及びHCVについて核酸増幅検査(NAT)を実施し、適合した血漿を本剤の製造に使用しているが、当該NATの検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した高力価の抗HBs抗体を含有する血漿を原料として、Cohnの低温エタノール分画で得た画分からポリエチレングリコール4000処理、DEAEセファデックス処理等により抗HBs人免疫グロブリンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において60℃、10時間の液状加熱処理及びろ過膜処理（ナノフィルトレーション）を施しているが、投与に際しては、次の点に十分注意すること。

報告企業の意見	今後の対応
少なくとも免疫抑制剤を投与されている臓器移植患者においては、HEV感染が慢性肝炎に進展し得るとの報告である。 本剤からHEVが伝播したとの報告はない。万一、原料血漿にHEVが混入したとしても、EMCおよびCPVをモデルウイルスとしたウイルスバリデーション試験成績から、本剤の製造工程において十分に不活化・除去されると考えている。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。

BRIEF REPORT

Hepatitis E Virus and Chronic Hepatitis in Organ-Transplant Recipients

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SUMMARY

Hepatitis E virus (HEV) is considered an agent responsible for acute hepatitis that does not progress to chronic hepatitis. We identified 14 cases of acute HEV infection in three patients receiving liver transplants, nine receiving kidney transplants, and two receiving kidney and pancreas transplants. All patients were positive for serum HEV RNA. Chronic hepatitis developed in eight patients, as confirmed by persistently elevated aminotransferase levels, serum HEV RNA, and histologic features of chronic hepatitis. The time from transplantation to diagnosis was significantly shorter and the total counts of lymphocytes and of CD2, CD3, and CD4 T cells were significantly lower in patients in whom chronic disease developed.

ACUTE HEPATITIS CAUSED BY THE HEPATITIS E VIRUS (HEV) IS ENDEMIC IN developing countries and appears to be an emerging disease in industrialized countries.[1,2] Seroprevalence studies have reported anti-HEV IgG antibodies in 6 to 16% of renal-transplant recipients.[3,4] This hepatotropic RNA virus is often not fully considered or routinely sought in cases of acute hepatitis in recipients of solid-organ transplants. Only three cases of acute HEV infection have been reported in organ-transplant recipients.[5-7] Even though two cases of persistent HEV infection have been reported,[8,9] HEV is considered an agent responsible for acute hepatitis that does not become chronic.[10]

We report here 14 cases of acute hepatitis E infection in organ-transplant recipients. We suggest that HEV infection may evolve to chronic hepatitis in immunocompromised patients.

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PATIENTS AND METHODS

Between January 1, 2004, and December 31, 2006, all recipients of liver, kidney, or kidney and pancreas transplants attending our outpatient and inpatient clinics who presented with unexplained short-term elevations of liver-enzyme levels were screened for HEV infection by serologic and molecular tools. Patients chronically infected with hepatitis B, C, or D viruses were excluded from the study. Biliary-tract complications were ruled out by abdominal ultrasonography. Toxin- and drug-related causes of abnormal liver-function test results were ruled out by patient history. Fourteen of 217 patients (6.5%) tested positive for serum HEV RNA.