innate antiviral responses during acute infection. Thus, some HCV infections may be "silent" because they minimally activate the TLR and/or IFN cellular defense systems. This would have obvious selective advantage for the virus and could contribute to the establishment of chronic infection. Alternatively, when a virus enters cells in a "noisy" fashion, it has a poor chance of establishing chronic infection because the innate antiviral responses would quickly shut down virus replication. Finally, stimulation of the IFN system by the HCV core protein may be required to balance the anti-IFN functions of other HCV proteins such as E2 (Taylor et al., 1999), NS5A (Gale et al., 1997; Polyak et al., 2001), and NS3 (Foy et al., 2003) during certain stages of the HCV replication cycle.

EXTRACELLULAR VERSUS INTRACELLULAR EFFECTS OF CORE

HCV core is found within infected cells as well as in patient serum (Kashiwakuma et al., 1996; Widell et al., 2002). Extracellular core protein likely affects the modulation of T cell function, TLR signaling and DC function as described above. Thus, it is important to consider the contribution of extracellular and intracellular core protein to the biological activity in question. Indeed, CD81 engagement by the HCV envelope glycoprotein E2 inhibits NK and T cell cytotoxic function and signal transduction (Crotta et al., 2002; Tseng and Klimpel, 2002; Wack et al., 2001), and induced pro-inflammatory chemokine expression in hepatocytes (Balasubramanian et al., 2003). Thus, immune function may be altered as cells "sample" the microenvironment through HCV-host interactions that are limited to molecules on the cell surface, such as the HCV core-TLR or core-C1qR interaction. Moreover, these extracellular HCV-host interactions may also contribute to HCV pathogenesis.

HCV CORE AND PATHOGENESIS

Recent work has demonstrated that the HCV core protein may also participate in the pathogenesis of liver disease. Development of fibrosis is characterized histologically with infiltration of inflammatory lymphocytes, hepatocellular apoptosis, and Kupffer cell activation. HSC proliferate and undergo and become highly activated, which involves secretion of large amounts of extracellular matrix proteins (Bataller and Brenner, 2005). Despite a large body of literature from clinical and animal studies on fibrosis development, very little is known about how HCV causes fibrosis.

A recent study found that addition of recombinant core protein to activated human hepatic stellate cells (HSC) stimulated intracellular signaling pathways, while viral transduction of HCV core into HSCs caused increased cell proliferation (Bataller et al., 2004). Interestingly, the HSC response appeared to differ between core and other HCV non-structural proteins. The data suggest that HCV core and non-structural proteins can modulate the activity of HSC, which may contribute to fibrosis. This study also reinforces the notion that HCV proteins can have intracellular as well as extracellular effects on a variety of cells.

A second important point from the study of Bataller et al., (Bataller and Brenner, 2005), is that HCV proteins including core induce oxidative stress on HSC which is involved in HSC activation. Indeed, antioxidant therapy reduces the effects of HCV proteins on HSCs. This finding is in line with the current thinking that oxidative stress is central to induction of fibrosis in many model systems. HCV core induced oxidative stress also affects mitochondrial physiology.

HCV CORE AND MITOCHONDRIAL DYSFUNCTION

Expression of HCV core protein in transgenic mice and in cell culture induces oxidative stress. It has been shown that core protein localizes to mitochondria, between the mitochondrial outer membrane and ER (Moriya et al., 1998; Moriya et al., 2001a; Okuda et al., 2002; Schwer et al., 2004; Suzuki et al., 2005), as described in the targeting section above. Core protein expression and mitochondrial localization inhibits electron transport at complex I, increases complex I reactive oxygen species (ROS) production, decreases mitochondrial glutathione, and increases mitochondrial permeability transition in response to exogenous oxidants such as alcohol (Korenaga et al., 2005; Okuda et al., 2002; Wen et al., 2004). These effects are associated with increased hepatocyte apoptosis in the presence of HCV core protein, ethanol and cytochrome P4502E1. Like the case with HSC, core and ethanol metabolism effects on apoptosis can be prevented with antioxidants (Otani et al., 2005).

HEPATITC STEATOSIS AND HEPATOCARCINOGENESIS

Evidence has been accumulating that HCV core protein is directly involved in pathogenesis (Giannini and Brechot, 2003; McLauchlan, 2000). As shown in Table 1, many cellular proteins, which interact with core protein have been identified. Several studies have suggested that the core protein plays a crucial role for hepatocarcinogenesis (Chang et al., 1998; Moriya et al., 1998; Ray et al., 1996).

Recent studies have highlighted steatosis as a basis of HCV-associated HCC (Lerat et al., 2002; Moriya et al., 1998). Steatosis, which is an accumulation of fat deposits in hepatocytes, is one of the histological features of chronic hepatitis C (Bach et al., 1992; Lefkowitch, 2003). In vitro studies have shown that HCV core protein associates with cellular lipid droplets, via direct interaction with apolipoprotein A2 (Barba et al., 1997; Shi et al., 2002). The mice transgenic for HCV core gene have been shown to develop steatosis and hepatocellular carcinoma (HCC) (Moriya et al., 1998; Moriya et al., 1997b). Steatosis in the core-transgenic mice is age-dependent and characterized by the appearance of micro- and macro-vesicular lipid droplets (Moriya et al., 1998). Lerat et al. have confirmed that transgenic mice expressing the whole genome of HCV also develops steatosis and HCC (Lerat et al., 2002).

Table 1. Cellular proteins that bind to the HCV core protein. The list contains cellular proteins with various cellular functions that interact with HCV core. The interaction of HCV core with these cellular proteins may have pathogenic implications. Please refer to the text for details.

Core-Interacting protein	Function	Reference
Apolipoprotein AII	lipid metabolism	Sabile et al., 1999; Shi et al., 2002
CAP-Rf	RNA helicase	You et al., 1999
complement receptor gC1qR	T-cell response	Kittlesen et al., 2000
cyclin-dependent kinase 7	cell cycle	Ohkawa et al., 2004
DEAD box protein	RNA helicase	Mamiya and Worman, 1999
DEAD box protein 3	RNA helicase	Owsianka and Patel, 1999
heterogeneous nuclear ribonucleoprotein K	transcriptional control	Hsieh et al., 1998
JAK1/2	signal transduction	Hosui et al., 2003
lymphotoxin-β receptor	cytotoxicity	Chen et al., 1997
p53	transcriptional control	Otsuka et al., 2000
p73	transcriptional control	Alisi et al., 2003
proteasome activator PA28γ	protein stability	Moriishi et al., 2003
retinoid X receptor α	transcriptional control	Tsutsumi et al., 2002
Smad3	transcriptional control	Cheng et al., 2004
Sp110b	transcriptional control	Watashi et al., 2003
STAT3	cell transformation	Yoshida et al., 2002
TAFII28	transcriptional control	Otsuka et al., 2000
Tumor necrosis factor receptor 1	apoptosis	Zhu et al., 2001
14-3-3 protein	signal transduction	Aoki et al., 2000

Although the molecular mechanisms of steatosis caused by the core protein is still unclear, the core protein may alter lipid metabolism by interacting with cellular proteins involved in lipid accumulation and storage in hepatocytes (Barba et al., 1997; Sabile et al., 1999; Shi et al., 2002). The concentration of carbon 18 monosaturated fatty acids were increased in the livers of the core-transgenic mice and chronic hepatitis C patients, suggesting that HCV core affects a specific pathway in lipid metabolism (Moriya et al., 2001b). Nonetheless, transgenic mouse lines established by other groups did not show either steatosis nor HCC (Kawamura et al., 1997; Pasquinelli et al., 1997). These discrepancies suggest that not only the viral proteins but also other factors are involved in hepatocarcinogenesis. These discrepancies may be due to differences in genetic backgrounds of the mice and expression levels of the viral proteins.

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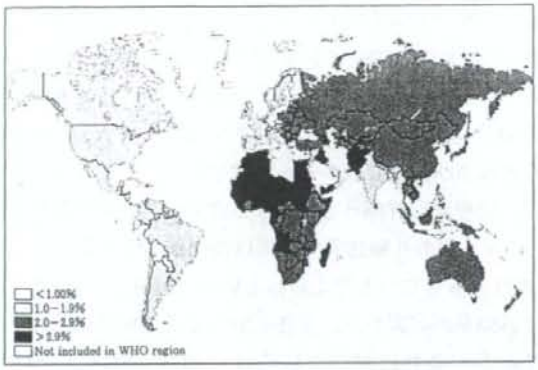
C型肝炎ウイルスの発揮する腫瘍原性

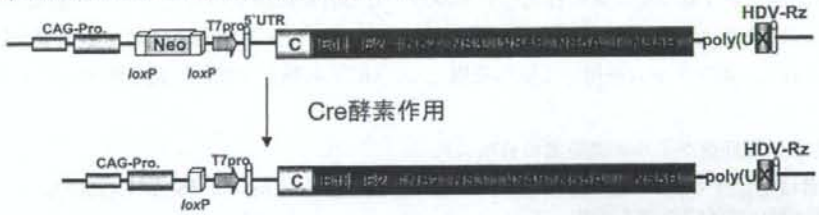
Ⅰ．世界におけるC型肝炎ウイルス感染者の分布



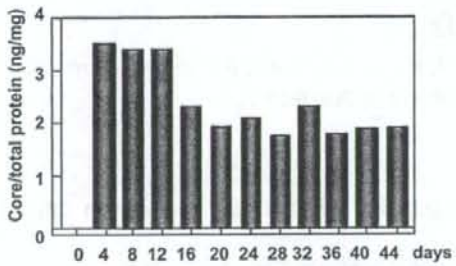
Ⅱ．C型肝炎ウイルスの生活環とウイルスゲノム構造

Ⅲ．C型肝炎ウイルスによる腫瘍原性亢進

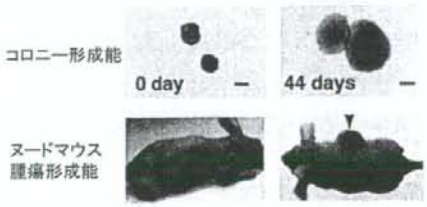
(a) Cre/loxPシステムによる全長HCV発現システム



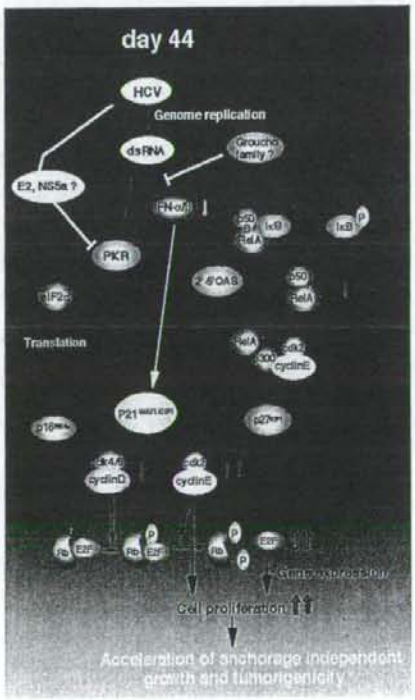
(b) HCVの持続発現(コア蛋白質)



(c) HCV発現継代細胞の腫瘍原性亢進



(d) HCV発現継代細胞で活性化するシグナル経路



写真の説明

肝炎の原因ウイルスは，1970年代までにA型およびB型肝炎ウイルスが発見されたが，同時にこれらのウイルスでは引き起こされない血液媒介性の肝炎，いわゆる非A非B型肝炎の存在が明らかとなった．非A非B型肝炎の病原体の分離には困難を極めたが，唯一の動物実験系であるチンパンジーを用いた感染実験でフラビウイルスに近縁のRNAウイルスである事が予測され，1989年に米国カイロン社のホートン博士らが遺伝子クローニングに成功してC型肝炎ウイルス（HCV）ゲノムの構造と塩基配列が同定された．この遺伝子産物を抗原として世界中の患者血液が調べられた結果，現在全世界では約1億2千万人の抗体陽性者がいると推定される（図Ⅰ）．我が国でも抗体陽性者は200万人前後いると推定されているが，さらに問題となっているのはHCVが持続感染を成立しやすく，肝硬変，肝癌へと進展する点で，日本の肝癌患者さんの多くはHCV抗体陽性である．HCVはRNAウイルスであり細胞質で主に複製増殖すると同時に，典型的な癌遺伝子は持たず宿主細胞のDNAに組み込まれる事もないと考えられている（図Ⅱ）．このようなHCVがいかに細胞を癌化するかを解析するためには感染系が必要だが，現在までのところ肝癌細胞以外には確立されておらず腫瘍原性解析は困難な状況である．これに対して私達は，HCV全長遺伝子をCre/loxPシステムを用いてどんな細胞でも必要な時に発現できるユニットを構築し腫瘍原性解析を可能にしている（図Ⅲ-a）．本ユニットでHCV蛋白質をスイッチング発現すると持続的に発現が維持されるので慢性感染時の肝細胞におけるウイルスの作用のモデル系として容易に解析が可能となる（図Ⅲ-b）．継代44日以降には細胞の腫瘍原性が亢進し（図Ⅲ-c），標的経路の1つはcdk-Rb-E2F経路である事を明らかにした（図Ⅲ-d）．さらに，本システムを用いて抗体を樹立し，HCVの新たな標的経路を解明している．

Ⅰ．世界におけるC型肝炎ウイルス感染者の分布

HCV感染者は全世界で約1億2千万人とされ（*Lancet Infect. Dis.*, 5: 558-567, 2005），エジプトなど一部の地域では高い抗体陽性率を示す．

Ⅱ．C型肝炎ウイルスの生活環とウイルスゲノム構造

肝臓細胞におけるHCVの複製の場は細胞質であり，ウイルス遺伝子はプラス1本鎖RNA（約9.6kb）でウイルス蛋白質は1本のポリプロテインから切断されて機能を持つ．

Ⅲ．C型肝炎ウイルスによる腫瘍原性亢進

(a) Cre/loxPシステムを用いた全長HCV遺伝子発現システム（*J. Biol. Chem.*, 279（15）: 14531-14541, 2004）
HCV遺伝子は，Cre酵素で遺伝子発現後，リボザイム配列で正確に切断される．

(b) (a)のユニットを持つ細胞株でのHCVコア蛋白質発現（ELISAによる定量）

(c) HCV発現継代細胞はコロニー形成能やヌードマウス腫瘍形成能が亢進している．

(d) HCV発現継代細胞で活性化されるシグナル経路

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Q6 最近口内炎がよく出来ます．肝臓が悪いことと関係があるのでしょうか？

患者背景 55歳 男性，AST 55 IU/L，ALT 85 IU/L，HCV抗体（+）

A C型肝炎ウイルスの持続感染者の方には，治りにくい口内炎が出来ることがよくあります．扁平苔癬という名前の病気で，長い間炎症が続き，自然に治ることはほとんどありません．無症状のこともありますが，食事の際に口の中の粘膜が"しみる"というのが特徴的な症状です．扁平苔癬は，やがて口腔癌（口の中の癌）に変化することもありますので，必ず専門医での診察が必要となります．なお，C型慢性肝炎で扁平苔癬を合併している方が，インターフェロン治療を受ける場合は，扁平苔癬が悪化しインターフェロン治療が行えない場合があります．したがって，インターフェロン治療を受ける予定の方は，口の中に自覚症状がなくても専門医での診察を受けておくようにしましょう．

Aのpoint

1．肝外病変とは

肝外病変

C型肝炎ウイルス（HCV）は，肝障害のみならず種々の臓器障害の原因にもなっていることが明らかにされている．HCVは肝臓以外の疾患を引き起こし（肝外病変と呼ぶ），その代表的な疾患としてクリオグロブリン血症，膜性増殖性糸球体腎炎，晩発性皮膚ポルフィリン症，シェーグレン症候群，悪性リンパ腫，筋炎，心筋障害，扁平苔癬，口腔癌，糖尿病，間質性肺炎，モーレン角膜潰瘍，関節リウマチ，慢性甲状腺炎などがある．HCVキャリア（HCV持続感染者）が少なくとも1つ以上の肝外病変を有する率は，retrospective studyでは74%（1,202/1,604人），prospective studyでは38%（122/321人）と報告されている．

HCVキャリア

肝外病変についての知識は医療従事者の中でも必ずしも十分に認識されているとはいえず，また引き起こされる病態も多岐にわたるため，臓器別診療体制の傾向が強い医療施設では，各診療科間の十分な連携のもとでHCVキャリアの経過観察が必要である．

2．扁平苔癬とHCV

扁平苔癬

慢性の角化異常を伴う炎症性疾患である扁平苔癬とHCV感染に関する報告は多数認められる（表6-1）．その感染率に差があるのは，各国でのHCV感染率の地域差，人種あるいは研究対象の選択の差等に影響していると考えられる．扁平苔癬の発症には，肝疾患の程度やウイルス側因子（HCV RNA量やHCV genotype）は関与しない．皮膚あるいは口腔粘膜上皮内において，HCV増殖が証明

表 6-1　扁平苔癬患者における HCV 感染率

国	報告者	報告年	対象人数（口腔扁平苔癬のみ／皮膚扁平苔癬のみ／口腔皮膚扁平苔癬）	LP 患者 HCV 抗体陽性率	LP 患者 HCV RNA 陽性率（%）	コントロール HCV 抗体陽性率（%）
日本	Nagao et al.	1995	45 (45/0/0)	62	60	コントロールなし
	Tanei et al.	1995	45 (28/8/9)	37.8	未施行	6.7% (3 of 45)
イタリア	Divano et al.	1992	46 (0/46/0)	32.6	未施行	コントロールなし
	Rebora et al.	1992	50 (50/0/0) (group 1 : without CLD)	4	未施行	コントロールなし
			29 (29/0/0) (group 2 : with CLD)	65	未施行	コントロールなし
			46 (46/0/0) (group 3 : with or without CLD)	24	未施行	コントロールなし
	Gandolfo et al.	1994	105 (105/0/0)	9.5	未施行	コントロールなし
	Carrozo et al.	1996	70 (70/0/0)	27.1	21.4	4.3% (3 of 70)
	Mignogna et al.	1998	263 (263/0/0)	28.8	未施行	3% (3 of 100)
	Mignogna et al.	2002	600 (600/0/0)	27.5	未施行	コントロールなし
スペイン	Bagan et al.	1994	187 (187/0/0)	15	未施行	コントロールなし
	Sanchez-Perez et al.	1996	78 (22/22/34)	20	16.7	2.4% (2 of 82)
	Bagan et al.	1998	100 (100/0/0)	23	未施行	5% (5 of 100)
フランス	Cribier et al.	1994	52 (4/48/0)	3.8	未施行	2.6% (3 of 112)
	Dupin et al.	1997	102 (102/0/0)	4.9	未施行	4.5% (14 of 306)
	Dupond et al.	1998	28 (28/0/0)	28.6	17.9	コントロールなし
イギリス	Ingafou et al.	1998	55 (55/0/0)	0	未施行	0% (0 of 110)
	Tucker et al.	1999	45 (13/32/0)	0	0	3.1% (1 of 32)
スコットランド	Roy et al.	2000	6 (6/0/0)	0	0	コントロールなし
USA	Bellman et al.	1995	30 (0/30/0)	23	16.7	4.8% (2 of 41)
	Chuang et al.	1999	22 (0/22/0)	55	未施行	25% (10 of 40) (control 1) 0.17%(255 of 149,756) (control 2)
	Beaird et al.	2001	24 (0/24/0)	17	未施行	5% (1 of 20)
	Chainal-Wu et al.	2001	31 (31/0/0)	45	未施行	コントロールなし
	Eisen	2002	195 (195/0/0)	0	未施行	コントロールなし
ドイツ	Imhof et al.	1997	84 (22/62/0)	16	14	1.1% (1 of 87)
	Grote et al.	1998	24 (24/0/0)	4.2	未施行	コントロールなし
オランダ	van der Meij et al.	2000	55 (55/0/0)	0	未施行	コントロールなし
トルコ	Ilter et al.	1998	75 (0/75/0)	0	未施行	0% (0 of 75)
	Kirtak et al.	2000	73 (27/46/0)	6.8	未施行	1.36% (1 of 73)
	Erkek et al.	2001	54 (0/54/0)	12.9	9.3	3.7% (2 of 54)
ネパール	Garg et al.	2002	64 (14/35/15)	0	未施行	0% (不明)
ナイジェリア	Daramola et al.	2002	57 (0/55/2)*	15.8	未施行	25% (6 of 24) (control A) 0% (0 of 24) (control B)
ブラジル	Figueiredo et al.	2002	68 (63/0/5)	8.8	未施行	0.6% (6 of 898)

CLD：慢性肝疾患，control 1：乾癬，control 2：ボランティア供血者，control A：扁平苔癬以外の皮膚疾患，control B：正常，*著者が Dr. Daramola に問い合わせた

(Nagao et al. J Gastroenterol Hepatol 2004 : 19 : 1101-1113)

され（*in situ* hybridization 法あるいは RT-PCR 法），HCV 特異的な T 細胞の関与が証明されている．

HCV 関連の肝外病変に対する治療として，インターフェロンやリバビリンによる治療効果が確認されている．現在までに，効果の認められた疾患として，膜性増殖性糸球体腎炎，クリオグロブリン血症，悪性リンパ腫，晩発性皮膚ポルフィリン症，扁平苔癬，モーレン角膜潰瘍などがある．難治性の HCV 関連の膜性増殖性糸球体腎炎やクリオグロブリン血症に対しては，インターフェロンならびにリバビリン併用療法が有効な治療法であると考えられ，期待される治療であるともいえる．しかしながら，必ずしも肝外病変に対するインターフェロン治療が有効な治療とはいえず，逆に肝外症状が悪化し，インターフェロン治療を中止せざるをえないケースも存在することやインターフェロンを中止すると再発することが問題視されている．特にびらん型の口腔扁平苔癬を合併する C 型慢性肝炎例に，

IFN 治療

インターフェロン療法を行うと皮膚や口腔病変が増悪する傾向があり，インターフェロン投与はきわめて慎重に行うことが肝要である．したがって，肝外病変に対するインターフェロン治療には注意が必要である．C型肝炎に対するインターフェロン治療前には，全身のスクリーニングと専門医への紹介を怠ってはならない．

口腔外科専門医

口腔粘膜病変に対する診断は，口腔外科専門医に紹介することを推奨する．ただし，口腔外科専門医名や口腔外科専門医施設は公表されていないのが現状であるが，2005年7月7日付けの口腔外科専門医の指定研修機関はhttp：//www.jsoms.or.jp/2_03_3.htmlで閲覧可能である．なお，口腔外科専門医であってもHCVと扁平苔癬について精通しているとは限らない．

〈佐田　通夫〉

Q55 キャリアの血液に触れたのですが，どのように対処したらよいでしょうか？

患者背景 キャリアの家族

A B型肝炎ウイルスに汚染した場合の積極的な感染予防策として，高力価HBs抗体含有免疫グロブリン（HBIG）とB型肝炎ウイルスのワクチンがあります．しかし現在，C型肝炎ウイルス感染予防のためのワクチンはありません．C型肝炎ウイルスを含む血液に触れた方は，まず接触直後にC型肝炎ウイルス抗体検査と肝機能検査を受け，その後1週間後，2週間後の2回を目安としてC型肝炎ウイルスRNA定性検査を受けながら，約6か月間経過をみます．万一感染したことがわかったときには，インターフェロンを投与することによりウイルス駆除が可能であり，慢性化を防止できることがわかっています．

なお，肝炎ウイルスの感染を避けるためには，感染している人の血液になるべく触れないことが大切です．①歯ブラシ，カミソリなどを他人と共用しない，②ほかの人の血液に触るときは，ゴム手袋を着ける，③注射器や注射針を共用して，覚醒剤や麻薬等の注射をしない，④口うつしで乳幼児に食べ物を与えない，⑤入れ墨やピアスをするときは，清潔な器具であることを必ず確かめる，⑥よく知らない相手との性行為にはコンドームを使用するといったことを守りましょう．

また，現在日本で行われている医療行為（歯科医療を含む）で，肝炎ウイルスに感染する可能性はまれと考えられています．また，理髪店においてもカミソリを共用しなければ，感染することはまれです．しかし，長期間にわたって血液透析を受けている方では，施設内での感染が発生しており，医療機関における感染予防が重要な問題となっています．

Aのpoint

1．感染予防

感染予防

B型肝炎ウイルス（HBV）もC型肝炎ウイルス（HCV）も日常生活（食事や入浴）で感染することはないが，血液による汚染を介して感染する．HBVの感染予防対策としては，2つの方法が存在する．

HBIG

a．高力価HBs抗体含有免疫グロブリン（HBIG）の投与

HBVに対して免疫を持たない人が，HBVを含む血液に汚染した場合には（汚染血液による針刺し事故，汚染血液による縫合針による誤刺，垂直感染予防時），48時間以内にHBIGを投与し，必要に応じてHBsワクチン接種を併用する．

HBsワクチン

b．HBsワクチンの接種

ワクチンの接種対象は，HBVキャリア妊婦からの出生児，血液に触れる機会の多いHBVキャリアの家族や医療従事者などである．HBsワクチンによるHBs抗体獲得率は約90%以上に及ぶ．