台北縣立醫院

肝衰竭的藥物治療現況及未來趨勢

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Introduction

- Liver failure is the inability of the liver to perform its normal synthetic and metabolic function as part of normal physiology.
- Two forms are recognised:

Acute liver failure (ALF) –
- development of hepatic encephalopathy (confusion, stupor and coma) and
- decreased production of proteins (such as albumin and blood clotting proteins) within **four weeks** of the first symptoms (such as **jaundice**) of a liver problem.

Chronic liver failure (CLF) –
usually occurs in the context of cirrhosis, itself potentially the result of many possible causes, such as
- excessive alcohol intake,
- **hepatitis B or C**,
- autoimmune,
- hereditary and
- metabolic causes (such as iron or copper overload or Steatohepatitis non-alcoholic fatty liver disease).

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Hepatitis B Virus

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Definition

- ✓ **Syndrome:**
  It is not a single disease, but rather a clinical and pathological syndrome.
- ✓ **Causes:**
  Viral, drug, autoimmune, unclassified, and specific types.
- ✓ **Charaterized by:**
  varing degree of hepatocellular necrosis and inflammation:
  ----- grading and staging (clinical, morphological)
  - ✓ **Chronicity:**
    - **A continuing disease without improvement.**
    - **It requires a time factor of at least six months duration including both clinical and laboratory features, but not a histological change.**
    - **Sometimes, diagnosis has already been made and therapy begun before such a time requirement.**
  - ✓ **Specific types are also included: (PBC, PSC, Wilson's d., α1-antitrypsin deficiency)**
  - ✓ **Alcohol abuse: not included ----- different histological pattern.**

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Mechanism of HBV infection

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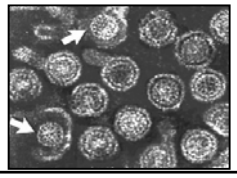
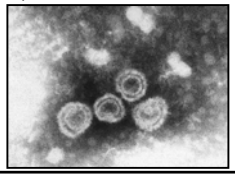
B型肝炎（hepatitis B）

病毒性肝炎

- 不完全雙股DNA病毒
- 分類上屬於hepadnavirus
- 大小約為42 nm
- 西元1965年 Blumberg 所發現“澳洲抗原”
  （1976 Nobel Prize）





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B型肝炎（hepatitis B）
病毒性肝炎

傳染方式

- 傳染途徑　B型肝炎病毒
- 潛伏期　約二個月或更久
- 傳染途徑
  （1）母子傳染（又稱垂直傳染）
  （2）水平感染

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How HBV infect to liver?

- HBV主要的致病機轉並不是直接殺死肝細胞，它是藉由人體的免疫機轉而導致肝細胞壞死的。
- 人體免疫系統內的T cell，平常不會攻擊體內的正常細胞，當體內的正常細胞遭受到病菌感染時，它就會將已受感染的細胞殺死，目的是為了要除去入侵的病菌。
- B型肝炎病毒導致肝炎就是經由這樣的途徑。T cell要將HBV「驅除出境」，然而HBV是在肝細胞內，所以在T cell欲除去HBV同時，肝細胞也跟著陪葬了。

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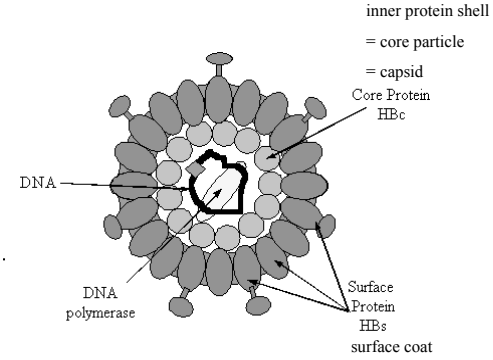
Hepatitis B Virus (HBV)



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Hepatitis B Virus (HBV)

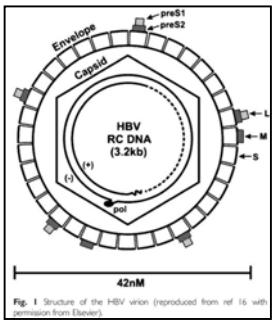


Fig. 1 Structure of the HBV virion (reproduced from ref 16 with permission from Elsevier).

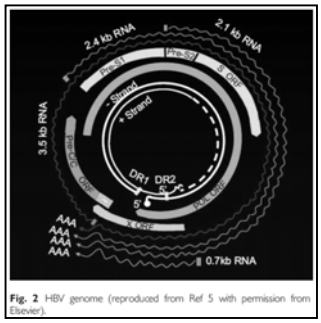
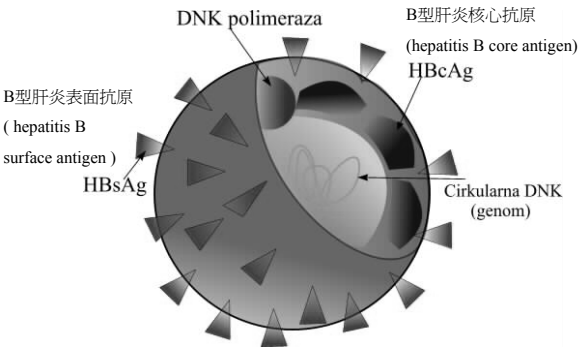


Fig. 2 HBV genome (reproduced from Ref 5 with permission from Elsevier).

Pharm Res
Received: 15 December 2009 / Accepted: 1 March 2010 DOI 10.1007/s11095-010-0112-z



核心抗原的一部份會被釋放到受感染的細胞外，
成爲B型肝炎e抗原 (hepatitis B e antigen, HBeAg)

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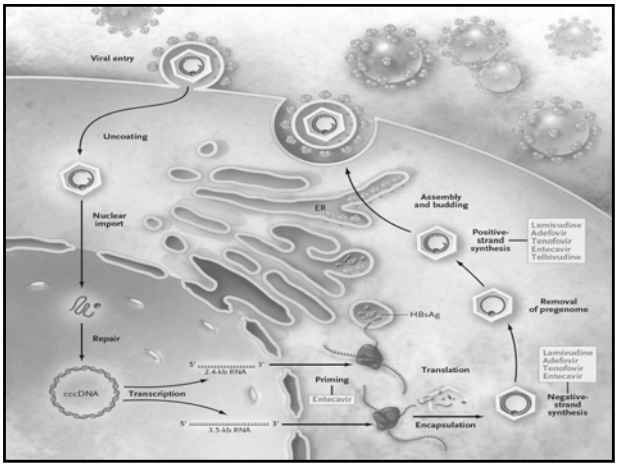
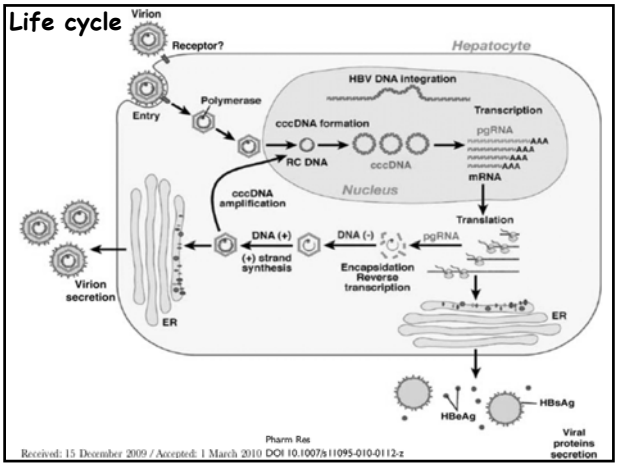


Life cycle



Epidemiology

1、2004年，慢性肝炎／肝硬化為國人的十大死因第6位。

2、2004年，肝炎為男性癌症死亡第1位，女性癌症死亡第2位。

3、全世界有超過3億5千萬人是**B型肝炎帶原者**，其中6千萬人中可能死於肝癌，而4千5百萬人可能死於肝硬化。

4、每年有50到100萬人死於HBV所導致的慢性肝炎、肝硬化及肝癌。

5、台灣成年人有15~20%的帶原者，20歲以下(台北市)則不到1%。

Epidemiology

1、根據WHO的報告，全世界大約有３％的人患有HCV。

2、HCV是造成慢性肝炎、肝硬化、肝癌和肝臟移植的原因，因為感染後，50%轉為慢性肝炎，其中10-20%在5-10年發展為 肝硬化，15%肝硬化患者發生肝癌。

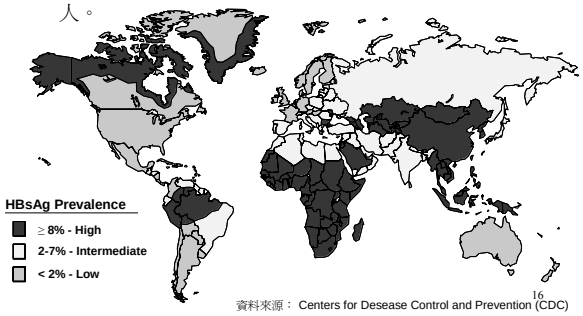
3、在美國，預測在1990-2015年間，罹患C型肝炎的人口數可能成長四倍。

4、在台灣，大約有2%-5%的人感染了C型肝炎，而經由C型肝炎演變成肝硬化和肝炎的比例大約有20%-30%。雲嘉地區某些村落，因為重複使用未消毒乾淨針頭和密醫氾濫，甚至全村有70%以上的人感染C型肝炎。

5、在台灣由於接受Ｂ型肝炎疫苗注射的人越來越多，所以Ｂ型肝炎會慢慢減少以後，以後罹患Ｃ肝炎的比例可能會越來越高。

全球B型肝炎患者分布情形

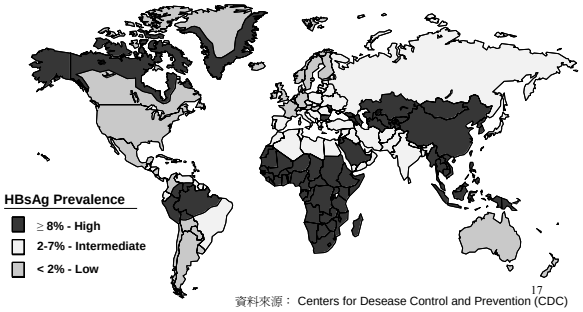
- 根據世界衛生組織的估計，全球約有二十億人感染Ｂ型肝炎病毒；其中慢性Ｂ型肝炎患者達三億五千萬人。



資料來源： Centers for Desease Control and Prevention (CDC)

全球B型肝炎患者分布情形

大部分慢性B型肝炎患者分布在亞洲、大洋洲及非洲，其中將近75%的患者來自亞洲。



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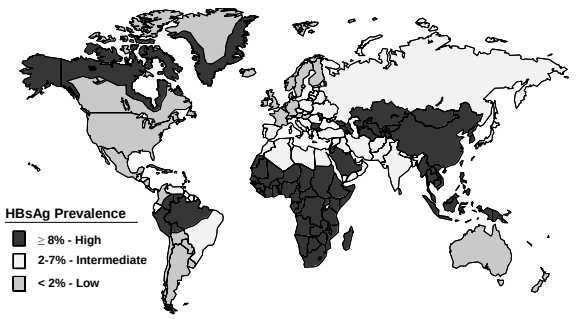
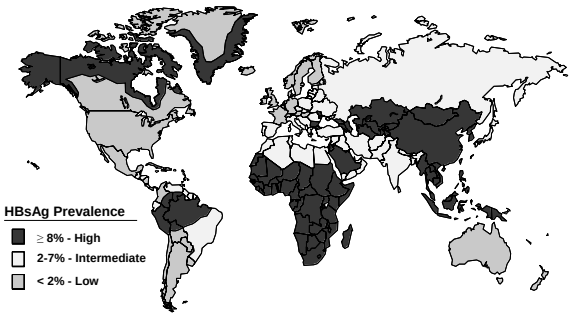


高度流行 (≥8%): 約佔全球人口的45%

–lifetime risk of infection >60%

–early childhood infections common



中度流行 (2%-7%):約佔全球人口的43%

–lifetime risk of infection 20%-60%

–infections occur in all age groups

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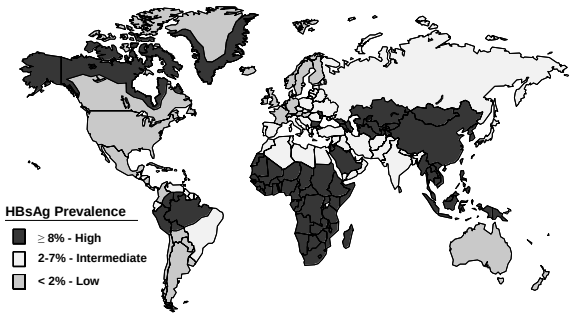

低度流行 (<2%):約佔全球人口的12%

–lifetime risk of infection <20%

–most infections occur in adult risk groups

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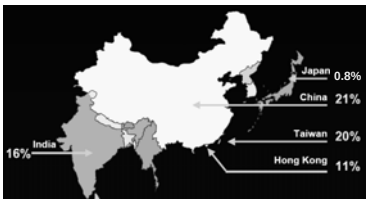
亞洲地區慢性B型肝炎感染情況



國家	流行度（％）	國家	流行度（％）
中國	>20	韓國	7.3
臺灣	15-20	新加坡	6
印度	16	菲律賓	5-16
香港	11	馬來西亞	3-5
越南	10.0	印度尼西亞	2.5-5.0
泰國	>8	日本	0.8

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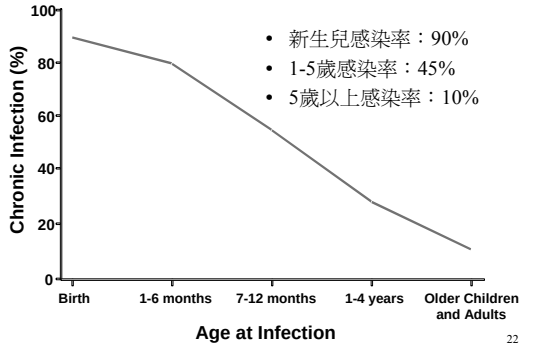
慢性B型肝炎感染年齡層



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資料來源： Centers for Desease Control and Prevention (CDC)

Signs & Symptoms

1. 最常見的症狀為**倦怠感**
2. 噁心
3. 上腹痛
4. 肌肉和關節酸痛
5. 黃疸等。
6. 生化檢查方面，血清轉胺(GOT/GPT)通常都會升高。

   臨床上將GPT升高分為三級：

   1）正常值三倍以下(<100U/L)：輕度發炎

   2）三至十倍(100-400U/L)：中度發炎

   3）十倍以上(>400U/L)：重度發炎。
7. 其它如血清膽色素、白蛋白和鹼性磷酸，在嚴重時也會異常。

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Lab data

1. AST/ALT(GOT/GPT)：代表的是肝細胞受到傷害的程度。
2. ALP(鹼性磷酸酶)：若ALP顯著升高時，即應高度懷疑為膽道阻塞。
3. Bilirubin (total/direct)(膽紅素)：當溶血過多、肝細胞有障礙或是膽道阻塞的情況下，都可能有Bilirubin上升的情形。
4. Albumin(血清白蛋白)：在肝細胞合成，所以當肝細胞的合成功能產生障礙時，血清的Albumin濃度下降。

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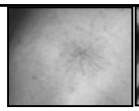
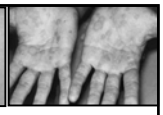
Diagnosis

1. 黃疸（罹膜或皮膚）：慢性肝炎的急性發作期常見。
2. 手掌紅斑。
3. 蜘蛛斑：通常位在前胸，nipple line以上，往往和estrogen的代謝有關。
4. 分布在腹部肚臍周圍擴張的靜脈
5. 腹水
6. 肝臟腫大或變小的肝臟（因為肝硬化）
7. 脾臟腫大：常見於肝硬化，病人的肝臟變小。

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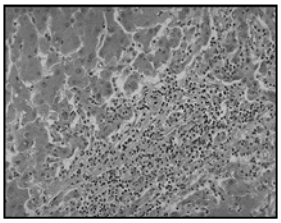
Biopsy

1. 確認診斷：例如實驗室檢驗到發現有B型肝炎表面抗原陽性或C型肝炎抗體陽性，可做切片再確認是否有慢性肝炎。
2. 猜測可能病因：不同原因引起的慢性肝炎，可能有其特殊的病理變化。
3. 發炎程度
4. 纖維化的程度
5. 確認肝硬化。
6. 評估治療。



Pathology

慢性肝炎之組織學變化：門脈區有**單核發炎細胞浸潤**

- 如果發炎細胞已**逾越門脈區外圍**，由肝細胞連成的限制板(limiting plate)，即造成**粥狀壞死**(piecemeal necrosis)。若有纖維化產生，將增加其嚴重性。
- 有時也會有類似急性肝炎的組織學變化，是以**肝小葉的發炎與壞死表現**為主，而會造成肝小葉的**局部壞死**(focal necrosis)。
- 若是相當數量的鄰近肝細胞同時壞死，可造成**融合性壞死**使肝小葉的網狀架構發生塌陷，肝內之血管系統互相連絡，形成**橋連壞死**(bridging necrosis)。
- 肝硬化是指**肝臟全面性的纖維化併結節**形成，正常的肝臟結構不能明確的辨視，這是慢性肝炎後的結果。

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Chronic hepatitis

1. 傳統上依肝臟組織病理型態，將慢性肝炎分為：
   1) 慢性持續性肝炎(CPH)
   2) 慢性小葉性肝炎(CLH)
   3) 慢性活動性肝炎(CAH)
2. 「**慢性持續性肝炎**」：為**門脈**的慢性發炎，並無粥狀壞死和纖維化，代表較為良性的發炎。
3. 「**慢性小葉性肝炎**」：門脈區僅有輕微變化，但於**肝小葉中**有局部小範圍的壞死細胞，可見**局部壞死**(focalne ncrosis)。
4. 「**慢性活動性肝炎**」：發炎細胞**已超過門脈外圍的限制板**，造成**粥狀壞死**，代表發炎較為嚴重，可能發展為肝硬化。

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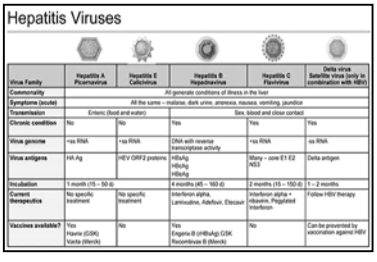
Etiology

1、慢性型B肝炎：DNA病毒，體液傳染，80~90%
2、慢性型D肝炎：RNA病毒，體液傳染(併發在B型肝炎裡)
3、慢性型C肝炎：RNA病毒，體液傳染，9~10%
4、自體免疫型肝炎
5、藥物相關
6、Wilson's disease

Hepatitis Viruses



virus Family	Hepatitis A Picornavirus	Hepatitis E Calicivirus	Hepatitis B Hepadnavirus	Hepatitis C Flavivirus	Delta virus Satellite virus (only in combination with HBV)
Commonality	All generate conditions of illness in the liver				
Symptoms (acute)	All the same - malaise, dark urine, anorexia, nausea, vomiting, jaundice				
Transmission	Enteric (food and water)		Sex, blood and close contact		
Chronic condition	No	No	Yes	Yes	Yes
Virus genome	+ss RNA	+ss RNA	DNA with reverse transcriptase activity	+ss RNA	-ss RNA
Virus antigens	HA Ag	HEV ORF2 proteins	HBsAg HBcAg HBeAg	Many – one E1 E2 NS3	Delta antigen
Incubation	1 month (15 – 50 d)		4 months (45 – 160 d)	2 months (15 – 150 d)	1 – 2 months
Current therapeutics	No specific treatment	No specific treatment	Interferon alpha, Lamivudine, Adefovir, Etecavir	Interferon alpha + ribavirin, Pegylated Interferon	Follow HBV therapy
Vaccines available?	Yes Havrix (GSK) Vaxta (Merck)	No	Yes Engerix B (rHBsAg) GSK Recombivax B (Merck)	No	Can be prevented by vaccination against HBV

Etiology

(一)慢性型D肝炎：須藉由Ｂ型肝炎病毒外套才能完成他的複製，而病毒外套的作用是讓其能進出肝細胞。

(二)自體免疫型肝炎：
1.肝臟細胞通常會有長期的壞死與發炎現象
2.易在短時間內變成肝硬化與肝衰竭
3.排除其他肝炎，找出血液中的自體抗體(ANCA)
4.女性為主

(三)藥物造成的肝臟損傷：
1.直接傷害：代謝的產物具有肝毒性，吃越多傷害越大，像：普拿疼。
2.特異體質的反應：又分metabolically 代謝性、immunologically免疫性。

(四)Wilson's disease：
肝細胞裡的高基氏體上的運輸蛋白產生突變，造成體內的銅離子在肝、腦、眼過量堆積。

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Hepatitis B

1.急性HBV感染：

- 2%→ 猛爆性肝炎
- 98%→ 慢性肝炎

【新生兒(90~95%)、幼兒(25%)、成人(5~10%)】

※是否會變成慢性感染，主要取決於**年齡**和**免疫力**。

2.慢性肝炎→致命進展性肝衰竭→肝癌→死亡

肝硬化→無代償性肝硬化

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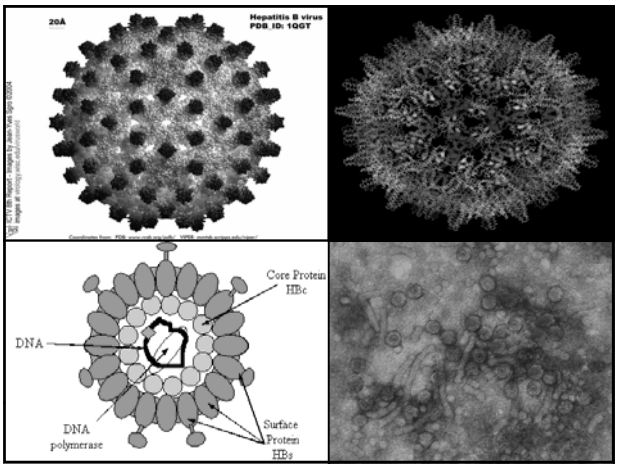

Antigen Test

※表示感染B型肝炎病毒的各種狀態提供診斷的依據。

Antigen	Monitor for
HbsAg（肝炎病毒表面抗原）	體內有B型病毒存在。
HbeAg（肝炎病毒e-抗原）	病毒的增殖旺盛、感染力強、傳染性高
anti-HBs（肝炎病毒表面抗體）	感染過B型肝炎病毒或疫苗接種有抗體，不會再感染。
anti-HBe（肝炎病毒e-抗體）	病毒的增殖低弱或感染力低。
anti-HBc（肝炎病毒核心抗體）	感染過或體內有B型病毒存在。

Process of hepatitis B

1.**Immune tolerance(免疫容忍期)**：

(1)小孩時感染病毒(垂直感染)。

(2)血清的HBeAg(ｅ抗原)陽性，B型肝炎病毒在肝細胞中大量複製，HBV的DNA濃度頗高。

(3)血清GOT、GPT值正常；輕微的慢性發炎

2.**Immune clearance(免疫清除期)**：

(1)到了10~30歲，辨認到病毒，所以**免疫反應增強**，T淋巴球攻擊被B型肝炎病毒感染的**肝細胞**，顯示CAH (慢性活動性肝炎)或CLH (慢性小葉性肝炎)。

(2)常伴有肝炎的急性發作和ｅ抗原的seroconversion(血清轉換)【即HBeAg變成Anti-HBe】；AST/ALT上升，HBV的DNA濃度下降。

(3)因為**反覆發炎**，可能會產生**肝硬化**，甚至**肝癌**。大多會復原，進入第三個時期(這樣的帶原者稱為健康帶原)。

3.**Residual Intergrated(嵌入或殘存期)**：

血清GOT、GPT值正常，ｅ抗原陰性，ｅ抗體陽性，HBV的DNA嵌鑲於肝細 胞DNA內；肝組織切片可顯示輕微變化或不活動性肝炎。

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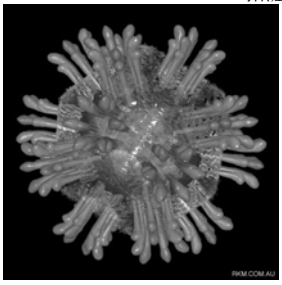
Infection of hepatitis C

急性C型肝炎→ 25%有症狀 → 10~20%恢復

75%無症狀 → 80~90%慢性感染



60~70%慢性肝炎(10年)

20~30%肝硬化(20年)

5~15%肝癌 (30年)

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Comparison of hepatitis B & C

1.C肝臨床**症狀較輕**：但**C型肝炎**在感染之後大多會演變成**慢性肝炎、肝硬化，**與**原發性肝癌**密切相關。

2.C肝**傳染力較低**：在C型肝炎的病人內發現每C.C.大約只有10的4-6次方的病毒；而B型肝炎則是每C.C.動輒10的8-10次方的病毒量，所以可能因為病毒較少的關係，C型肝炎的傳染力比較差一點。

3.**年齡較大**：C肝在成年人變成慢性肝炎較B肝多很多。

4.**輸血史較多**：

5.血清白蛋白及膽固醇值較低

6.臨床症狀較輕：C肝常常沒有症狀，所以病人不會來看醫生，加上他的病程很快，就算病人定期檢查，也認為肝指數不會太高，因此就把他忽略了，所以是非常危險的。

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Drugs for hepatitis in current

- 目前經由美國FDA核准上市的B型肝炎用藥可分為干擾素(interferon)和核苷類似物(nucleotide analogue):
  - **Interferon**
    - Intron A
      - 主要成份為recombinant interferon α-2b，由Schering-Plough製造
  - **Nuleotide analogue**
    - Epivir-HBV
      - 主要成份為lamivudine，簡稱3TC，由GlaxoSmithKline製造
    - Hepsera
      - 主要成份為adefovir dipivoxil，由Gilead Sciences製造

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Drugs for hepatitis in current -Intron A

- **簡介：**Intron A中interferon α-2b的作用是使B 型肝炎病毒由高活性變成低活性，可以降低日後發生肝硬化甚至肝癌的機會
- **作用機制：**Interferon由受病毒感染的宿主細胞產生的一種糖蛋白， 能作用在其他宿主細胞上，刺激未受感染的細胞，使細胞進入抗病毒狀態，產生許多antiviral effector molecules，這些分子會改變細胞表面蛋白質抗原的組成，使得病毒不易感染細胞；另一方面受干擾素刺激的細胞會活化RNAse-L，將mRNA分解；還能磷酸化eIF2，降低轉譯的效率，干擾病毒蛋白質的合成。關於其作用機制尚有很多不清楚的地方。
- **副作用：**產生像感冒般的症狀，掉頭髮，情緒不穩定，抑制骨髓造血功能，肝衰竭等等

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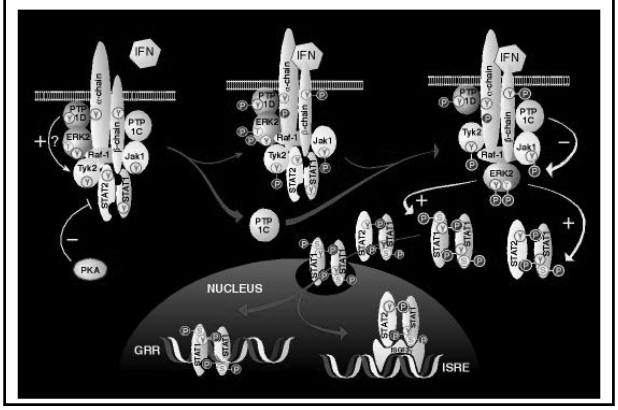
Interferon Signal Transduction



Drugs for hepatitis in current -Epivir-HBV

- **簡介：**Lamivudine是一個化學合成的核苷類似物(nucleoside analogue)，本來是用來治療愛滋病毒的，在較低劑量時也能對抗B型肝炎病毒，故而有醫師將之用來治療慢性B型肝炎
- **作用機制：**Lamivudine (2', 3'-dideoxy,3'-thiacytidine)是可以抑制病毒反轉錄酵素之藥物(NRTI, nucleotide analog reverse transcriptase inhibitor)，可以阻斷病毒DNA的合成而抑制病毒的複製
- **副作用：**極少，但較易產生抗藥性

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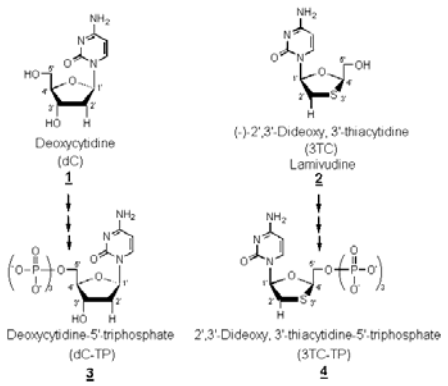

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Drugs for hepatitis in current -Adefovir Dipivoxil

- **簡介：**Adefovir原本是一種治療愛滋病的藥物，後來研究發現對於抑制B肝病毒也有療效。Adefovir可抑制B型肝炎病毒複製，改善肝功能指數及肝組織發炎
- **作用機制：**Adefovir dipivoxil (9-(2-phoshonyl-methoxyethyl)-adenine) 是一個deoxyadenosine monophoshate analogue，可以在病毒的複製時進行chain termination。它是一個化學合成的核苷酸類似物(nucleotide analogue)
- **副作用：**極少，產生抗藥性的機率低，但長期服用可能產生腎臟方面的問題

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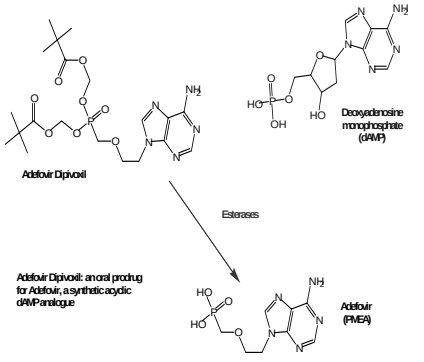

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Drugs for HBV in US

Table I FDA-Approved Drugs for the Pharmacotherapy of HBV Infection

Drug family	Drug	Commercial name (Company)	FDA approval[a]	Dosage forms	Adult dose
Immunomodulators (IMPs)	IFN-α2B	Intron-A® (Schering Corporation)	1992	Powder for injection (10 MIU/mL 18 MIU/mL; 50 MIU/mL), solution for injection in vials (10 MIU single dose, 18 and 25 MIU multidose), solution in multidose pens (3 MIU)	5 to 10 MIU thrice a week, for 16–24 weeks
	PEG IFN-α2A	Pegasys® (Roche)	2005	Solution for injection in vials (180 μg/mL), solution for injection in prefilled syringes (180 μg/0.5 mL)	180 μg s.c. once weekly for 48 weeks
Nucleos(t)ide analogues (NAs)	Lamivudine	Epivir-HBV® (GlaxoSmithKline)	1998	Tablets (100 mg)	100 mg once daily
	Adefovir Dipivoxil	Hepsera® (Gilead Sciences)	2002	Tablets (10 mg)	10 mg once daily
	Entecavir	Baradude® (Bristol-Myers Squibb)	2005	Tablets (0.5 mg and 1 mg); Oral Solution (0.05 mg/mL)	0.5–1 mg once daily
	Telbivudine	Tyzeka® (Novartis)	2006	Tablets (600 mg)	600 mg once daily
	Tenofovir Disoproxil Fumarate	Viread® (Gilead Sciences)	2008	Tablets (300 mg)	300 mg once daily

Pharm Res
DOI 10.1007/s11095-010-0112-z

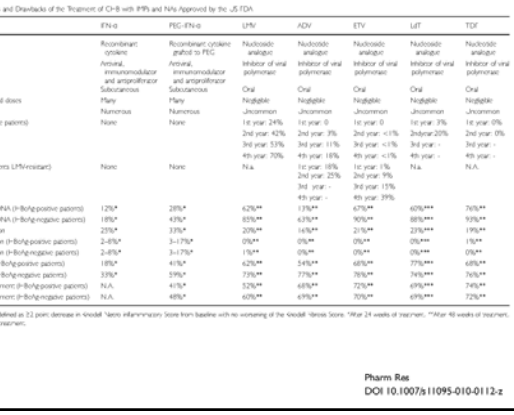

Table II Advantages and Drawbacks of the Treatment of CHB with IFNs and NAs Approved by the US FDA

	IFN-α	PEG-IFN-α	LMV	ADV	ETV	LdT	TDF
Properties	Recombinant cytokine	Recombinant cytokine grafted to PEG	Nucleoside analogue	Nucleoside analogue	Nucleoside analogue	Nucleoside analogue	Nucleotide analogue
Mechanism of action	Antiviral, immunomodulator and antiproliferator	Antiviral, immunomodulator and antiproliferator	Inhibitor of viral polymerase	Inhibitor of viral polymerase	Inhibitor of viral polymerase	Inhibitor of viral polymerase	Inhibitor of viral polymerase
Route	Subcutaneous	Subcutaneous	Oral	Oral	Oral	Oral	Oral
Side effects at licensed doses	Many	Many	Negligible	Negligible	Negligible	Negligible	Negligible
Contra-indications	Numerous	Numerous	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon
Drug-resistance (naive patients)	None	None	1st year: 24% 2nd year: 42% 3rd year: 53% 4th year: 70%	1st year: 0 2nd year: 3% 3rd year: 11% 4th year: 18%	1st year: 0 2nd year: <1% 3rd year: <1% 4th year: <1%	1st year: 3% 2nd year:20% 3rd year: - 4th year: -	1st year: 0% 2nd year: 0% 3rd year: - 4th year: -
Drug-resistance (patients LMV-resistant)	None	None	N.a.	1st year: 18% 2nd year: 25% 3rd year: - 4th year: -	1st year: 1% 2nd year: 9% 3rd year: 15% 4th year: 39%	N.a.	N.A.
Undetectable HBV DNA (HBeAg-positive patients)	12%*	28%*	62%**	13%**	67%**	60%***	76%**
Undetectable HBV DNA (HBeAg-negative patients)	18%*	43%*	85%**	63%**	90%**	88%***	93%**
HBeAg seroconversion	25%*	33%*	20%**	16%**	21%**	23%***	19%**
HBeAg seroconversion (HBeAg-positive patients)	2–8%*	3–17%*	0%**	0%**	0%**	0%***	1%**
HBeAg seroconversion (HBeAg-negative patients)	2–8%*	3–17%*	1%**	0%**	0%**	0%***	0%**
ALT normalization (HBeAg-positive patients)	18%*	41%*	62%**	54%**	68%**	77%***	68%**
ALT normalization (HBeAg-negative patients)	33%*	59%*	73%**	77%**	78%**	74%***	76%**
[†]Histological improvement (HBeAg-positive patients)	N.A.	41%*	52%**	68%**	72%**	69%***	74%**
[†]Histological improvement (HBeAg-negative patients)	N.A.	48%*	60%**	69%**	70%**	69%***	72%**

[†] "Histologic response defined as ≥2 point decrease in Knodell "necro-inflammatory" Score from baseline with no worsening of the Knodell "fibrosis" Score. *After 24 weeks of treatment. **After 48 weeks of treatment. ***After 52 weeks of treatment.
N.A.: not available.
N.a.: not applicable.

Pharm Res
DOI 10.1007/s11095-010-0112-z

Drugs for HBV in Taiwan

藥品	干安能 (Lamivudine)	干適能 (Adefovir)	貝樂克 (Entecavir)	喜必福 (Telbivudine)
包裝規格	100 毫克/顆	10 毫克/顆	0.5、1 毫克/顆	600 毫克/顆
健保給付	通過慢性 BC 型肝炎治療試辦計畫核准後，給付 12-18 個月。			
價錢	90-100 元/顆	180-220 元/顆	0.5 毫克：250 元/顆；1 毫克：350 元/顆	160-180 元/顆
劑量	1 顆 / 天	1 顆 / 天	1 顆 / 天	1 顆 /天
副作用	胃腸不適、血液病變、頭痛、掉髮、周邊神經炎 (停藥可改善)	腎臟毒性 (停藥可改善)	頭痛、疲倦、腹瀉 (停藥可改善)	眩暈、頭痛、腹瀉、皮疹、疲倦 (停藥可改善)
懷孕分級	C	C	C	B
抗藥性	使用 5 年後發生機率 69%	使用 5 年後發生機率 29%	使用 5 年後發生機率 1.2% ◎已產生干安能抗藥性者：第五年：50%	使用 2 年後發生機率 22%

Resistant of Anti-viral Drugs

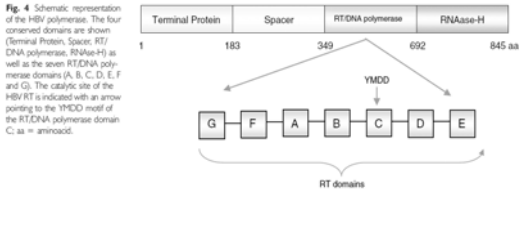

Fig. 4 Schematic representation of the HBV polymerase. The four conserved domains are shown (Terminal Protein, Spacer, RT/DNA polymerase, RNAse-H) as well as the seven RT/DNA polymerase domains (A, B, C, D, E, F and G). The catalytic site of the HBV RT is indicated with an arrow pointing to the YMDD motif of the RT/DNA polymerase domain C; aa = aminoacid.

Pharm Res
Received: 15 December 2009 / Accepted: 1 March 2010 DOI 10.1007/s11095-010-0112-z

NOVEL ANTI-HBV DRUG CANDIDATES

- Zinc Finger Proteins (ZFPs)
  - *Cys2His2 DNA-binding proteins that can be designed to target novel DNA sequences with high specificity and affinity.*
- Nitazoxanide
  - Recent data have shown an eventual role as therapy for influenza virus infection, chronic hepatitis C virus infection and CHB.
- Nosiheptide
  - a poorly-water-soluble natural polypeptide antibiotic that has been shown to inhibit hepatitis B virusDNA, HBsAg and HBeAg secreted by an HBV-transfected cell line (HepG2.2.15) (114).
- Small Interfering RNA (siRNA)
  - RNA interference (RNAi) is a natural conserved process by which double-stranded siRNA induces sequence-specific, post-transcriptional gene silencing by binding to its complementary mRNA and triggering its elimination.

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NOVEL ANTI-HBV DRUG CANDIDATES

- Heteroarylpyrimidines (HAP)
  - In 2003, a new group of compounds that specifically targets the encapsidation step before viral replication occurs has been identified.
- Phenopropenamides
  - Another group of compounds that would inhibit the encapsidation step are the phenopropenamides
- Antisense Oligonucleotides (asODN)
  - agents that produce their effects through an antisense mechanism offer the possibility of developing highly specific alternatives to traditional pharmacological antagonists, thereby providing a novel class of therapeutic compounds that act at the level of gene expression.

Alternative Drugs for hepatitis

真珠草清除B肝病毒具潛力

- 真珠草（Phyllanthus urinaria）是一年生的草本植物
- 依據《本草綱目》〈拾遺〉中記載，真珠草具有平肝清熱與利水解毒的效果
- 韓國、台灣中南部、東部乾燥山區
- 韓國鄭泰浩博士
- 2002年六月，真珠草更在韓國完成第三階段的臨床試驗

資料來源：生技時代 Vol. 11 September 2002

Alternative Drugs for hepatitis

真珠草清除B肝病毒具潛力

- 治療B肝
  - 抑制HBV逆轉錄酶(HBV reverse transcriptase)及HBV DNA聚合酶(HBV DNA polymerase)作用

- 保肝
  - 保護肝細胞膜、抗脂質過氧化、促進蛋白質合成、調節免疫系統
- 『肝淨』 2003年4月 獲中華民國衛生署批准臨床試驗。

Conclusion

以 B 肝而言

1. 注射干擾素(免疫調節劑)

   根據國內研究顯示可以減少肝癌發生機會。每週打 3 次；現在還有新的長效型「干擾素」，每週只要打一次針即可。

2. 口服「干安能」®（**Lamivudine**）

   可以減緩B型肝炎併肝硬化的患者惡化成為末期肝病的速度及減低併發肝癌的機會，不過長期使用干安能所伴隨的抗藥性仍是目前使用本藥的一大顧忌。目前健保給付干安能〔Lamivudine〕最高18個月，患者每月僅需部分負擔一千元。

3. 口服「肝適能」®（**Adefovir**）

   因抗藥性較低，是干安能產生抗藥性後的另一選擇用藥，或者可合併使用。

C 肝治療

比 B 肝治療更方便、有效，每週打一次長效型「干擾素」合併口服「雷巴比林 (Ribavirin)」即可，連打 24 週。

Conclusion

中西醫比較

	西藥	中藥
作用機制	降低活性	增強免疫力
治療方式	注射、口服（源自治療AIDS）	口服
副作用	較嚴重	無相關資料
治療對象的選擇	有	有

Vaccine of HBV

Vaccine of HBV -development

- 1970s—
  將健康帶原者的血漿經過處理以後，純化出B型肝炎表面抗原以製成疫苗，打入人體以後刺激產生表面抗體，以達到保護的目的。這種血漿製疫苗（plasma-derived vaccine）含有22 nm大小的B型肝炎表面抗原顆粒，其成份只是病毒表面的蛋白質，本身不含有完整的病毒，所以不具有感染性。
- 1980s—
  基因重組疫苗—將B型肝炎病毒的*S*基因，選殖到可以在酵母菌中表現蛋白的plasmid中，再大量培養酵母菌以製造出表面抗原，然後純化這些抗原做成疫苗。

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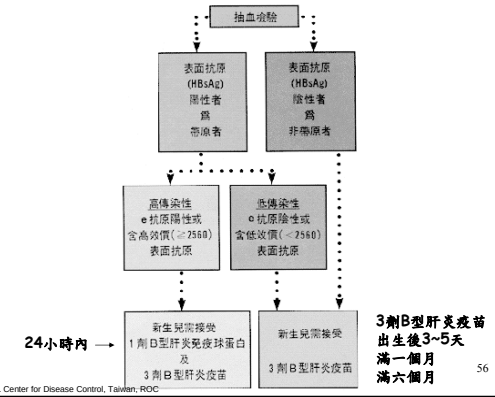
新生兒B型肝炎疫苗接種



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Vaccine of HBV -protective efficacy

- 一般而言，疫苗約可持續五年的效力。
- 觀察e抗原陽性母親所生的嬰兒，在接種疫苗以後免於受到感染的比率。

(1)同時注射B型肝炎免疫球蛋白 (hepatitis B immune globulin) 與第一劑B型肝炎疫苗，其保護效力都在 80% 到 100% 之間。

(2)不注射B型肝炎免疫球蛋白，則保護效力會下降到 46-75%。

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Vaccine of HBV in current

- B型肝炎疫苗是全球疫苗產業的主要產品之一 ，目前市場值約14億美金，佔全球疫苗市場的35%
- 主要廠商市佔率：GlaxoSmithKline 25%, Pasteur-Merieux-MSD 24%, and Aventis 18%

單位：百萬美金

產品名稱	上市時間	廠商	銷售額(2003年)
Pediarix	2003	Glaxo Smith Kline	$684
Twinrix	2001		
Engerix B	1982		
Recombivax HB	1999	Aventis Pasteur and Merck & Co.	$73.6
COMVAX	1996		
Hepavax-Gene	1996	Rhein Biotech	***
Bio-Hep B	2001	Bio-Technology General Corp	***
Hepagene	1999	Cell Tech R&D Inc.	***

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*** Data not available

資料來源： GSK 2003 Financial Report
Merk 2003 Financial Report

Liver failure -Hepatitis to Cirrhosis

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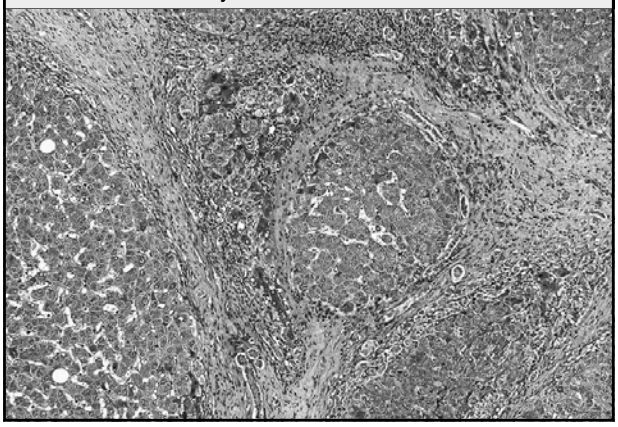
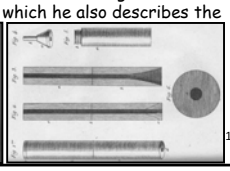
Hepatic Cirrhosis



Introduction

- Cirrhosis is a chronic degenerative disease in which normal liver cells are damaged and are then replaced by scar tissue.
- Cirrhosis is most commonly caused by **alcoholism**, hepatitis B and C, and **fatty liver disease** but has many other possible causes. Some cases are idiopathic, i.e., of unknown cause.
- The word "cirrhosis" derives from Greek κιρρός, meaning **tawny** (the orange-yellow colour of the diseased liver). While the clinical entity was known before, it was **René Laennec** who gave it the name "**cirrhosis**" in his 1819 work (in which he also describes the stethoscope).

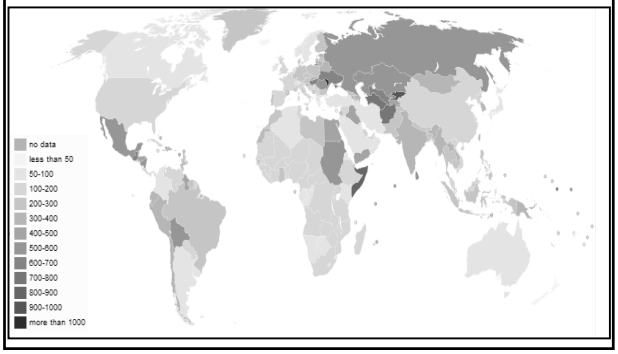
Introduction


Description

- Cirrhosis changes the structure of the liver and the blood vessels that nourish it. The disease reduces the liver's ability to manufacture proteins and process hormones, nutrients, medications, and poisons.
- Cirrhosis gets worse over time and can become potentially life threatening. This disease can cause:
  - **excessive bleeding (hemorrhage)**
  - **impotence**
  - **liver cancer**
  - **coma due to accumulated ammonia and body wastes (liver failure)**
  - **sepsis (blood poisoning)**
  - **death**
- Cirrhosis is the seventh leading cause of disease-related death in the United States. It is the third most common cause of death in adults between the ages of 45 and 65. It is twice as common in men as in women.
- The disease occurs in more than half of all malnourished chronic alcoholics, and kills about 25,000 people a year.
- In **Asia** and **Africa**, however, most deaths from cirrhosis are due to chronic **hepatitis B**.

Cirrhosis of the liver world map

- DALY - WHO2004



How common is hepatic cirrhosis in Taiwan?

附表 1、全國勞工與全國人口十大死亡原因統計- 97 年

順位	全國勞工 死亡原因	死亡人數	每十萬人口死亡率	96 年死亡率	全國人口 死亡原因	死亡人數	每十萬人口死亡率	96 年死亡率
	所有死亡原因	12,165	130.10	185.93	所有死亡原因	142,283	618.68	608.17
1	惡性腫瘤	5,153	55.11	75.44	惡性腫瘤	38,913	169.20	175.87
2	事故傷害	1,697	18.15	27.26	心臟疾病	15,726	68.38	56.74
3	心臟疾病	863	9.23	12.85	腦血管疾病	10,663	46.37	56.18
4	慢性肝病及肝硬化	705	7.54	11.56	肺炎	8,661	37.66	25.72
5	腦血管疾病	650	6.95	10.64	糖尿病	8,036	34.94	44.64
6	糖尿病	533	5.70	9.09	事故傷害	7,077	30.77	31.11
7	腎炎腎徵候群及腎性病變	248	2.65	3.71	慢性下呼吸道疾病	5,374	23.37	
8	肺炎	163	1.74	2.03	慢性肝病及肝硬化	4,917	21.38	22.52
9	傳染病及寄生蟲病	127	1.36	1.96	自殺	4,128	17.95	17.16
10	高血壓性疾病	90	0.96	0.96	腎炎腎病症候群及腎病變	4,012	17.45	22.25
	其他	1,936	20.99	20.70	其他	34,776	151.22	147.34

How common is hepatic cirrhosis in Taiwan?

附表 3、勞工與全國人口癌症排序比較

民國九十七年全國勞工 死亡原因	死亡數	死亡率	死因百分比	96 年死亡率	民國九十七年全國人口 死亡原因	死亡數	死亡率	死因百分比	96 年死亡率
全部惡性腫瘤	5,153	55.11	100.00	75.44	全部惡性腫瘤	38,913	169.2	100.0	175.87
1.肝癌	1,090	11.66	21.15	16.43	肺癌	7,777	33.82	19.99	34.88
2.肺癌	740	7.91	14.36	10.89	肝癌	7,651	33.27	19.66	34.07
3.口腔癌	514	5.50	9.97	7.95	結腸直腸癌	4,266	18.55	10.96	19.50
4.結腸直腸癌	459	4.91	8.91	6.18	女性乳癌	1,541	13.54	3.96	13.71
5.女性乳癌	387	4.14	7.51	4.81	胃癌	2,292	9.97	5.89	10.80
6.食道癌	307	3.28	5.96	3.91	口腔癌	2,218	9.64	5.70	10.09
7.胃癌	235	2.51	4.56	3.74	攝護腺癌	892	7.68	2.29	8.65
8.鼻咽癌	170	1.82	3.30	2.29	子宮頸癌	710	6.24	1.82	7.36
9.攝護癌	147	1.57	2.85	2.18	食道癌	1,433	6.23	3.68	6.27
10.白血病	132	1.41	2.56	0.39	攝護癌	1,364	5.93	3.51	5.91
11.膽囊癌	128	1.37	2.48	1.91	非何杰金淋巴癌	900	3.91	2.31	5.66
12.非何杰金淋巴癌	128	1.37	2.48	2.51	白血病	878	3.82	2.26	3.76
13.子宮頸癌	121	1.29	2.35	1.43	卵巢癌	406	3.57	1.04	3.58
14.卵巢癌	76	0.81	1.47	1.06	鼻咽癌	748	3.25	1.92	3.48
15.腎臟癌	69	0.74	1.34	1.13	膀胱癌	689	3.00	1.77	3.51

How common is hepatic cirrhosis in Taiwan?

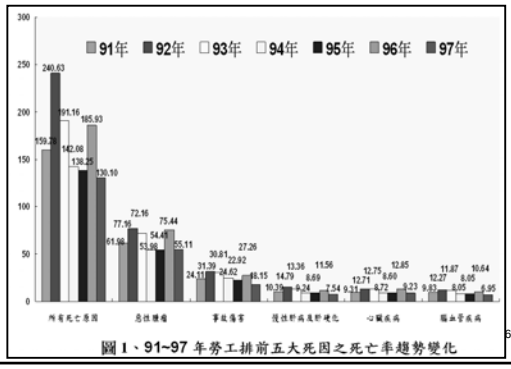


圖 1、91~97 年勞工排前五大死因之死亡率趨勢變化

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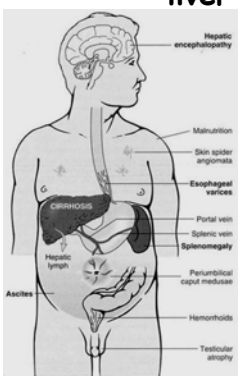
Cirrhosis result of many chronic liver disorders



- Severe damage to structure & function of normal cells.
- Inhibits normal blood flow
- Decrease in functional hepatocytes
- Results in portal hypertension & ascites.
- Portal systemic shunting
  - □Blood bypasses the liver via shunt, thus bypassing **detoxification.**
  - □Toxins remain in circulating blood
  - □Neurtoxic substances can precipitate hepatic encephalopathy

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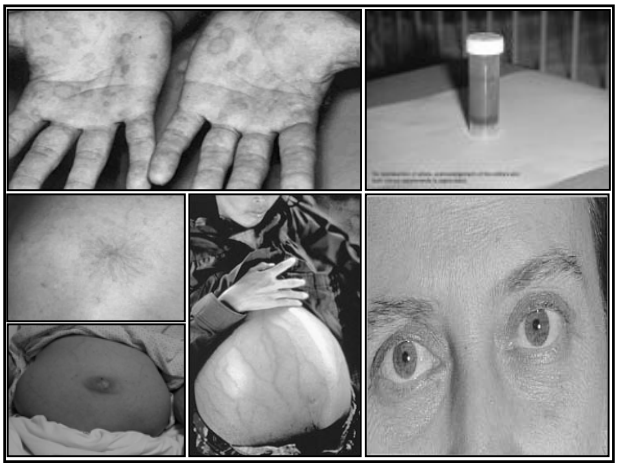


Types of Shunts

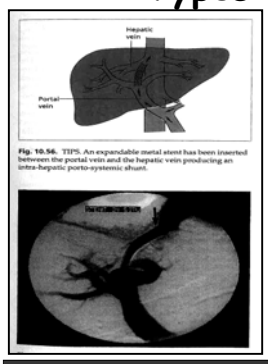
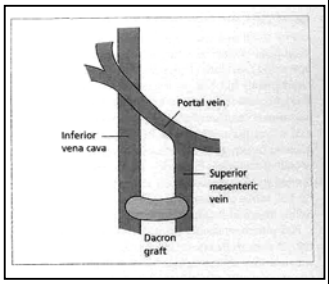


Fig. 10.56. TIPS. An expandable metal stent has been inserted between the portal vein and the hepatic vein producing an intra-hepatic porto-systemic shunt.

TIPS (Transjugular intrahepatic portosystemic shunt)



Surgical shunt

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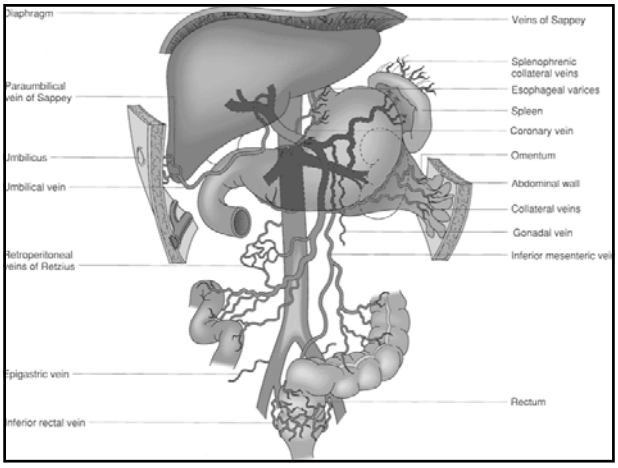

Signs and symptoms

- constipation
- diarrhea
- dull abdominal pain
- fatigue
- indigestion
- loss of appetite
- nausea
- vomiting
- weakness
- weight loss
- slurred speech
- tremors

- anemia
- bleeding gums
- decreased interest in sex
- fever
- fluid in the lungs
- hallucinations
- lethargy
- lightheadedness
- muscle weakness
- musty breath
- painful nerve inflammation (neuritis)

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Types of cirrhosis

- Portal or nutritional cirrhosis is the form of the disease most common in the United States. About 30-50% of all cases of cirrhosis are this type. Nine out of every 10 people who have nutritional cirrhosis have a history of alcoholism. Portal or nutritional cirrhosis is also called Laënnec's cirrhosis.
- Biliary cirrhosis is caused by intra-hepatic bile-duct diseases that impede bile flow. Bile is formed in the liver and is carried by ducts to the intestines. Bile then helps digest fats in the intestines. Biliary cirrhosis can scar or block these ducts. It represents 15-20% of all cirrhosis.
- Various types of chronic hepatitis, especially hepatitis B and hepatitis C, can cause postnecrotic cirrhosis. This form of the disease affects up to **40%** of all patients who have cirrhosis.
- Metabolism cirrhosis : Disorders like the inability to metabolize iron and similar disorders may cause pigment cirrhosis (hemochromatosis), which accounts for 5-10% of all instances of the disease.
- Cardiogenic cirrhosis 5%
- Parastic cirrhosis 1~3%

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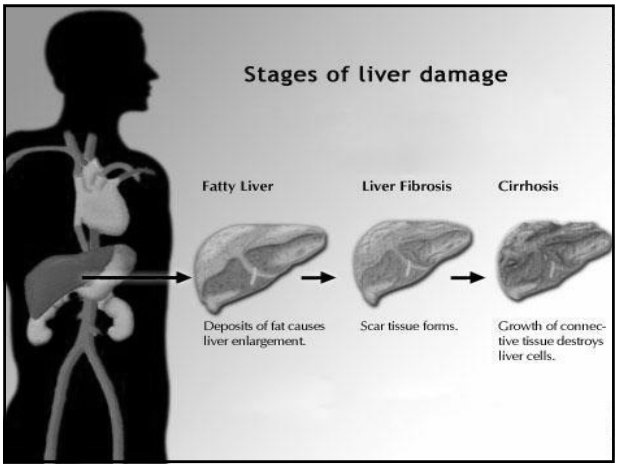
Others causes hepatic cirrhosis

- Liver injury, reactions to prescription medications, exposure to toxic substances, and repeated episodes of heart failure with liver congestion can cause cirrhosis. The disorder can also be a result of diseases that run in families (inherited diseases) like:
  - a lack of a specific liver enzyme (alpha1-antitrypsin deficiency)
  - the absence of a milk-digesting enzyme (galactosemia)
  - an inability to convert sugars to energy (glycogen storage disease)
  - an absorption deficit in which excess iron is deposited in the liver, pancreas, heart, and other organs (hemochromatosis)
  - a disorder characterized by accumulations of copper in the liver, brain, kidneys, and corneas (Wilson's disease)
- Obesity has recently been recognized as a risk factor in nonalcoholic hepatitis and cirrhosis. Some surgeons are recommending as of 2003 that patients scheduled for weight-reduction surgery have a liver biopsy to evaluate the possibility of liver damage.
- Poor nutrition increases a person's risk of developing cirrhosis. In about 10 out of every 100 patients, the cause of cirrhosis cannot be determined. Many people who have cirrhosis do not have any symptoms (often called compensated cirrhosis). Their disease is detected during a routine physical or when tests for an unrelated medical problem are performed.



Diagnosis

- Aminotransferases - AST and ALT are moderately elevated, with AST > ALT. However, normal aminotransferases do not preclude cirrhosis.
- Alkaline phosphatase - usually slightly elevated.
- GGT - correlates with AP levels. Typically much higher in chronic liver disease from alcohol.
- Bilirubin - may elevate as cirrhosis progresses.
- Albumin - levels fall as the synthetic function of the liver declines with worsening cirrhosis since albumin is exclusively synthesized in the liver
- Prothrombin time - increases since the liver synthesizes clotting factors.
- Globulins - increased due to shunting of bacterial antigens away from the liver to lymphoid tissue.
- Serum sodium - hyponatremia due to inability to excrete free water resulting from high levels of ADH and aldosterone.
- Thrombocytopenia - due to both congestive splenomegaly as well as decreased thrombopoietin from the liver. However, this rarely results in platelet count < 50,000/mL.
- Leukopenia and neutropenia - due to splenomegaly with splenic margination.
- Coagulation defects - the liver produces most of the coagulation factors and thus coagulopathy correlates with worsening liver disease.
- There is now a validated and patented combination of 6 of these markers as non-invasive biomarker of fibrosis (and so of cirrhosis) : Fibro Test
- Other laboratory studies performed in newly diagnosed cirrhosis may include:
  - Serology for hepatitis viruses, autoantibodies (ANA, anti-smooth muscle, anti-mitochondria, anti-LKM)
  - Ferritin and transferrin saturation (markers of iron overload), copper and ceruloplasmin (markers of copper overload)
  - Immunoglobulin levels (IgG, IgM, IgA) - these are non-specific but may assist in distinguishing various causes
  - Cholesterol and glucose
  - Alpha 1-antitrypsin

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Diagnosis

- Computed tomography scans (CT), ultrasound, and other imaging techniques can be used during diagnosis. They can help determine the size of the liver, indicate healthy and scarred areas of the organ, and detect gallstones.
- Cirrhosis is sometimes diagnosed during surgery or by examining the liver with a laparoscope.
- **Liver biopsy** is usually needed to confirm a diagnosis of cirrhosis. In this procedure, a tissue sample is removed from the liver and is examined under a microscope in order to learn more about the organ.
- A newer and less invasive test involves the measurement of **hyaluronic acid** in the patient's blood serum. As of 2003, however, the serum hyaluronic acid test is **most useful in monitoring the progress of liver disease**; it is unlikely to completely replace liver biopsy in the diagnosis of cirrhosis.

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Child-Pugh score

是利用臨床病人是否有肝昏迷、腹水，加上白蛋白、凝血酶原時間、膽紅素等三項的檢驗結果算出來的肝功能指標，總分：5-6分為A級，7-9分為B級，10-15分為C級。可以精確地評估病患的肝功能狀態，是一個非常有用的指標。

Child-Pugh score

分數	膽紅素 (mg/dl)	白蛋白 (g/dl)	凝血酶原時間延長秒數 (sec)	肝昏迷 (grade)	腹水
1	<2	>3.5	1-4	None	None
2	2-3	2.8-3.5	4-6	1-2	Mild
3	>3	<2.8	>6	3-4	Severe

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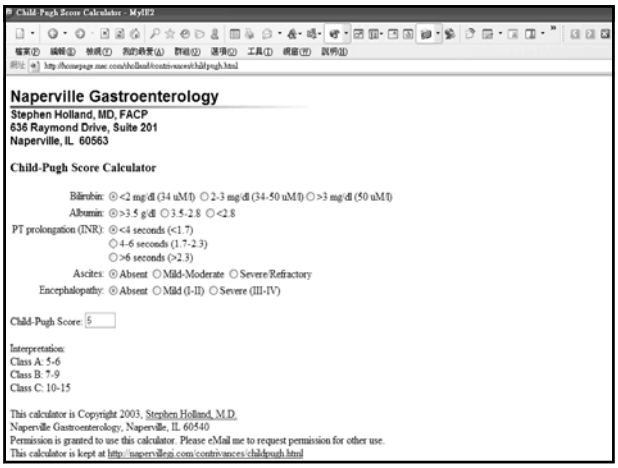

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Child-Pugh Score Calculator

Bilirubin: ⊙ <2 mg/dl (34 uM/l) ○ 2-3 mg/dl (34-50 uM/l) ○ >3 mg/dl (50 uM/l)
Albumin: ⊙ >3.5 g/dl ○ 3.5-2.8 ○ <2.8
PT prolongation (INR): ⊙ <4 seconds (<1.7) ○ 4-6 seconds (1.7-2.3) ○ >6 seconds (>2.3)
Ascites: ⊙ Absent ○ Mild-Moderate ○ Severe/Refractory
Encephalopathy: ⊙ Absent ○ Mild (I-II) ○ Severe (III-IV)

Child-Pugh Score: 5

Interpretation:
Class A: 5-6
Class B: 7-9
Class C: 10-15

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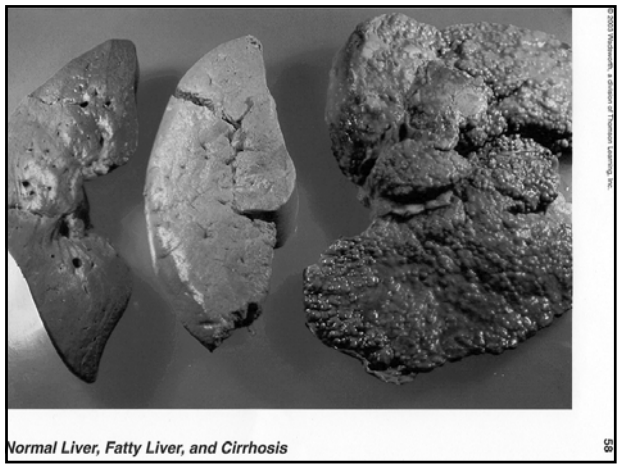
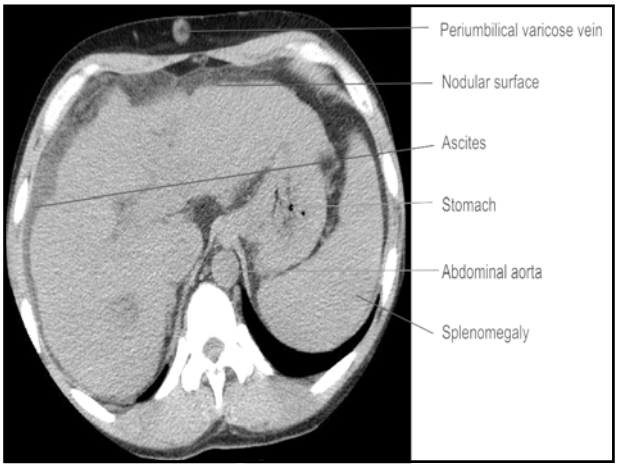
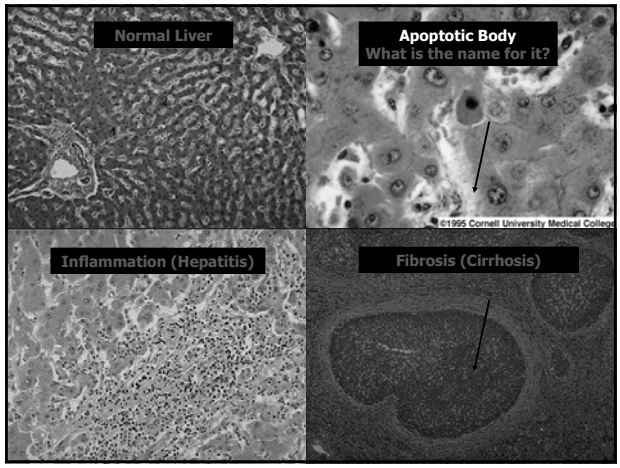
This calculator is kept at http://napervillegi.com/contrivances/childpugh.html







Treatment

- The goal of treatment is to cure or reduce the condition causing cirrhosis, prevent or delay disease progression, and prevent or treat complications.
- Salt and fluid intake are often **limited**, and **activity** is encouraged. A diet high in calories and moderately high in protein can benefit some patients.
- Tube feedings or vitamin supplements may be prescribed if the liver continues to deteriorate. Patients are asked **not to consume alcohol**.

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Medications

- Iron supplements, diuretics, and antibiotics may be used for anemia, fluid retention, and ammonia accumulation associated with cirrhosis.
- Vasoconstrictors are sometimes needed to stop internal bleeding and antiemetics may be prescribed to control nausea.
- Laxatives help the body absorb toxins and accelerate their removal from the digestive tract.
- Beta blockers may be prescribed to control cirrhosis-induced portal hypertension.
- Interferon medicines may be used by patients with chronic hepatitis B and hepatitis C to **prevent** post-hepatic cirrhosis.

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Surgery

- Medication that causes scarring can be injected directly into veins to **control bleeding** from varices in the stomach or esophagus.
- Varices may require a special surgical procedure called balloon tamponade ligation to stop the bleeding.
- It is sometimes necessary to remove diseased portions of the spleen and other organs.
- Liver transplants can benefit patients with advanced cirrhosis. However, the new liver will eventually become diseased unless the underlying cause of cirrhosis is removed.
- The incidence of liver cancer related to cirrhosis in the United States has increased 75% since the early 1990s. Partial surgical removal of the liver in patients with **early-stage** cancer of the liver appears to be as successful as transplantation, in terms of the 5-year survival rate.

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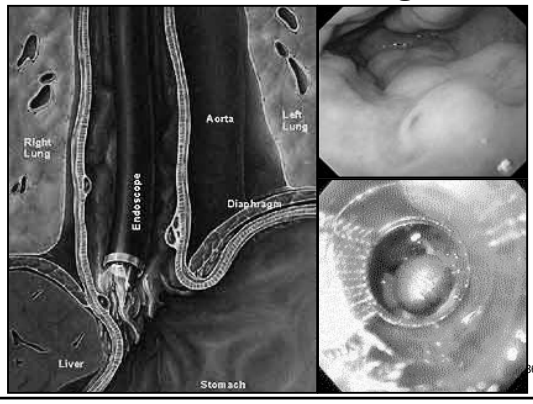
Variceal Banding



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Alternative Treatments

- Alternative treatments for cirrhosis are aimed at promoting the function of healthy liver cells and relieving the symptoms associated with the disease.
- Several herbal remedies may be helpful to cirrhosis patients.
  - Dandelion (Taraxacum officinale) and rock-poppy (Chelidonium majus) may help improve the efficiency of liver cells.
  - Milk thistle extract (Silybum marianum) may slow disease progression and significantly **improve survival rates** in alcoholics and other cirrhosis patients.
  - Practitioners of homeopathy and traditional Chinese medicine can also prescribe treatments that support healthy liver function.

中藥治療

在肝硬化的全過程均可應用中醫藥治療，在其早期（代償期）可以中醫藥治療爲主，在其晚期（失代償期）如沒有並發症出現，也可以用中醫藥治療爲主。當有並發症出現時，則需要中西醫結合治療，而其善後調理則又可以用中醫藥治療爲主。

中醫藥治療對早期病人除能改善症狀、改善肝功能外，還有抗肝硬化作用，部份病人可痊愈或長期緩解。對晚期病人則能減輕症狀，改善全身狀況，提高生存質量，阻止肝硬化進一步發展，減少並發症的發生，延長壽命，減少西藥的毒副作用。個別病人亦能痊愈或長期緩解。

中醫藥還可用於肝硬化前期病變的治療，如各種肝炎、膽道系統疾病、慢性炎症性腸病、肝纖維化等。

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肝硬化的中醫治療原則

1、合理的飲食與營養：
有利於恢複肝功能，穩定病情
高維生素及適量微量元素的飲
先兆時，應嚴格限制蛋白質食
2、改善肝功能：
中藥用辨證施治及可根據病情
五味子、丹參、冬蟲夏草、靈
3、抗肝硬化治療：
中藥辨証治療及合理選用紫甲
川芎等，西藥應用促肝細胞生
一定的效果。
4、積極防治並發症：
肝硬化失代償期並發症較多，
破裂出血、腹水、肝性腦病、
行之有較的治療方法，一般需
中藥可適當配合，起協同作用
療效。然後主要用中藥調理善

圖為活血化瘀藥材，由左上方至右依序是何首烏、川芎、莪术、赤芍、丹參、鬱金，具有抗肝纖維化的功效。

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中醫如何治療肝硬化？

⑴肝鬱脾虛型：疏肝健脾，兼以活血。柴胡疏肝散合四君子湯加減。

⑵氣滯血瘀型：疏肝理氣，活血消積。化瘀湯加減。

⑶水濕內阻型：運脾利濕，理氣行水。胃苓湯加減。

⑷瘀血阻絡型：祛瘀通絡，活血利水。膈下逐瘀湯加減。

⑸肝腎陰虛型：滋補肝腎，育陰利水。一貫煎加減。

⑹脾腎陽虛型：健脾溫腎，化氣行水。附子理中湯合五苓散加減。

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Prevention of complications

門脈高壓及食道靜脈曲張：

預防：

1. 避免用力的動作。會增加腹壓及胸壓。
2. 避免進食粗糙食物，會造成食道損傷。
3. 避免進食辛辣食物，會造成食道黏膜損傷。
4. 有出血現象前應擬定一套緊急救護計劃。
5. 避免服用阿斯匹靈。

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腹水及水腫：

預防：

1. 服用醫師所開的藥物，例如：利尿劑、白蛋白。
2. 採取低鈉飲食及限制液體的攝取。
3. 除非是有肝性腦病變否則可攝取適量蛋白質。
4. 每3天磅體重，監測體液是否滯留。
5. 觀察是否有水腫現象產生。
6. 有腹水產生的病人，可採半坐臥或高坐臥位，以利呼吸。
7. 有出現下肢水腫情形，鼓勵活動和將下肢抬高，以促進靜脈回流。

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肝性腦病變：

預防：

1. 意識改變時，減少食物中蛋白質的攝取。
2. 按時定量服用藥物，例如：Neomycin、Lactulose以降低腸內道細菌產生氨。
3. 有肝昏迷症狀的病人：

a. 臥床休息時予床欄拉上，並在床欄加上護墊，防碰撞引起損傷。

b. 協助口腔護理以減輕肝臭的異味。

c. 安排安靜的環境避免刺激病人。

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Prognosis

肝硬化病人保養之道之一就是給予適當營養。如果誤信「保肝偏方」，這樣反而有可能使肝硬化惡化得更快。了解肝硬化的營養照顧，讓您吃的更均衡、健康。食物選擇以自然、多樣化為主，應儘量避免食用有添加人工防腐劑、人工色素及加工食品。在各項營養素的攝食原則如下：

1. 採『適當蛋白質』、『高熱量』、『低脂肪』之飲食。
2. 禁止酒精攝取。
3. 補充綜合維他命。
4. 腹水的病人，應食用低鈉飲食，並限制水份一天不超過1500-2000cc。
5. 有食道靜脈曲張應避免粗糙堅硬食物，食用冷軟食並注意細嚼慢嚥。

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Prognosis

一、定期門診追蹤：以早期發現及治療腹水/下肢水腫，減少腹水應可以減少發生自發性細菌性腹膜炎的機會。

二、接受上消化道內視鏡檢查：以確定是否有胃食道靜脈曲張，若有應該一上述原則加以處理以預防出血。

三、每3-6個月定期接受血清甲種胎兒蛋白質(αFP)檢測及腹部肝臟超音波掃描：以早期發現肝癌早期治療以提高存活率。

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