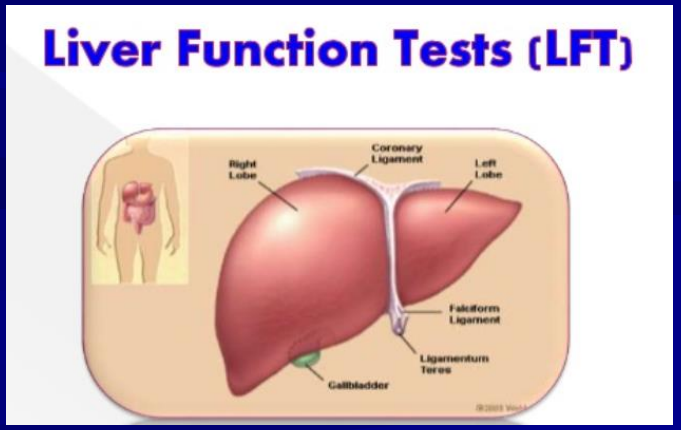
PGY1必修課程
NP essential course
Clinical application of Laboratory data (2024)
善用臨床檢驗

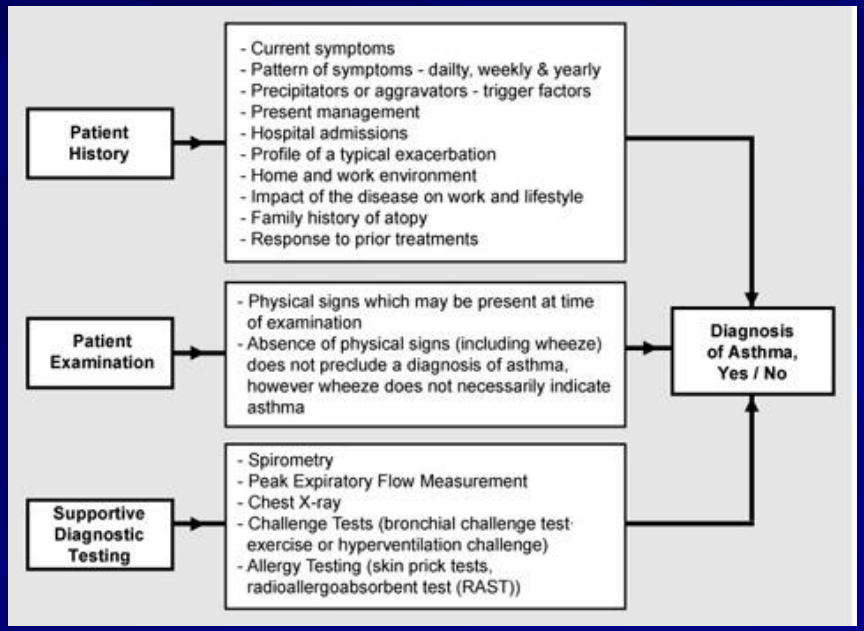
Cheng-Yi WANG

2024.03.01.



臨床診斷中重要的藉助

診斷步驟:三從,四得



- 好好問病史,會得到新的資訊.
- 好好檢查身体,(PE)會得到疾病的變化--->診斷的証據
- 好好注意檢驗數據、會得到診斷的線索-→診斷的証據
- 綜合以上各個異常,會得到整体的印象以確定診斷.

Laboratory tests

Laboratory tests之價值

- **Diagnostic—直接指出疾病**
- AC sugar : 200，HbA1c: 7.7-→DM
- Severity ---看出嚴重性,
- CRP>12, Bilirubin > 5 mg/dl, HB :<8 gm/dl
- 某一些疾病/狀態之可能性
- CEA>5,→ Cancer or false positive
- MCV<80-→ microcytic change-→**Fe. Deficiency or**
- **chronic blood loss(Gi bleeding—cancer/ulcer)**
- 特殊應用
- BUN/ Cr. >30 indicated bleeding in UGI tract
- < 25 no more UGI bleeding

BUN to Cr. ratio

The plasma BUN/creatinine ratio is usually 10 to 15:1 (when both are expressed as mg/dl)

- BUN: exogenous + endogenous,
- Cr: endogenous
- **BUN/Cr : normally 10-20**

BUN:Cr	Urea:Cr	Location	Mechanism
>20:1	>100:1	Prerenal (before the kidney)	BUN reabsorption is increased. BUN is disproportionately elevated relative to creatinine in serum. Dehydration or hypoperfusion is suspected.
10-20:1	40-100:1	Normal or Postrenal (after the kidney)	Normal range. Can also be postrenal disease. BUN reabsorption is within normal limits.
<10:1	<40:1	Intrarenal (within kidney)	Renal damage causes reduced reabsorption of BUN, therefore lowering the BUN:Cr ratio.

- Upper Gi bleeding was suspected when BUN/Cr.> 30
- Lower Gi bleeding When BUN/Cr remained 10-20

CY Wang et al (1973),
First APCDE in Kyoto

Gastrointestinal bleeding

- The ratio is useful for the diagnosis of bleeding from the gastrointestinal (GI) tract in patients who do not present with overt vomiting of blood. **In children, a BUN:Cr ratio of 30 or greater has a sensitivity of 68.8% and a specificity of 98%** for upper gastrointestinal bleeding.[5]
- A common assumption is that the ratio is elevated because of amino acid digestion, since blood (excluding water) consists largely of the protein hemoglobin and is broken down by digestive enzymes of the upper GI tract into amino acids, which are then reabsorbed in the GI tract and broken down into urea. However, elevated BUN:Cr ratios are not observed when other high protein loads (e.g., steak) are consumed. *Renal hypoperfusion secondary to the blood lost from the GI bleed has been postulated to explain the elevated BUN:Cr ratio*. However, other research has found that renal hypoperfusion cannot fully explain the elevation.[6]

- 5.Urashima M, Toyoda S, Nakano T, et al. (July 1992). "BUN/Cr ratio as an index of gastrointestinal bleeding mass in children". *J. Pediatr. Gastroenterol. Nutr*. **15** (1): 89–92

Overt UGI bleeding

- Manifest symptoms for three hours or more.
- Not fresh blood vomiting only.
- Tarry stool passage (+)

- **BUN:Cr ratio of 30 or greater indicated bleeding from the upper g-I tract.**
- **Check urgent UGI endoscopy**
- **Lesions (+)**
- **Evidence of bleeding (+)**

檢驗的思考羅輯

- 1.事前思考:我為何作這個檢驗:**目的**在診斷還是排除一個疾病.
- 2.**期待值**是什麼: 正常值,還是不正常?
- 3. **結果**是什麼?
- 期待值或非期待值-→
- 4. 那代表何種意義.
- **診斷確立**,嚴重度知,
- 還是**意料之外**,另有問題

1. Biochemical data Ex.-pancreatitis

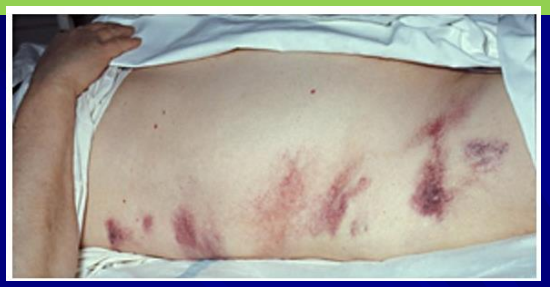
- *** Amylase,lipase, and CRP in different periods of pancreatitis

I. Amylase : 1240 (24 hours after onset)----pancreatitis
Amylase :120 (84 hours after onset)-----not diagnostic

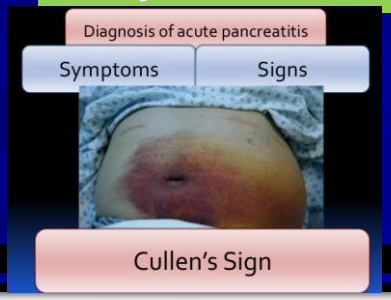
- II. Lipase : 680, CRP: 0.3 (24 hours after onset): CRP: normal
- Lipase : 310 (84 hours after onset)------→diagnostic for pancreatitis
- III. CRP: 0.6 (28 hours after onset)---data was still normal,
- CRP : 3.8 (84 hours after onset) ----indicated active pancreatitis
- CRP: 18.6 (126 hours after onset : pancreatitis still active -→necrotizing pancreatitis
- amylase : 80, lipase :178 (126 hours after onset) : reduced, still not normal

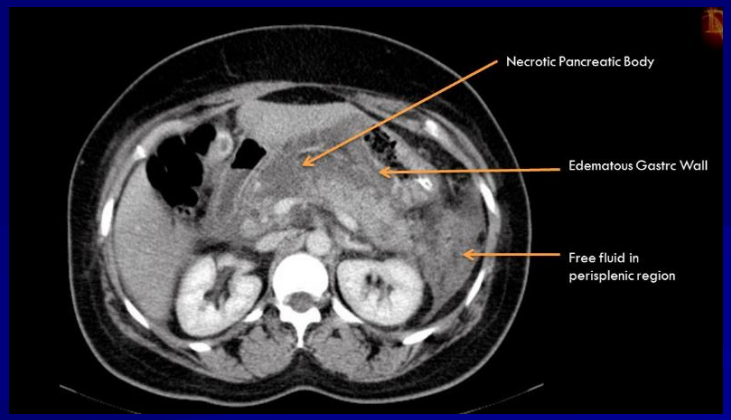
急性胰臟炎之診斷:.診斷依據

- 1, 診斷急性胰臟炎必需符合以下三個條件之二:
  - (1) 典型的上腹痛—向前灣屈較輕,躺平加重、會痛到背後
  - (2) **Serum amylase** 及 **lipase** 明顯升高, 即正常值之3倍以上.
    - **Amylase > 500 .**
    - **Lipase :>200**
  - (3) **Images : US, CT, MR**可見胰臟腫大,出水或有壞死或一般X光上出現片段性小腸腫大**(sentinel loop).**



Grey Turner's sign





Acute Pancreatitis - Diagnosis and Classification

- Diagnosis (two of three features)
  - Abdominal pain
  - Serum lipase or amylase ≥ 3 times upper limit of normal
  - Characteristic findings on imaging study (CT, MRI or ultrasound)
- Revised Atlanta Classification of Acute Pancreatitis (2012)*
  - **Categories**: interstitial edematous and necrotizing
  - **Mild**: no organ failure, no local or systemic complications, and generally resolves within 1 week
  - **Moderate**: transient organ failure, local complications, or exacerbation of co-morbid disease
  - **Severe**: persistent organ failure (>48 hours)
    - Mortality higher (~ 30%) in patients with severe AP
    - Severe disease accounts for ~15-25% of presentations

Acute severe pancreatitis
predicted from lab. data

- **Role of Clinical, Biochemical, and Imaging Parameters in predicting the Severity of Acute Pancreatitis.**
- Zerem D[1],et al (Bosnia) : Euroasian J Hepatogastroenterol. 2017 Jan-Jun;7(1):1-5.
- 84 patients (65.6%) had mild and 44 (34.4%) had severe AP. The severity markers were significantly different between the mild and the severe groups ($p < 0.001$). **Leukocyte count, serum albumin level, C-reactive protein (CRP), Ranson, acute physiology and chronic health evaluation II (APACHE II), and Glasgow score** were the factors associated with radiological **severity** grade. Leukocyte count, CRP, Ranson score, APACHE II, and Glasgow score were the factors associated with the number and appearance of acute fluid collections (AFCs). A significant association was found between the number of AFCs and the occurrence of **complications** [odds ratio 4.4; 95% confidence interval 2.5-7.6]. was significantly longer in the group with severe disease as compared with the group with mild disease ($p < 0.001$).
- **Leukocyte count, serum albumin level,**
- **C-reactive protein (CRP),**
- **Ranson, acute physiology and chronic health evaluation II (APACHE II), and Glasgow score**

Lipase D1很高、D2下降一半以上表示severe

- **Predicting severe acute pancreatitis in children based on serum lipase and calcium: A multicentre retrospective cohort study.** Bierma MJ[1], et al(Australia) : Pancreatology. 2016 Jul-Aug;16(4):529-34.
- 175 AP episodes (including 50 severe episodes [29%]) were identified. Serum lipase ≥50% decrease on D2 (sensitivity 73%, specificity 54%) **and calcium trough ≤2.15 mmol/L (8.6)**within 48 h (sensitivity 59%, specificity 81%) were identified as statistically significant predictors for severe AP. By combining the newly identified predictors with the previously validated predictor serum lipase ≥7× ULN on D1 (sensitivity 82%, specificity 53%), specificity improved to predict severe AP on D2 with the addition of: (i) serum lipase ≥50% decrease (sensitivity 67%, specificity 79%), or (ii) trough calcium ≤2.15 mmol/L (sensitivity 46%, specificity 89%).
- **Severe :lipase D2/D1 < 50 % + Ca : < 8.6 mg/dl**

2. Tumor markers

- **Tumor markers :

  AFP and CEA : 判斷primary or metastatic liver cancer.

  AFP, abnormal, >200----→HCC

  CEA, > 20 -----→Metastatic cancer,

Primary or secondary liver cancers

- 1. History of chronic liver disease, which was associated with HCV or HBV,
- 2. Chronic history of HBsAg carrier
- 3. **AFP was more than 400**.單一腫瘤/多個腫瘤
- ----------
- 4. History of primary cancer at other organ.
- 5.Primary cancer was not treated radically within 2-3 years.
- 6. **CEA was abnormal and high** (more than 20)
- 7. Multiple tumors scattered in both lobes.

3. Electrolytes-ex. Ca.

- Hypocalcemia—**serum Ca : <8.8 mg/dl**
  - Hypocalcaemia, also spelled hypocalcemia, is low calcium levels in the blood serum.The normal range is 2.1–2.6 mmol/L (**8.8–10.7** mg/dl, 4.3–5.2 mEq/L) with levels less than 2.1 mmol/l defined as hypocalcemia. Mildly low levels that develop slowly often have no symptoms. Otherwise symptoms may include numbness ...
  - Ex. *Acute pancreatitis, --severe and with necrotizing changes, usually noticed at the 2nd-3rd day of disease.*
- **Hypercalcemia—serum ca : >10.7 mg/dl**
  - Ex. Most cases are due to primary hyperparathyroidism or cancer.[1] Other causes include sarcoidosis, tuberculosis, Paget disease, multiple endocrine neoplasia (MEN), vitamin D toxicity, familial hypocalciuric hypercalcaemia, and certain medications such as lithium and hydrochlorothiazide.[1][2][3] Diagnosis should generally include either a corrected calcium or ionized calcium level and be confirmed after a week.[1] Specific changes, such as a shortened QT interval and prolonged PR interval, may be seen on an electrocardiogram (ECG).[

hypocalcemia

成人體內總鈣量約1000~1300g，99%以骨鹽形式存在於骨骼和牙齒中，其餘存在於各種軟組織中，細胞外液鈣僅佔總鈣量的0.1%，約1g左右。成人血鈣水平約為2.2~2.6mmol/L(8.8~10.4mg/dl)，主要以三種形式存在：①遊離鈣（50%），也稱離子鈣；②蛋白結合鈣（40%）；③可擴散結合鈣（10%）。

當血清白蛋白濃度在正常範圍時，血鈣低於2.2mmol/Ll(8.8mg/l) 正常值2.2~2.70 mmol/L，時稱為低鈣血症。不同醫院血鈣化驗參考值有小的差異，也有血鈣低於

: Blood :serum Ca < 2.1 mmol/L

Trousseau's sign (hand/finger spasms)

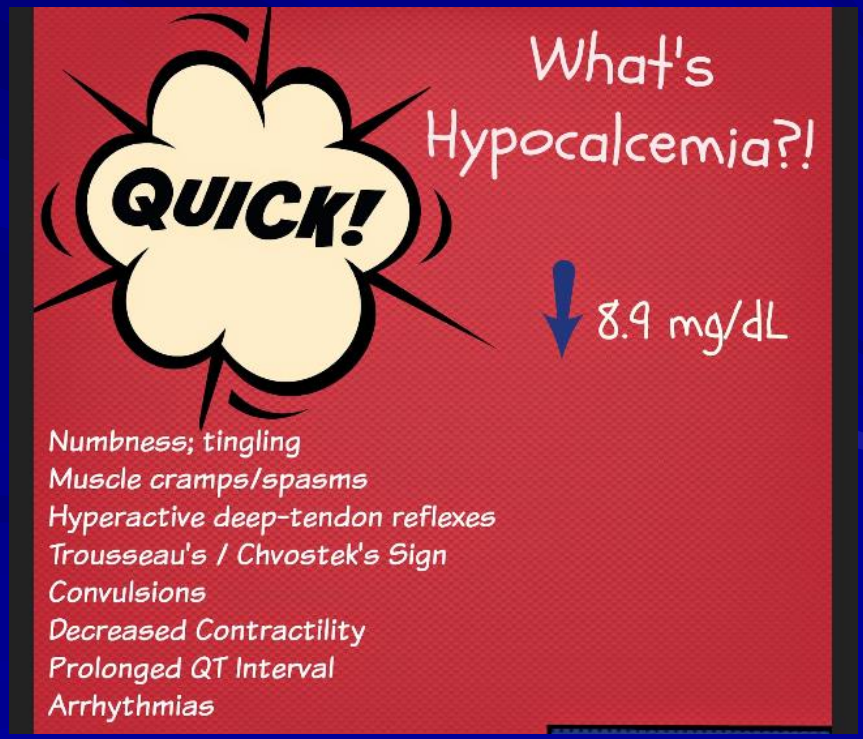
Watch for arrhythmias
(Prolonged QT interval, cardiac arrest…)

Increase in bowel sounds, diarrhea

Tetany

Chvostek's sign (facial twitching)

Hypotension, Hyperactive DTR

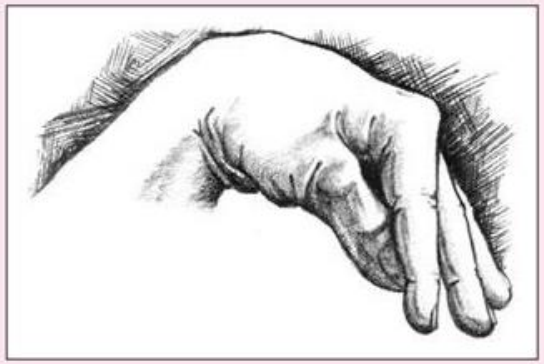


Hypocalcemic tetany

EXAMINATION TIP

Recognizing carpopedal spasm

In the hand, carpopedal spasm involves adduction of the thumb over the palm, followed by flexion of the metacarpophalangeal joints, extension of the interphalangeal joints (fingers together), adduction of the hyperextended fingers, and flexion of the wrist and elbow joints. Similar effects occur in the joints of the feet.



Trousseau's sign

Uncomfortable and very painful.

- A blood pressure cuff is inflated to 20mm Hg above systolic blood pressure level.
- arterial blood flow to the hand is occluded for 3 to 5 minutes.
- Carpopedal spasm:
  * flexion at the wrist
  * flexion at the MCP joints
  * extension of the IP joints
  * adduction thumbs/fingers

Chvostek sign

- The **Chvostek sign** (also **Weiss sign**) is one of the signs of tetany seen in hypocalcemia.
- It refers to an abnormal reaction to the stimulation of the facial nerve.
- When the facial nerve is tapped at the angle of the jaw (i.e. masseter muscle), the facial muscles on the same side of the face will contract momentarily due hyperexcitability of nerves.

Hypercalcemia related to cancer

Can Fam Physician. 2010 Mar; 56(3): 244–246.

PMCID: PMC2837688
PMID: 20228307

Cancer-related hypercalcemia

Dori Seccareccia, MD CCFP(EM) MClSc

Palliative care physician in the Department of Psychosocial Oncology & Palliative Care at Toronto General Hospital in Toronto, Ont.

Hypercalcemia affects up to 10% to 30% of cancer patients, and cancer-related hypercalcemia is the leading cause of hypercalcemia in hospitalized patients.[1,2] Patients with breast cancer, lung cancer, and myeloma are most commonly affected, but hypercalcemia can also occur with other malignancies, including renal, gynecologic, and head and neck cancers.[3,4] Unfortunately, cancer-related hypercalcemia has a poor prognosis, as it is most often associated with disseminated disease. Eighty percent of patients will die within a year, and there is a median survival of 3 to 4 months.

Hepatoma 也會出現 hypercalcemia

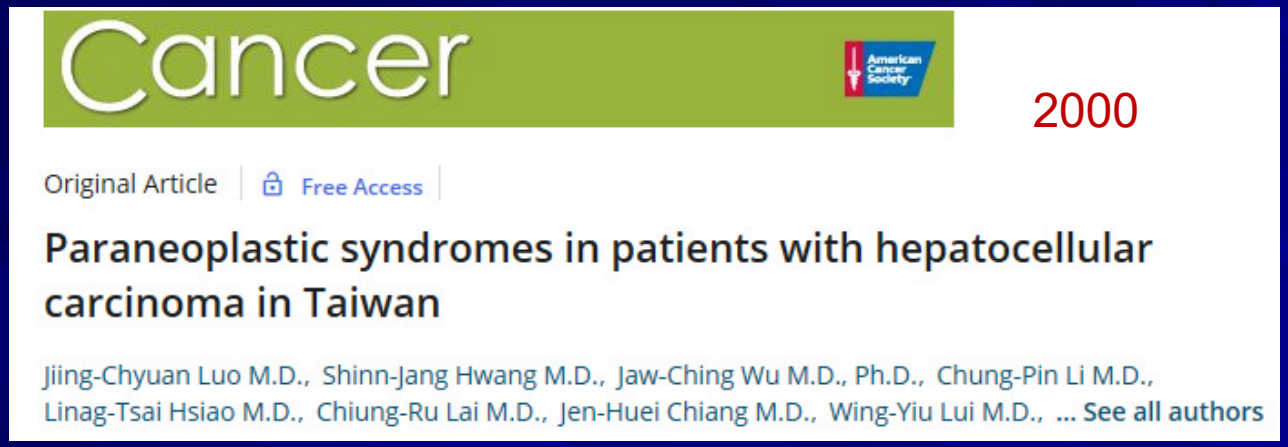
Hypercalcemia Secondary to a Primary Hepatoma

Reed T. Keller, MD; Irving Goldschneider, MD; Frederic W. Lafferty, MD

JAMA. 1965;192(9):782-784. doi:10.1001/jama.1965.03080220046020

1965

Hepatoma associated with hypercalcemia



Cancer

2000

Original Article | Free Access

Paraneoplastic syndromes in patients with hepatocellular carcinoma in Taiwan

Jiing-Chyuan Luo M.D., Shinn-Jang Hwang M.D., Jaw-Ching Wu M.D., Ph.D., Chung-Pin Li M.D., Linag-Tsai Hsiao M.D., Chiung-Ru Lai M.D., Jen-Huei Chiang M.D., Wing-Yiu Lui M.D., ... See all authors

19.4 % in patients with hepatoma

A total of 232 of 1197 patients (19.4%) had paraneoplastic syndromes. HCC patients with paraneoplastic syndromes had significantly higher serum AFP; higher rates of initial main portal vein thrombosis, metastasis, and bilobal tumor involvement; larger tumor volume; and shorter survival than those without these syndromes. Patients with HBV-related HCC had a significantly higher prevalence of paraneoplastic syndromes than patients with HCV-related HCC (20.1% vs. 11.2%, $P = 0.005$). In a stepwise multivariate logistic regression analysis, AFP >50,000 ng/mL and tumor volume >30% were significant predictive variables associated with the presence of paraneoplastic syndromes in HCC patients.

- A total of 232 of 1197 patients (19.4%) had paraneoplastic syndromes during the clinical course of HCC, of whom 177 had a single paraneoplastic manifestation, and 55 had multiple paraneoplastic manifestations.

- Single manifestation: 177/232 (76%)
- Multiple manifestations.

  55/232 (24 %).

Hypercholesterolemia-12.1 %

Hypoglycemia ----------5.3 %

Hypercalcemia ----------4.1 %

Erythrocytosis ----------3.1 %

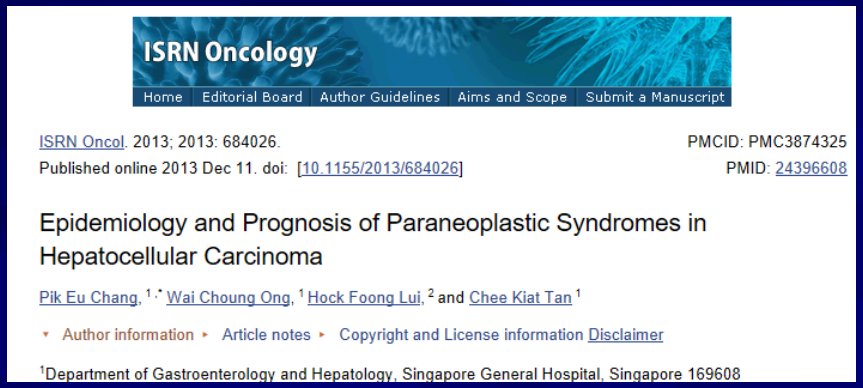
Characteristic	HCC patients with paraneoplastic syndromes (n = 232)	HCC patients without paraneoplastic syndromes (n = 965)	*P* value
Age (yrs)	61 ± 14	63 ± 11	0.042
Gender (male:female)	211:21	833:132	0.074
HBV:HCV related	154:21	609:166	0.006
Mean Child–Pugh score	6.8 ± 2.1	6.8 ± 2.2	0.894
Mean initial α-fetoprotein (ng/mL)	122,084 ± 280,188	23,719 ± 106,116	<0.001
Median (range)	2895 (3–1,621,700)	196 (3–1,892,500)	
Mean peak α-fetoprotein (ng/mL)	171,803 ± 352,790	35,695 ± 167,960	<0.001
Median (range)	8701 (3–2,055,300)	459 (3–2,975,570)	
Initial MPV tumor thrombosis (+:−)	60:172	125:840	<0.001
Initial metastasis (+:−)	61:171	112:853	<0.001
Tumor volume (%)	47.0 ± 25.1	20.1 ± 16.2	<0.001
Bilobal tumor involvement (+:−)	120:112	353:612	<0.001
Therapy for HCC (+:−)	100:132	523:442	0.003
Tumor cell arrangement (trabecular:mixed:acinar)	36:11:3	131:42:17	0.792
Tumor cell differentiation (Grade 1:2:3:4)	12:33:7:2	30:121:46:7	0.331
Median survival (days)	152	634	<0.001

Difference between HCC patients with or without paraneoplastic syndromes

Table 2. Comparison of Clinical and Laboratory Data and Tumor Features between Hepatitis B Virus- and Hepatitis C Virus-Related Hepatocellular Carcinoma Patients with Paraneoplastic Syndromes

Characteristic	HBV-related HCC with paraneoplastic syndromes (n = 154)	HCV-related HCC with paraneoplastic syndromes (n = 21)	*P* value
Age (yrs)	58 ± 14	67 ± 9	<0.001
Gender (male:female)	137:17	19:2	1.000
Mean Child–Pugh score	7.8 ± 2.4	7.2 ± 2.2	0.316
Mean α-fetoprotein (ng/mL)	182,218 ± 350,400	24,146 ± 54,989	<0.001
Median (range)	3598 (3–1,621,700)	597 (4–165,330)	
MPV tumor thrombosis (+:−)	54:100	4:17	0.224
Metastasis (+:−)	39:115	6:15	0.958
Tumor volume (%)	49.3 ± 23.7	42.5 ± 29.4	0.367
Bilobal tumor involvement (+:−)	79:75	9:12	0.469
Therapy for HCC (+:−)	40:114	9:12	0.175
Tumor cell arrangement (trabecular:mixed:acinar)	26:9:2	5:1:0	0.749
Tumor cell differentiation (Grade 1:2:3:4)	8:25:5:2	1:4:1:0	0.937
Median survival (days)	153	152	0.480

Difference between HBV-related and HCV related hepatomas



ISRN Oncology

Home | Editorial Board | Author Guidelines | Aims and Scope | Submit a Manuscript

ISRN Oncol. 2013; 2013: 684026.
Published online 2013 Dec 11. doi: [10.1155/2013/684026]
PMCID: PMC3874325
PMID: 24396608

Epidemiology and Prognosis of Paraneoplastic Syndromes in Hepatocellular Carcinoma

Pik Eu Chang,[1,*] Wai Choung Ong,[1] Hock Foong Lui,[2] and Chee Kiat Tan[1]

▾ Author information ▸ Article notes ▸ Copyright and License information Disclaimer

[1]Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore 169608

The prevalence, clinical characteristics, and survival of PNS among 457 consecutive HCC patients seen in our department over a 10-year period and compared them with HCC patients without PNS.

- *Results.*
- 1. PNS were present in 127 patients (27.8%).
- 2,The prevalence of paraneoplastic hypercholesterolemia,:24.5%
  hypercalcemia, 5.3 %
  erythrocytosis 3.9%,

3. Patients with PNS had significantly higher alpha-fetoprotein levels, more advanced TNM stage, and shorter survival.

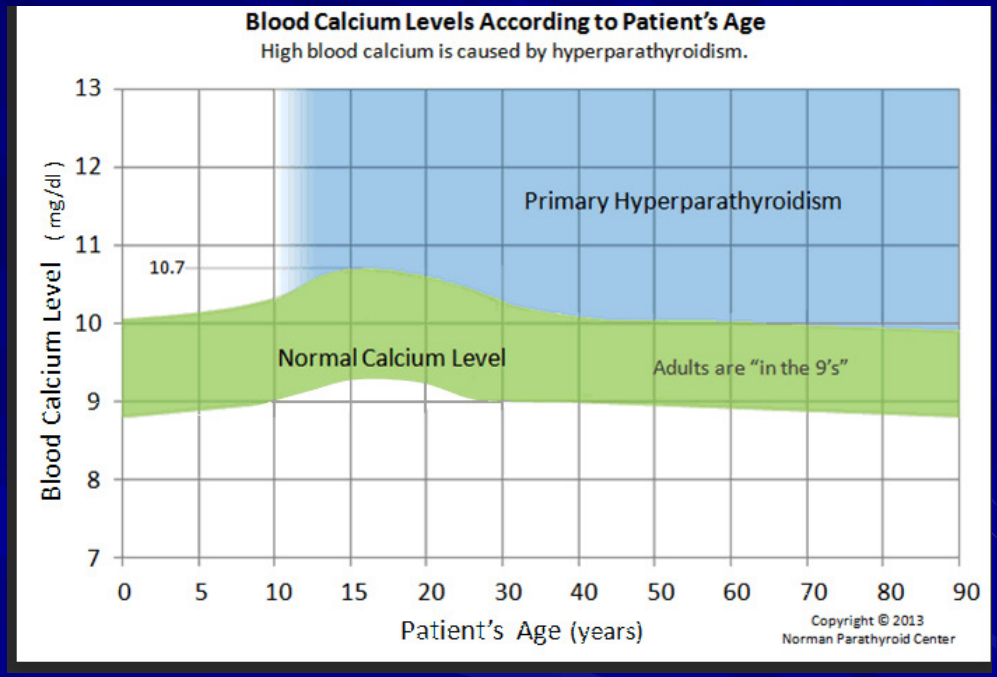
Corrected calcium
for albumin level

Correct calcium for albumin level

- Normal serum level: 8.5–10.2 mg/dL
- 40% transported on albumin
- If hypoalbuminemia, use corrected calcium

Corrected calcium (mg/dL) =

serum calcium (mg/d) + 0.8(4.0 – serum albumin g/dL)



– corrected [Ca] in mmol/L =
= measured total [Ca] (mmol/L) + 0.02 x (40 – serum albumin in g/L)

Lab. Data 之來由

- 病人抽血→ 運送至 lab.
- 血液處理
- **檢驗**、人/機器

- Reading results → printed out → Hospital information networks醫院電腦索統
- Lab. **Quality assurance**: 很重要
- →read and **interpreted** by clinicians
- 作對,但**讀错了還是滿盤全輸**

從數據之讀取到分析→處理

- 從數據之讀取到分析---(臨床意義)--→**處理**
  Planning and action-→再評估其結果
- Normal----改善(由不正常變正常)
- Exclude a disease or diseases
- 排除某一種病
- Abnormal(High or low)---abnormal—true
- abnormal: **false**(false positivity)
- 增加—惡化
- 減輕:改善

1. Lab data 常是診斷的依據

- 一個datum→ 一個病:或問題(potential or presenting problems, even emergency)
- AFP > 10,000 ---→ hepatoma (DD)

  >400---------→ hepatoma
- HBsAg (+) ------→ HBsAg carrier
- GPT> 300------→ liver cell necrosis
- Triglyceride > 300-→Hyper-triglyceridemia
- Lipase > 2,000---→ acute pancreatitis
- Glucose < 40----→ hypoglycemia

疾病代表病情及危急性

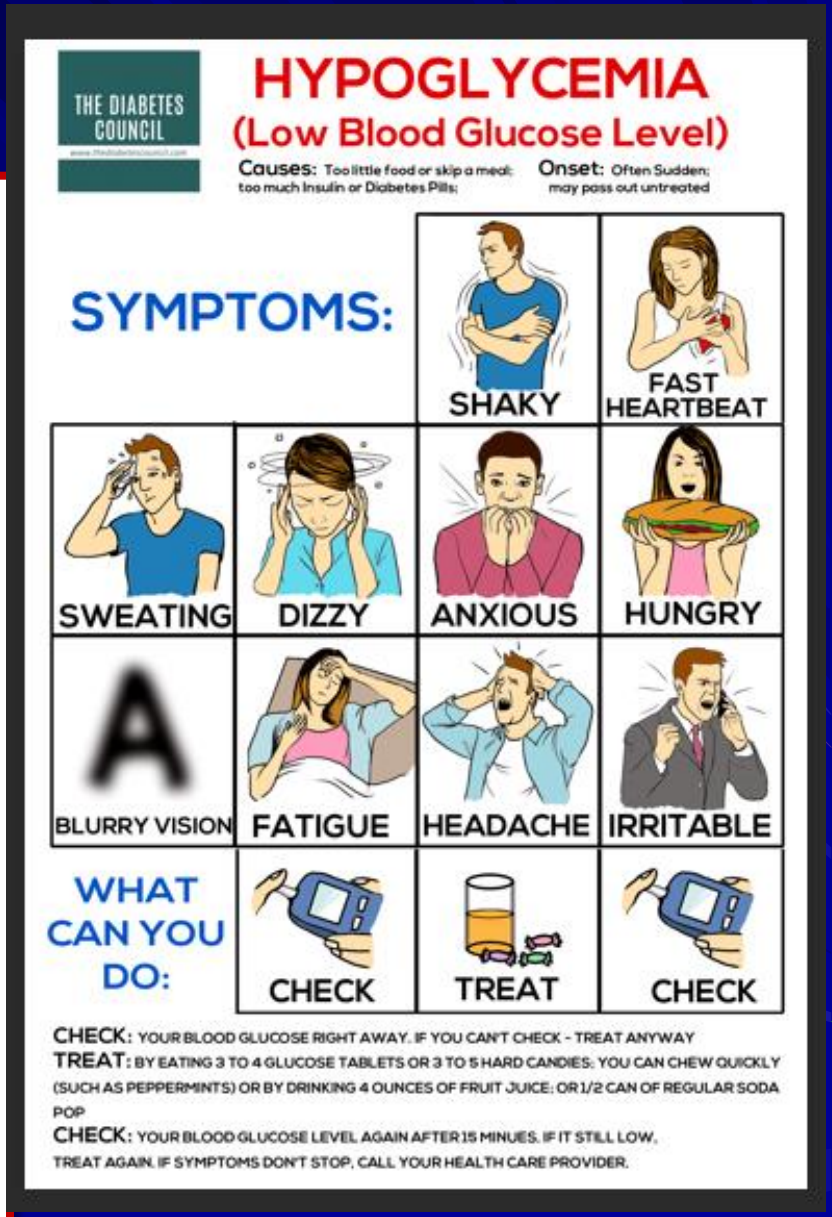
- hypoglycemia ---立即治療否則 coma→ 死亡
- Abnormal CEA→意義 **false (+)** or true (+)
  What kinds of pathology related :要去找
  很多 **cancer** 早期並無症狀.
- HBsAg (+) 一生要注意的問題 –liver disease→ cirrhosis →HCC.(LONG TERM PROBLEM)
- Lipase 高→ Acute pancreatitis或輕或重,或生或死/全靠是否處置得宜

Hypoglycemia

What are the symptoms of low blood sugar?

Symptoms of low blood sugar can occur suddenly. They include:

- blurry vision
- rapid heartbeat
- sudden mood changes
- sudden nervousness
- unexplained fatigue
- pale skin
- headache
- hunger
- shaking
- dizziness
- sweating
- difficulty sleeping
- skin tingling
- trouble thinking clearly or concentrating
- loss of consciousness, seizure, coma



Treatment of hypoglycemia

Treatment of Hypoglycemia

Conscious Patient

Unconscious Patient

★Hypoglycemia is an emergency and needs to be treated **immediately**

- Give the patient 15-20 grams of quick acting carbohydrate
  - ✓ 4-6 oz Regular soda
  - ✓ 8-10 Candies
  - ✓ 4-6 oz Orange Juice
- Repeat in 15 minutes if no improvement
- Longer acting carbohydrate
  - ✓ Crackers with peanut butter or cheese

★ Immediate notification of health care provider especially if symptoms do not subside

- Subcutaneous or IM injection of 1 mg Glucagon
- IV administration of 50 mls of 50% Glucose

Follow up blood sugar after treatment within two hours→then-----

2.代表disease的嚴重度(合併症)

- 1. WBC > 15,000 severe infection
  > 30,000 leukemoid reaction
- 2. CRP >8 severe inflammation
  severe tissue destruction
- 3. CEA >30 : advanced cancer(? METASTASS)
- 4. T. bilirubin > 2.0 decompensate cirrhosis
- 5. Serum ca < 8.0 mg/dl : necrotizing pancreatitis
- 6. Prothrombin time> 20 sec: **severe bleeding tendency—liver failure(poor outcome)**
- 7. **NH3 > 180 – hepatic coma**,

3.指出疾病的線索(診斷及原因)

- 1. **TG > 2,000-→** acute pancreatitis due to hyperlipidemia.
- 2. Hyperamylasemia + increased lipase
  → acute pancreatitis
- 3. Severe anemia +microcytic anemia (MCV < 80)→**Chronic bleeding** (GI? Hemorrhoids, menstruation?)→ colon cancer.
- 4. **Bilirubin 0.2/2.0** → hemolytic process.
- 5. GGT >200 :obstructive jaundice or alcoholic liver disease.**(GGT: biliary enzyme)**

Anemia (blood pictures 相同)

- Age, sex and historical presentation.
- Young female with menstrual problem--→ hypermenorrhea
- Old age, man, with pallor of the face and symptoms of severe anemia →colon cancer at the right side colon.
- **Young man with history of IBD** (UC) noticed frequent bloody diarrhea and severe anemia

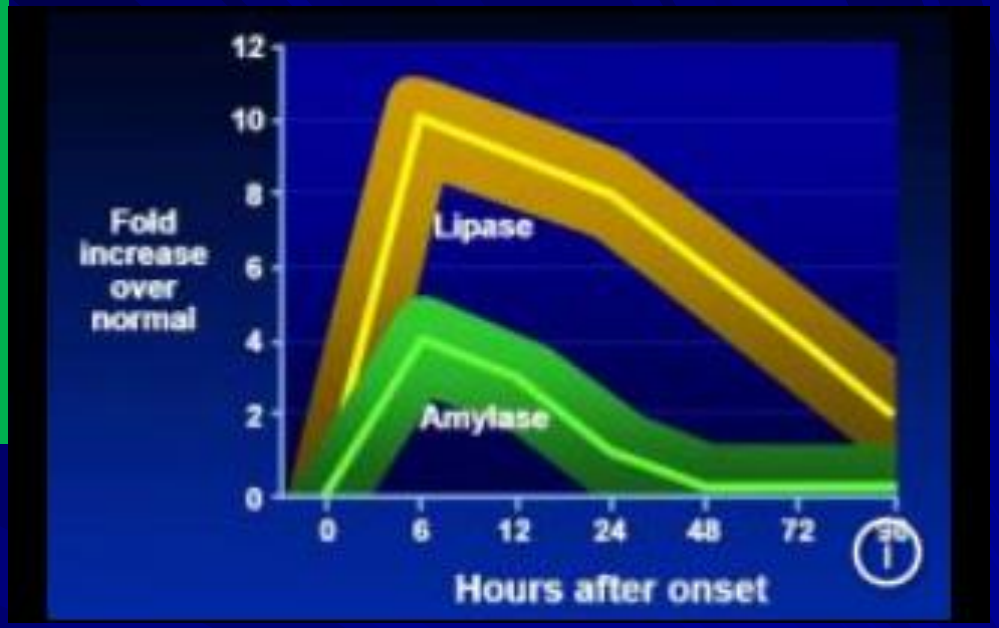
4. 檢驗數據可以判定治療之效果/特殊問題(predictive value)

- 1. CRP abnormal data → 減少→ normal
- Improved, 改善
- 2. CEA 由 abnormal 變 normal, Improved,
- 改善, 或原因消失 (smoking)
- 3. Hb : 增加 , Hb 8.0增至 12, Effects of blood transfusion + 出血已停止
- 4. Bilirubin , 黃疸色素 下降 → normal, improved, 改善. Obstructive jaundice after ERCP and papillotomy.

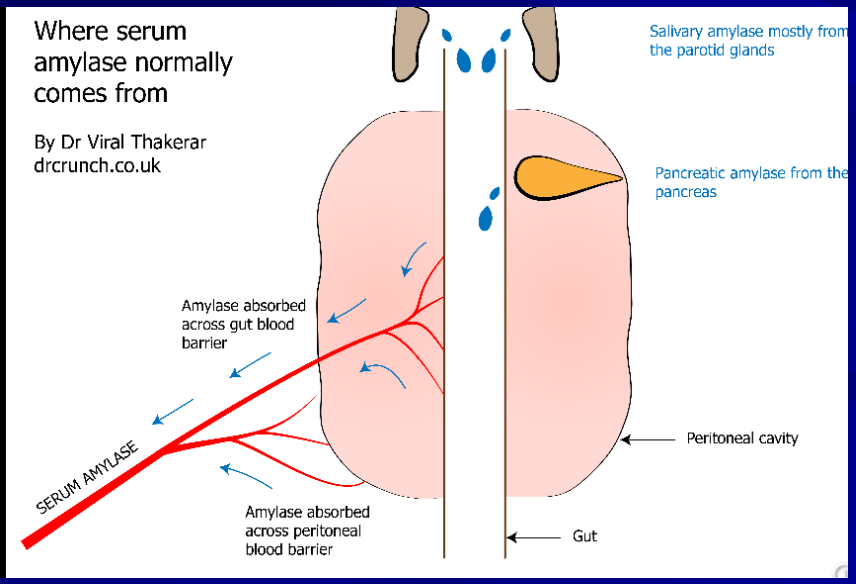
5. Natural course 之變化?

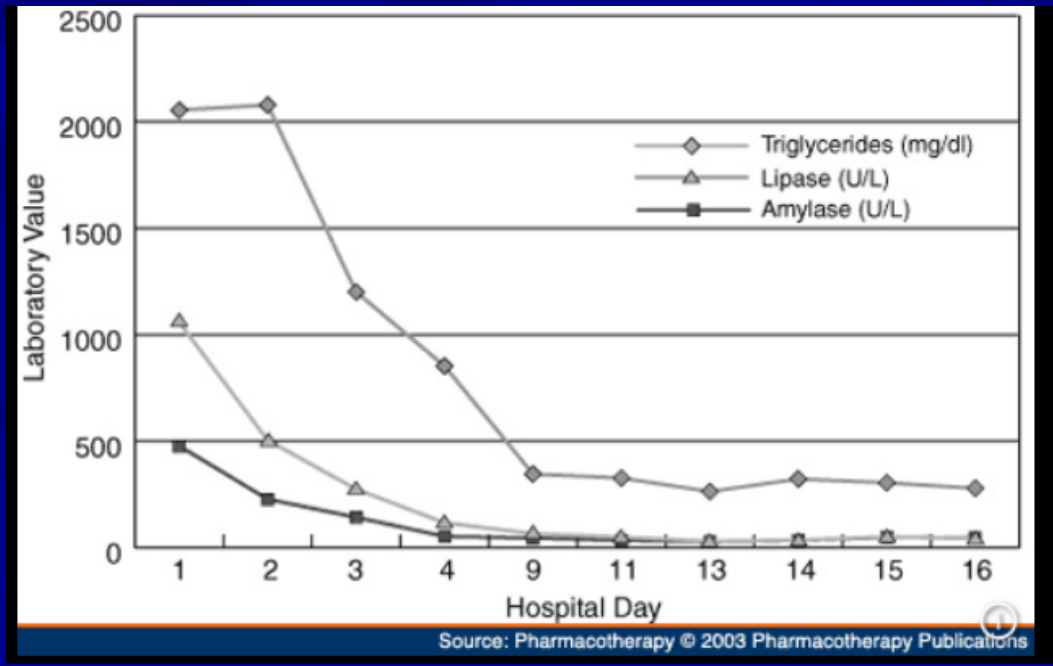
- Serum amylase : 1200 U (on the second day)
- Serum amylase : 160 U (on the fourth day of AP)
- (1) acute pancreatitis 之後已慢慢改善
- (2) 入院之後未喝酒,致病原因消失
- (3) Gall stone impacted at CBD → relieved after papillotomy, 治療有效.
- **Timing of lab examination(發病後第x天)** and also **interpretation** 需考慮各種狀況(**not only one reason.)**

Amylase and lipase in acute pancreatitis



TG >1,000mg/dl might be cause of Acute pancreatitis





Difficulty of diagnosis of acute pancreatitis beyond 3 days

- Usually serum amylase became normal.

- Urine amylase was still abnormal.
- Total daily urinary amylase output > 8,000 U.
- Amylase/ Cr. Clearance ratio > 3.0 if no renal disease.
- Lipase was still abnormal.

What is the Significance of the Amylase/Creatinine Clearance Ratio Blood and Urine Test Result?

The significance of the Amylase/Creatinine Clearance Ratio Blood and Urine Test result is explained:

- A high test value may indicate:
  - Pancreatitis
  - Diabetic ketoacidosis
  - Renal insufficiency
  - Duodenal perforation
  - Pancreatic cancer
  - Myeloma
  - Light chain disease
  - Urinary obstruction
  - Kidney disease, including acute and chronic kidney failure
  - Acromegaly
- A low test value may indicate:
  - Anemia
  - Muscular dystrophy
  - Severe liver disease
  - Macroamylasemia

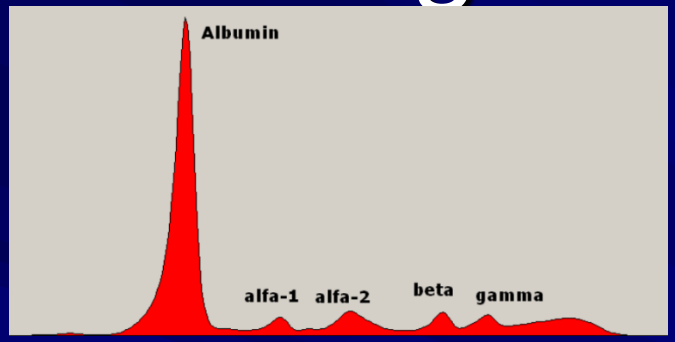
$$\frac{\text{Amylase clearance}}{\text{Creatinine clearance}}(\%) = \frac{\dfrac{[\text{urine amylase}]}{[\text{serum amylase}]} \times \text{urine volume per unit time}}{\dfrac{[\text{urine creatinine}]}{[\text{serum creatinine}]} \times \text{urine volume per unit time}} \times 100.$$

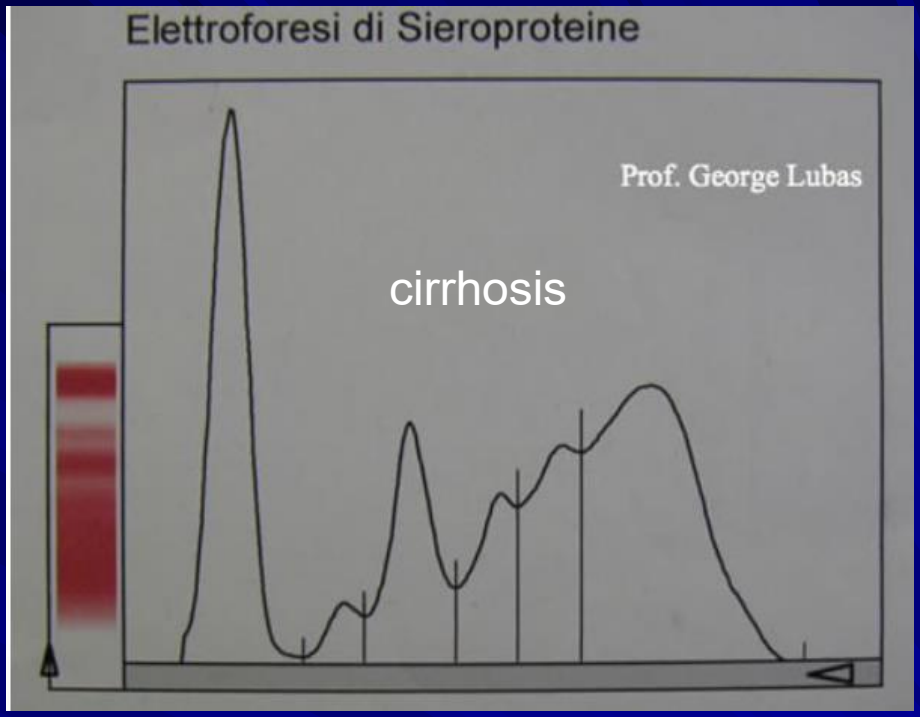
$$= \frac{[\text{urine amylase}]}{[\text{serum amylase}]} \times \frac{[\text{serum creatinine}]}{[\text{urine creatinine}]} \times 100.$$

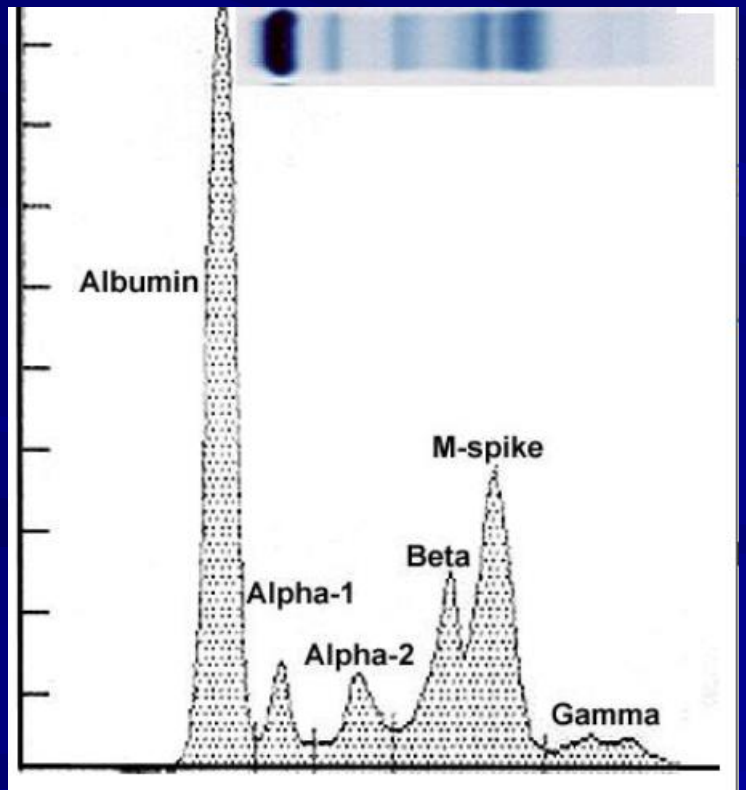
6, 綜合各個數據以判斷 cirrhosis

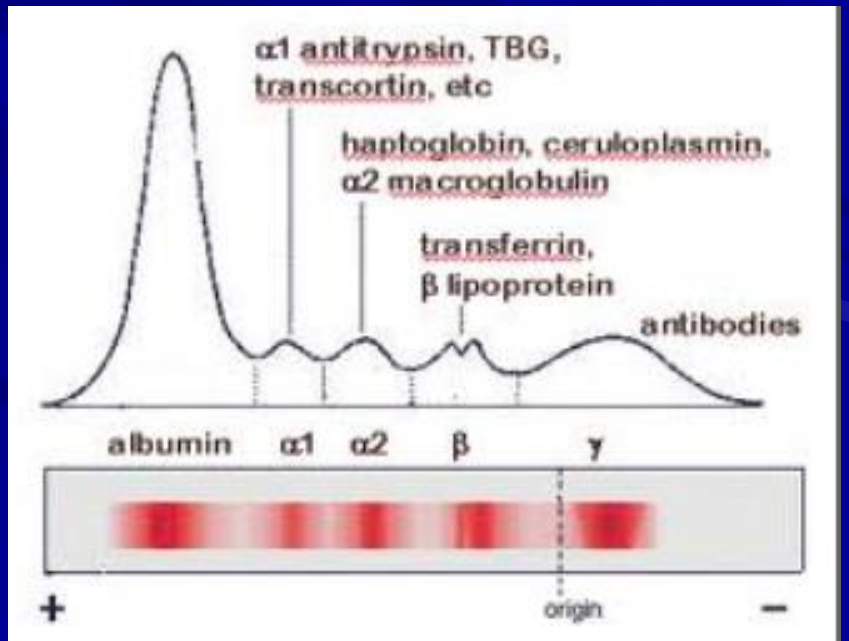
- Leukopenia < 3,500
- Thrombocytopenia : < 120,000
- **A/G reversed** : alb : <3.3 gm/dl, Glo: >3.5
- Beta-gamma linkage –protein electrophoresis
- Mild bilirubinemia : >1.2 but less than 2.5
- GOT>GPT (ratio : >1.0~2.0)

Beta-gamma linkage









Cirrhosis + HCC ? (3 %/yr)

- Typical patterns of liver function tests
- A. Cirrhosis---hyper-bilirubinemia, mild
- direct bilirubin >0.4,<2
- total bilirubin>1.2,<4
- SGOT>GPT ratio(1~2))
- A/G : reversed, Alb<3, Glo:>3.5
- Pro-thrombin time: prolonged. >14sec. <18sec.
- B.HCC---------GGT>150 (3-10倍)
- -------ALP>1.5倍
- SGOT/GPT: >3.
- worsen rapidly (bilirubin increased)

Protein fraction

- A/G reversed in cirrhosis
- G. increased rapidly after attack (10-14 days) by Kunkel test (in CAH)
- Serum protein electrophoresis – beta-gamma linkage→ cirrhosis
- **IG G4/IG G** increased in autoimmune diseases, AIP----
- Rapid reduction of serum albumin in AH-→ severe liver failure

SHORT COMMUNICATION

Paraproteinemia: Predictive Value of Kunkel's Zinc Sulfate Turbidity Test

CECILE A. LOVETT-MOSELEY, M.Sc.,* *Toronto*

IMMUNOELECTROPHORETIC analysis (IEPA) is an effective method for determining paraproteinemia. However, because of the scarcity of technologists with the necessary skills, and also because of the cost of equipment and antisera, the technique is routinely available in only a small proportion of hospitals, mostly in the larger centres. Clinicians outside these hospitals must either depend on the results of simple electrophoresis, or send the suspect serum elsewhere for analysis.

A simple and accurate screening test for paraproteinemia would be of value to small hospitals and individual practitioners. One test which has been widely used is the dilution test of Sia and Wu.[12] However, the predictive value of this test is low; about 50% of sera containing an IgM paraprotein give negative reactions.[7] The test may also be positive in hyperimmunoglobulinemic sera without detectable paraproteins.[6]

were of analytical grade; the final pH of the reagent was 7.5 ± 0.1. The solution was stored in polyethylene bottles at room temperature; no deterioration was observed after four weeks.

Technique.—A 0.05-ml. portion of serum was pipetted into 3 ml. of zinc sulfate reagent in a clean 12 × 100 mm. test tube. The tube was shaken and allowed to stand at room temperature. After 30 minutes, the optical density was determined at 650 mμ., using a Bausch and Lomb Spectronic 20 colorimeter. The optical density was converted to zinc turbidity units (ZTU), using the barium sulfate standard described by Kunkel.[5] An optical density of 0.48 was accepted as equivalent to 20 ZTU.

Sera.—Four hundred sera, comprising 200 sera from apparently healthy blood donors and 200 pathological sera submitted to this laboratory for IEPA, were tested. All sera were examined by IEPA, using our standard method.[9] Sixty-eight of the pathological sera, but none of the normal (donor) sera, contained paraproteins.

Valuable screening test

TABLE II.—Distribution of Zinc Sulfate Turbidity Values in Pathological and Normal Sera

Sera	Percentage of sera with turbidity in the range 0 - 5	6 - 10	11 - 15	16 - 20	20
Pathological					
—hyperproteinemic, paraprotein	34.4	12.5	9.4	10.9	32.8
—hyperproteinemic, no paraprotein	8.3	26.2	27.8	26.2	11.5
—normoproteinemic	64.9	33.3	1.8	0.0	0.0
—hypoproteinemic	94.4	0.0	0.0	0.0	5.6
Normal	93.0	6.0	1.0	0.0	0.0

Summary Comparison of the zinc sulfate turbidity with the protein level in 200 pathological sera was used to predict the presence or absence of paraproteinemia. Prediction was correct in 84.5% of the cases. Seven cases of paraproteinemia out of 68 were not detected by the technique.

It is suggested that the zinc sulfate turbidity test, combined with protein determination, provides a valuable screening test for paraproteinemia.

- ZTT > 16 indicated Presence of paraproteinemia
--→Indicated chronic change.
- **Acute hepatitis 出現 gamma globulin通常是4週之後.**
- **chronic hepatitis with acute exacerbation 在2週之內即出現**

7.代表病人的配合度不好

- **Hb A1C . >8.0: DM 病人DIET CONTROL** 不好
- UC + CRP > 3.0 – relapsed.

  No medication

  Increased stress or busy or heavy meal
- **CEA 增加** (6.0→ 12) in smoker: 又再抽菸
- **GGT : 30--→ 103 in drinker** 又再喝酒了
- Glucose 又降至40 mg/dl 以下:有打針 (insulin) 沒有吃食物.，insulinoma.

Peculiar case example

- Aged 88 male, ex-smoker for 20 years.
- CEA : increased definitely up to 7
- Reviewing his smoking history: no more smoking for 20 years but **exposed to a heavy smoker in the park** every morning during exercise.→ recheck CEA→still high.
- Chest X-ray and chest CT showed a small **mass 1.0 cm., in size**. It was then resected. CEA down to normal after operation.

Elevated CEA in cancer patients

- Key points：在解釋 abnormal data
- True (+) or false (+)
- false (+)的條件?
- 不妨 查Chest X-ray and CT.
- Follow up.

- **High False-Positive Rate of Elevated CEA Seen in Patients With Resected Colorectal Cancer**
  By Charlotte Bath August 15, 2014
  The ASCO Post
- *Litvak A, et al: J Natl Compr Canc Netw 12:907–913, 2014.*
- *1.* 49% false-positive of carcinoembryonic antigen (CEA)
- 2. **Confirmation of an ongoing increase in CEA level should be universal practice** before an extensive workup is initiated,

CEA: abnormal
in cancer patients

- 728 cases of CRC
  Memorial Sloan Kettering who underwent resection for stage I, II, or III colorectal cancer between 2003 and 2012, and who had an increase in CEA level above the normal after a normal perioperative CEA level.
- 358 had a **false-positive** elevation of CEA level,
- 335 had a true-positive elevation indicative of **recurrent** [colorectal cancer],
- 35 had a true-positive elevation indicative of the development of a **new**, [non–colorectal cancer] malignancy,"

- **1. no evidence of cancer on either imaging studies** or other diagnostic procedures,
- **2. follow –up** of (1) **at least 1 year** since the first abnormal CEA or
- (2) abnormal CEA elevations followed by **spontaneous normalization,**
- **(3)** with at least **2 consecutive subsequent normal CEA** measurements in the absence of a therapeutic intervention,

- @@@ 247 patients with 2 or more confirmed false-positive CEA level elevations, only 5 (2%) had measurements greater than 15 ng/mL, and no confirmed elevation greater than 35 ng/mL was a false-positive,
- FALSE (+) 很少 >15,
- False (+) 不會超過 35

Same conclusion in 1977, Special lecture
False (+) often around 5-10, rarely > 15,
IT was definitely abnormal when CEA>20

8.代表治療反應好或不好

Improvement　轉好

- 1. CRP　減少
- 2. WBC　return to normal
-
- 3. Amylase return to normal
- 4. Hb: 增加/貧血改善,
- 　　出血停止

Downhill效果不好

- 1.CRP 增加
- 2.Leukocytosis.
  Leukemoid reaction
  WBC增加
- 3. relapse of pancreatitis
- 4. 減少, 貧血加重或繼續出血

很好的 assessment parameters

怎樣選assessment parameters

- 對疾病深入瞭解,
- 善於利用各種 lab data
- 發病日(期間,staging) 會影響改變
- Normal or abnormal.
- Individual variation個別差異/治療之影響
- 挑本**案例差異**(不正常)最明顯的項目.

那個檢查最能看出疾病之進行 active disease

- Presenting data –
- Tumor markers– CEA,
- UC :Inflammatory parameters– ESR,CRP, and WBC.
- Hypoglycemia—sugar
- Hypokalemia –K, (ECG)
- Acute necrotizing pancreatitis :Ca. CRP and lipase

9. 檢驗錯誤或 false positive Ex. CEA

- 1. CEA – 5~ 10 --→smoker ? Or other condition
- 2. EIA or RIA
- EIA ---data 穩定性不夠， RIA：比較可靠
- 3. 增加 -→ Lab error ?，Cancer 更厲害, 未控制住, 吸菸故態復萌
- 4. > 20: 可能已有 metastases.
- 5. *不同醫院不同的* ***Lab.*** *不宜直接比較(參考)*
- *別人論文上之結果可參考,不可直接比較*

10. 好好思考、紀錄、處理

- 跟 Present illness 的關係
- 1. Diagnostic evidence
- 2. Indicates severity
- 3. Indicates therapeutic response better or worse.
- 4. **Associated diseases.**
- 5. Treatment regimen. Change or modify.
- 6 Express the opinion at recording of the lab data

11.基本的檢查項目一定要熟習
(a) normal range (b)臨床意義

- CBC, differential counting,
- blood smear
- Urinalysis
- Stool examination, OB, Parasite, Fat
- **LFT: GOT, GPT and GGT---**
- RFT : BUN, Cr, UA
- Electrolyte: Na, K Cl. and Ca,
- CRP
- AC sugar, PC, and Hgb A1c
- Arterial blood gases analysis

- Normal range
- Clinical significance
- Critical value
- How to manage.
- Diagnosis
- Screening
- Outcome.

11.基本的檢查項目-原則

- 一定要很熟悉,各種狀況都知道(Dx and DD)
- Normal ranges
- Interpretation:
  - Definite, --diagnosis
  - Possibility of abnormalities各種可能性:
  - False positive之情形
- 記載結果及評估-→一定記入病歷
- 即時處理/立即處理(訂定工作規範、電腦上及時顯現處置方式、)

(三)要處理: 處理的種類-極端值

- 1.極端值---危險值/判斷是True or false
- True---立即處理,有相關的症狀,立即治療務必改善,治療後,追蹤檢查→判斷已改善/未改善
- Sugar:25mg/dl----cold sweating + palpitation-→hypoglycemia-→IV glucose-→better after treatment—recheck sugar
- Serum K:2.2mEq/L---無症狀但 ECG 有變化, IV drip補充-→better after treatment仍要再查確定K

(三)要處理: 處理的種類2.異常值:
思考檢驗值不正常之意義並記在病歷上

- 2.不正常值—先知道代表的臨床意義:
- 本病例是否有此情形
- → 疾病/合併症/病情的一部分
- False:偽陽性之狀況
- False: Lab quality有問題—作錯
- False: Lab.檢體弄錯人
- False: 抄錯結果
- **Lab error: 5 %, acceptable**
- **Normal variation.**

兩個例子

- Total bilirubin—1.49mg/dl 代表 不同疾病
  - *Post-hepatitis hyperbilirubinemia
  - *Non-conjugated hyperbilirubinemia
- AFP: 29----------*(GOT and GPT:每3個月一次連續3年均正常,不像CAH引起,也無cirrhosis, Abd. CT and Sono也無HCC.)
  - * Unexplained increase ?
  - * **Normal variation** —increased production without disease

Long-term follow up.

12.All abnormal data 要 Follow up,作為下一步處理之依據(住院病人至少每一週)(OPD, q2-3 months.)

- 1. Turn to be normal – Improved, healed, better than before, effective in treatment, no more active (disease activity)
  2. Aggravated or increased--- became abnormal, worse, downhill, complicated, not effective in treatment. Still active
  3. Remain the same extent—the same condition, not effective in treatment.

13.出院前要再確認一次

- Normalized-→ treated and improved.
- Still abnormal—但已減小,改善(好很多)
- **Still abnormal---未變好/甚至更高-→尚未好轉,**
- 有未查出的問題,→ readmission reasons
- 值得注意,再 follow up.
- 絕不可置之不理或等閑視之
- Abnormal data—正代表問題或其結果

14. CBC in Cirrhosis

- Hb---- 正常或稍低

  明顯低 (Hb:<12gm/dl)—有出血史?
- WBC: 低<4500

  低於3000---Hypersplenism(>2,000)

  低於2,000---另有原因
- Platelet:低—<150,000 (100,000~130,000)

  明顯低<100,000 (50,000~80,000)

  很低---around 30,000~50,000– *Hypersplenism*

  非常低 <30,000----另有原因

15.Thrombocytosis

- **Platelet > 400,000**
- **causes :**
- **1. BM: over production**
- **2. Spleen :reduce destruction of platelet**

Thrombocytosis cause

Essential (primary)

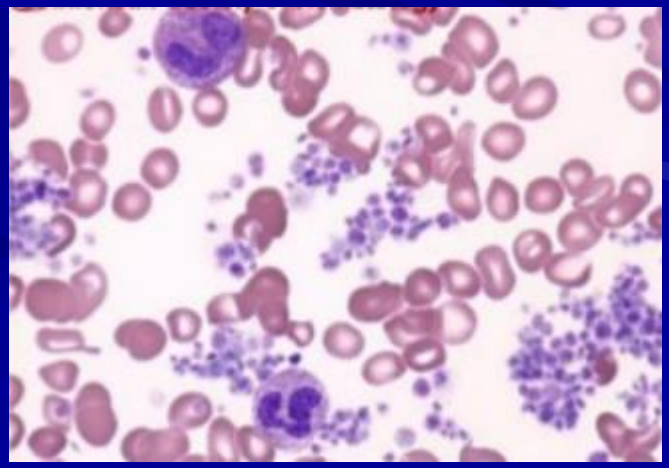
- Essential thrombocytosis (a form of myeloproliferative disease)
- Other myeloproliferative disorders such as chronic myelogenous leukemia, polycythemia vera, myelofibrosis

Reactive (secondary)

- Inflammation
- Surgery (which leads to an inflammatory state)
- Hyposplenism (decreased breakdown due to decreased function of the spleen)
- Asplenia (the absence of normal spleen function)
- Hemorrhage and/or iron deficiency

Over-medication with drugs that treat thrombocytopenia may also result in thrombocytosis

- **Refer all thrombocytosis patients for cancer check,**
- *Thrombocytosis has an 11.6% positive predictive value for cancer in men and 6.2% in women, according to research published in the British Journal of General Practice (BJGP).*
- David Millett on the 23 May 2017 at GP

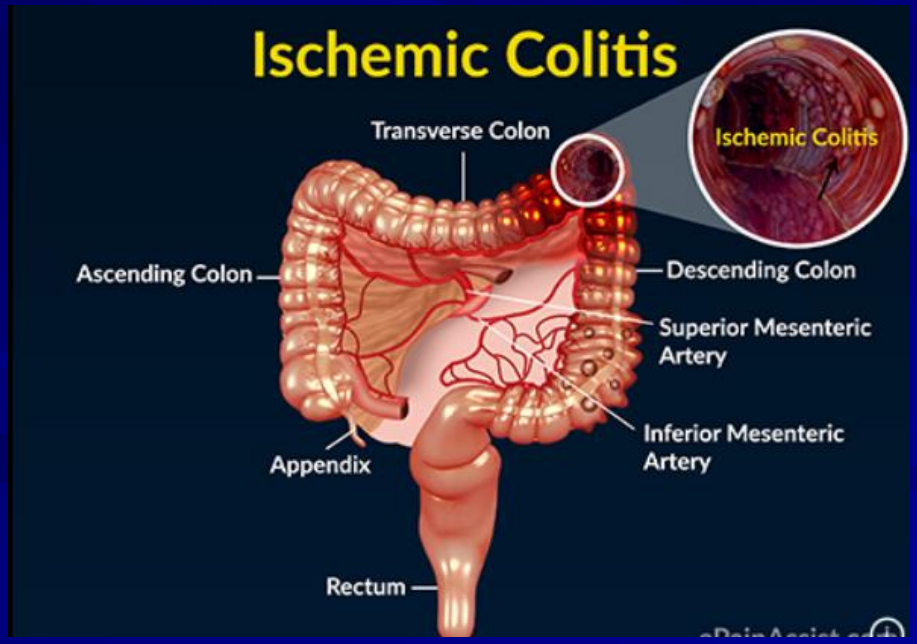


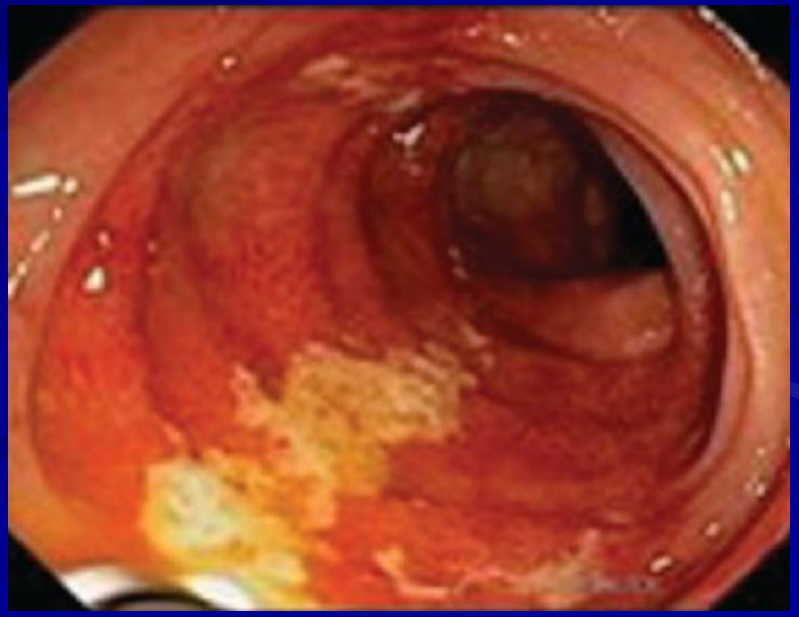
16. Thrombotic tendency

- **Thrombotic tendency:** A disorder of HEMOSTASIS in which there is a tendency for the occurrence of THROMBOSIS.
- 1. Thrombocytosis
- 2. Polycythemia
- 3. Extreme hyperglobulinemia
- 4. Auricular fibrillation
- 5. Presence of cryo-globulinemia
- 6. Vascular injury (ex. During cardiac cathe,)

First case of ischemic colitis due to polycythemia

- RBC: 6,5 m
- WBC: 18,900
- Thrombocytosis: 650,000





Mesenteric infarction due to Procrit.

- **Mesenteric infarction due to iatrogenic polycythemia.** Skoog K,et al (*University of Florida School of Medicine,US):*World J Emerg Med. 2013; 4(3): 232–234.
- a patient with a history of non-small cell lung cancer undergoing maintenance oral chemotherapy on tarceva and adjunctive use of procrit. The patient presented to emergency department with an acute abdomen and was found to have ischemic bowel from unmonitored **procrit,** which lead to **hyperviscosity** of blood and mesenteric infarction. **PROCRIT（EPOETIN ALFA）注射液**
- A 50-year-old man with a history of stage IV non-small cell lung cancer. His CBC was checked on December 5, 2011 and H/H at that time was 19/58.6, and it trended up to 23/66 on December 11, 2011.
- Exploratory laparotomy showed that he had a significant amount of necrotic bowel from the sigmoid to the ileum. The operation included an enterectomy and subtotal colectomy.

19.Complete liver function tests for evaluation

- 只要任何一項出現不正常GOT, GPT and GGT– **screening → complete tests.**
- Bilirubin: Total and conjugated bilirubin.
- AFP: normal or abnormal.
- WBC →leukopenia ?
- Platelet < 123,000
- Low serum albumin
- High serum globulin
- Pro-thrombin time

一定要同時查
Total bilirubin and conjugated bilirubin.
A/G ratio.

20.小便變紅是血尿?茶色尿?

- Tea color urine or hematuria一定要問清楚!
  「像血那麼紅嗎?」
- **Tea color urine+ Clay color stool --→ obstructive jaundice**

  Tea color urine (無灰色便)→一般之黃疸症

  --→*hepatitis(conjugated hyperbilirubinemia)*

  Urinalysis 可以證明有無血尿,確定診斷.

  一定查complete liver functions**. (AST, ALT,Bilirubin,ALP,GGT,A/G,prothrombin time---)*

Obstructive jaundice 最早出現的變化是 tea color urine

21.Anemia要好好查腸胃疾病

- GI bleeding—minor blood loss,
- --chronic,不一定會警覺。
- Colon cancer, right sided
- Gastric cancer, NSAID,
- Small bowel lesions, small or occult
- * **microcytic hypochromic** anemia
- 急性出血在24hours之後才維持平衡,真實的data.出血病人滿一天後一定要查
- Treatment: Blood transfusion 使Hb 達到10gm/dl以上老人家要慢慢輸血。

22. Evidence of liver cell damage

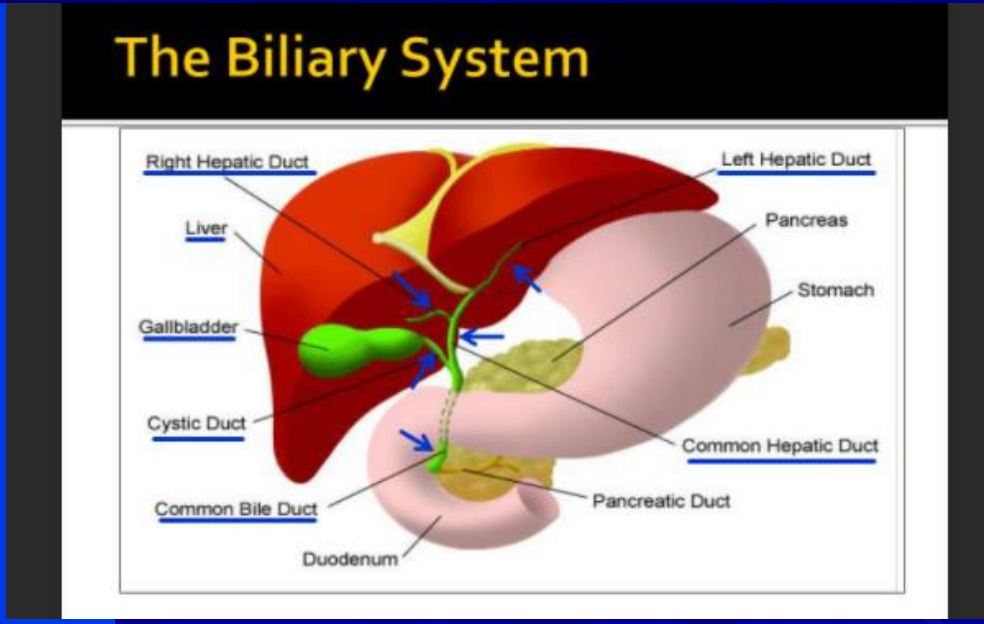
- 1. GOT or GPT >100 (recent 1-2 months)
- 2. GOT or GPT> 300 (mostly recent)
- 3. Change of serum bilirubin: increased
- 4. Prolonged prothrombin time
- 5. Clinical jaundice
- 6. Bleeding tendency
- 7. hepatic coma
- 8. evidence/signs of chronic liver disease

23. Evidence of obstructive jaundice

- Striking increase in GGT and alkaline phosphatase. **Biliary enzymes:要同時查Alk-P-tase及rGT可作疾病變化之指標**
- Mild or moderate hyperbilirubinemia
- Tea color urine + clay color stool
- CBD : dilated/intrahepatic biliary dilatation
- Itching

Biliary enzymes

- Alk-P-tase & bilirubin
  rGT and alcoholic liver disease
  5'-nucleotidase
    - Alcoholic liver disease
    - HCC and metastatic cancers
    - Cholestasis,
    - Biliary obstruction—
      obstructive jaundice



24. What kinds of changes indicate severe liver damage and failure ?

✦**A: 1. 相關數值顯示劇烈變化**：

- SGOT/SGPT：持續2-3週以上都是在300以上
- Bilirubin：直線上升，total bilirubin超過10
- direct bilirubin 超過4mg/dl
- **Prothrombin time ：延長至20sec 以上**
- NH3 ：上升
- Albumin： **急性病人降低至3.0gm/dl 以下**，特別是2.5 以下

  慢性病人降低至2.5gm/dl 以下，且出現大 量腹水

A2. 死亡交叉

- **(a)Bilirubin 上升，而SGOT/SGPT反而下**
- **降(至100以下)**
- **(b) 黃疸↑，但肝反而縮小liver atrophy**
- (c) Bilirubin ↑ // 肝反而縮小~意識變差
- (d) Consciousness 變差~
- Prothrombin time 延長
- (d) **Bilirubin ↑/ Prothrombin time 延長**

25. Acute liver failure
找原因及去除原因最重要

- Acute liver failure:
- 立刻找出原因及去除原因
  - 1.急性B肝→HBIG, Antiviral+supportiveTx.
  - 2.Drugs---Dc responsible drugs
  - 3.Alcohol-→DC alcohol
  - 4.Acetaminophen –antidote
  - 5. Others: unknown---**treat and observe.**
- @@Treatment of hepatic encephalopathy
- @@Liver transplantation

26. What kinds of changes indicate chronicity ?

- 1. **Globulin was abnormal, more than 3.5**
- **gm/dl.**
- 2. A/G was reversed. (in cirrhosis)
- 3. **SGPT was often more than SGOT**.
  especially GOT was normal
- 4. Globulin fraction increased greatly within 2 weeks after acute liver damage. It might be noticed by Globulin value or **ZTT**(Zinc turbidity test or Kunkel test)

27 What kinds of changes indicate **HCC** in the patients with chronic liver diseases.

1.Sudden deterioration of liver function—
with jaundice– etc.

- 2. RUQ pain with hepatomegaly
- 3. Bloody ascites.
- 4. **Increase in AFP** without recent severe liver cell damage
- 5. SGOT/SGPT ratio : more than 2.5
- 6. Chronic HBV liver disease or chronic HCV hepatitis associated with alcoholic liver disease.

28.B肝帶原的病人:
好好關心他的過去

- Case1. 媽媽帶原? 但是**3個兄弟都有 HCC**表示媽媽帶原很明顯,

HBV→Chronic liver diseases→LC→HCC

15 years ago (at 35)---知道肝功能不正常,有 chronic changes

5 years ago---有liver cirrhosis(因 gall stone 手術)

現在 **LFT 有問題: GOT /GPT=210/44**

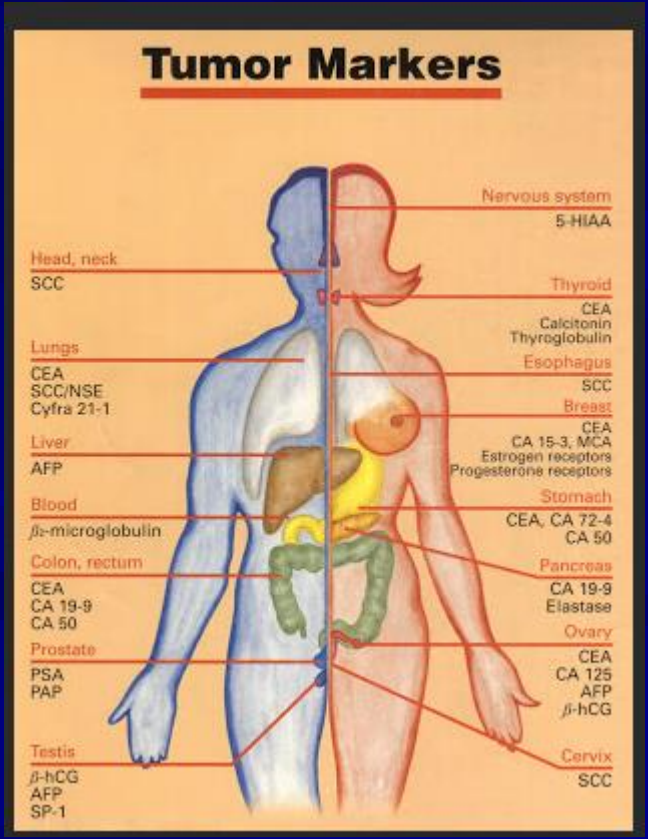
AFP>40 (44)

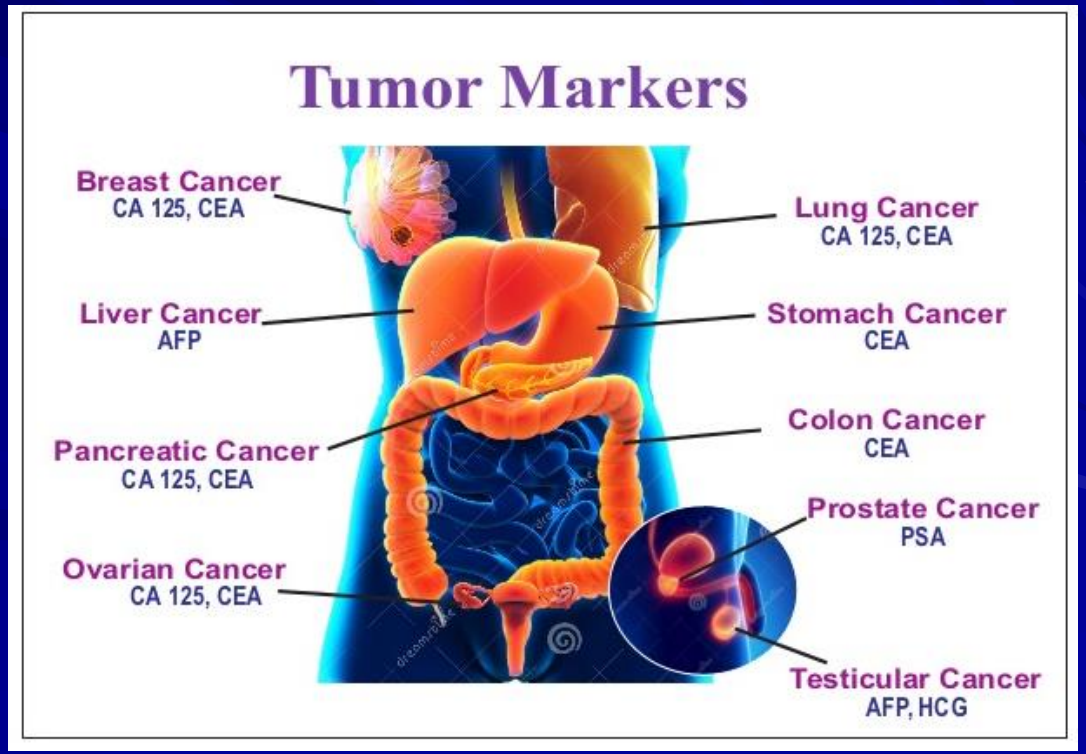
Abdominal sono– liver mass noted.

重要里程碑:Universal HBV vaccination in Taiwan from July, 1986. (age factor)

29. Tumor markers：not 100 % sensitive and also not specific

- CEA: 40-44 % for CRC
- AFP：about 70 % for HCC (abnormal)





一個tumor marker不只代表一個器官的腫瘤

Serum Tumor Markers	
Marker	**Associated Cancers**
α-fetoprotein	Hepatocellular carcinoma, nonseminomatous testicular germ-cell tumors (yolk sac tumor)
β-human chorionic gonadotropin (hCG)	Trophoblastic tumors, choriocarcinoma
Calcitonin	Medullary carcinoma of the thyroid
Carcinoembryonic antigen (CEA)	Carcinoma of the lung, pancreas, stomach, breast, colon
CA-125	Ovarian cancer
CA 19-9	Pancreatic cancer
Placental alkaline phosphatase	Seminoma
Prostatic acid phosphatase	Prostate cancer
PSA	Prostate cancer
S-100	Melanoma, neural-derived tumors, astrocytoma
Tartrate-resistant phosphatase (TRAP)	Hairy cell leukemia

Tumor markers

- 1.注意 normal ranges
- 2.causes of elevation
  - Cancer, Benign, false positive
- 3.注意 follow up.
- 4.不同的 histology ,有不同的tumor markers,
- 5.尚待發掘new and ideal tumor markers

TABLE **Tumor markers in ovarian masses**

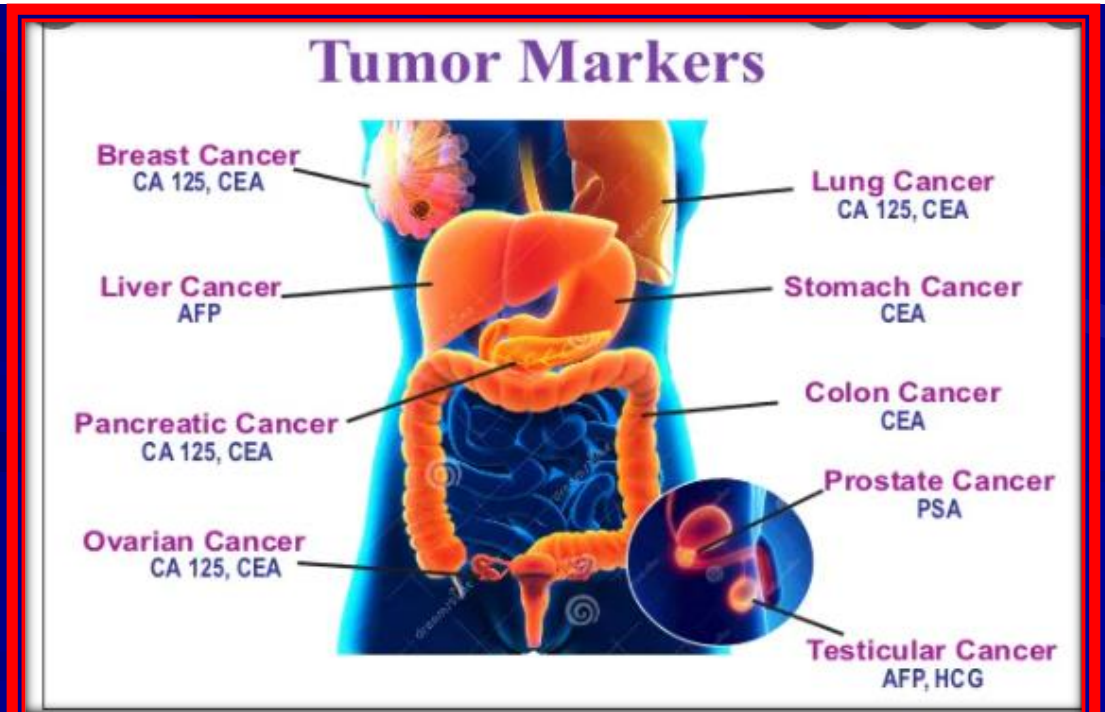
Tumor marker	Ovarian neoplasm
CA-125	Epithelial ovarian cancer
CEA	Mucinous ovarian cancer
HCG	Embryonal carcinoma Choriocarcinoma
Inhibin A or inhibin B	Granulosa cell tumor
Lactate dehydrogenase	Dysgerminoma
α-Fetoprotein	Endodermal sinus tumor Embryonal carcinoma

Abbreviations: CEA, carcinoembryonic antigen; HCG, human chorionic gonadotropin.

Tumor markers, circulating

Circulating tumor markers can be found in the blood, urine, stool, or other bodily fluids of some patients with cancer. Circulating tumor markers are used to:

- estimate prognosis
- determine the stage of cancer
- detect cancer that remains after treatment (residual disease) or that has returned after treatment
- assess how well a treatment is working
- monitor whether the treatment has stopped working



Review > Updates Surg. 2017 Dec;69(4):441-449. doi: 10.1007/s13304-017-0491-3. Epub 2017 Sep 16.

Tumor markers of uterine cervical cancer: a new scenario to guide surgical practice?

Gaetano Valenti [1], Salvatore Giovanni Vitale [2], Alessandro Tropea [1], Antonio Biondi [1], Antonio Simone Laganà [3]

Affiliations – collapse

Affiliations

1 Department of General Surgery and Medical Surgical Specialties, University of Catania, Catania, Italy.

- Researches have made efforts to individuate cancer markers as indicator of specific cancer events. Some markers were showed to be able to detect those intraepithelial lesions have more chance to evolve to invasive forms **($p16^{ink}4a$, p16, E-cadherin, Ki67, pRb, p53).** Markers such as CEA, SCC-Ag, CD44, have been developed to detect invasive forms. Although cancer markers actually are not used only for early diagnosis, they may be useful in others fields of application such as evaluation and monitoring of treatments to improve diagnosis and treatment of CC.

> Zhonghua Fu Chan Ke Za Zhi. 2020 Nov 25;55(11):784-790.
doi: 10.3760/cma.j.cn112141-20200520-00428.

[Clinical value of p16 ^{INK4a} immunocytochemistry in cervical cancer screening]

[Article in Chinese]
F B Song [1], H Du [1], A M Xiao [1], C Wang [1], X Huang [1], P S Yan [1], Z H Liu [1], X F Qu [1], J E R O M E L Belinson [2], R F Wu [1]

Affiliations – collapse

Affiliations

1 Department of Obstetrics and Gynecology, Peking University Shenzhen Hospital, Shenzhen Key Laboratory on Technology for Early Diagnosis of Major Gynecological Diseases, Shenzhen 518036, China.
2 Preventive Oncology International, Cleveland Heights, OH, United States of America, 44101.

P 16

Methods: Between 2016 and 2018, 5 747 non-pregnant women aged 25-65 years with sexual history were recruited and underwent cervical cancer screening via high-risk (HR)-HPV/liquid-based cytological test (LCT) test in Shenzhen and surrounding areas. All slides were immuno-stained using p16^{INK4a} technology, among them, 902 cases were offered p16^{INK4a} detection during primary screening, and the remaining 4 845 cases were called-back by the virtue of abnormal HR-HPV and LCT results for p16^{INK4a} staining.

Results: (1) One-thousand and ninety-seven cases with complete data of p16^{INK4a} and histology were included.
Pathological diagnosis: 995 cases of normal cervix, 37 cases of low grade squamous intraepithelial lesion (LSIL), 64 cases of HSIL and one case of cervical cancer were found. Among them, 65 cases of HSIL (CIN Ⅱ)$^{+}$ and 34 cases of HSIL (CIN Ⅲ)$^{+}$ were detected. The positive rate

P16^{ink}4a (p16)

- **p16** (also known as **p16^{INK4a}**, **cyclin-dependent kinase inhibitor 2A**, **CDKN2A**, **multiple tumor suppressor 1** and numerous other synonyms), is a protein that slows cell division by slowing the progression of the cell cycle from the G1 phase to the S phase, thereby acting as a tumor suppressor. It is encoded by the *CDKN2A* gene. A deletion (the omission of a part of the DNA sequence during replication) in this gene can result in insufficient or non-functional p16, accelerating the cell cycle and resulting in many types of cancer.[

Review > J Clin Oncol. 1998 Mar;16(3):1197-206. doi: 10.1200/JCO.1998.16.3.1197.

Role of the p16 tumor suppressor gene in cancer

W H Liggett Jr [1], D Sidransky

Affiliations – collapse

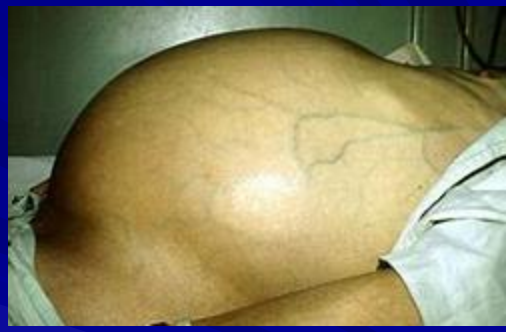
Affiliation

1 Department of Otolaryngology-Head and Neck Surgery and The Johns Hopkins Oncology Center, Johns Hopkins Hospital, Baltimore, MD 21205-2195, USA.

Since its discovery as a CDKI (cyclin-dependent kinase inhibitor) in 1993, the tumor suppressor p16 (INK4A/MTS-1/CDKN2A) has gained widespread importance in cancer. The frequent mutations and deletions of p16 in human cancer cell lines first suggested an important role for p16 in

30, What are **decompensate signs** of liver cirrhosis(hepatic failure)

- 1. Jaundice – serum bilirubin不正常
- 2. Ascites ---serum albumin低
- 3. Hepatic encephalopathy --
- Hepatic odor
- **Flapping tremor**
- NH3 increased
- EEG change: triphasic wave.



31.炎症指標,不同疾病之變化不同

Inflammatory parameters

WBC

DC─ : PMN : Shift to left

Neutrophilia(>5,000)

CRP

ESR

LDH

……

①normal range

②data 變化,判斷

Progression

Improvement

32. 表示severe inflammation and tissue reaction

- WBC>15,000甚至>20,000
- Neutrophils >85% or >10,000
- **CRP>8 甚至>12**
- severe Infection-
- **Sepsis--Blood cultures**
- Abscess: liver or retroperitoneal
- - CT and abd sono--aspiration
- SBE->infectious endocarditis
- PE and cardiac echo.

33, CRP>20

- 危險值,
  - Tissue reaction→ necrosis
  - Intestinal perforation (ileus)
  - UC- severe, associated with active bleeding
  - Toxic megacolon in UC, CMV, amebic, PMC
  - sepsis, critical

- Interpretation of data :

  0.8—3.0 --------
  mild

  3.0-8.0 ----------
  moderate

  8 --20 severe

  More than 20 ---- very high , cautious.

34.腫瘤記號, should be carefully evaluated.

Tumor markers

AFP

CEA

Ca 199

Ca 125

PSA, f-PSA

- 現在值
- 過去data 比較
- 測定方法、RIA or non-RIA
- Presence of false positivity—smoking
- Clinical evaluation by imaging
- Risk factors.

35. HCC: 甲型胎兒蛋白

AFP：代表肝細胞之再生及惡化

less than 20…仍有30%HCC，AFP不增加

20-200---20 % 是HCC

200-400　90%是HCC

>400 …　99%以上是HCC

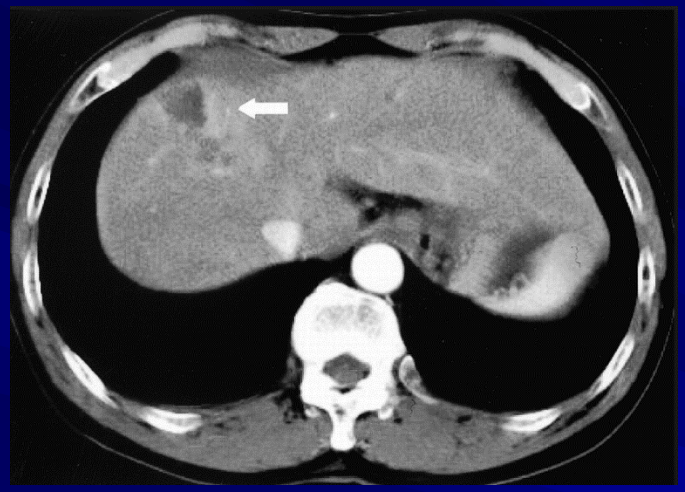
>5,000 …　99.99 %以上是HCC

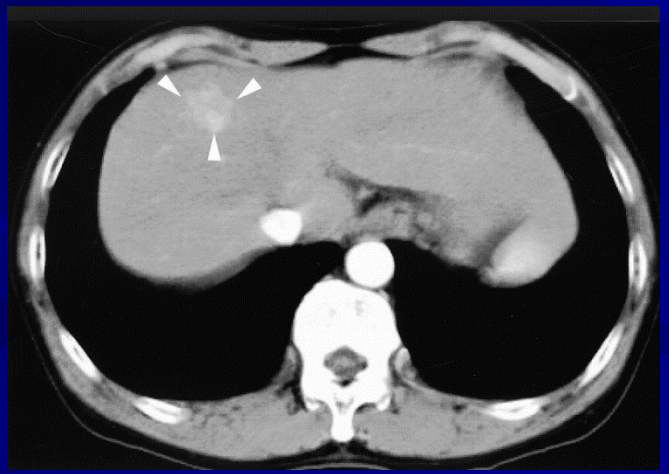
>10,000　100%是HCC

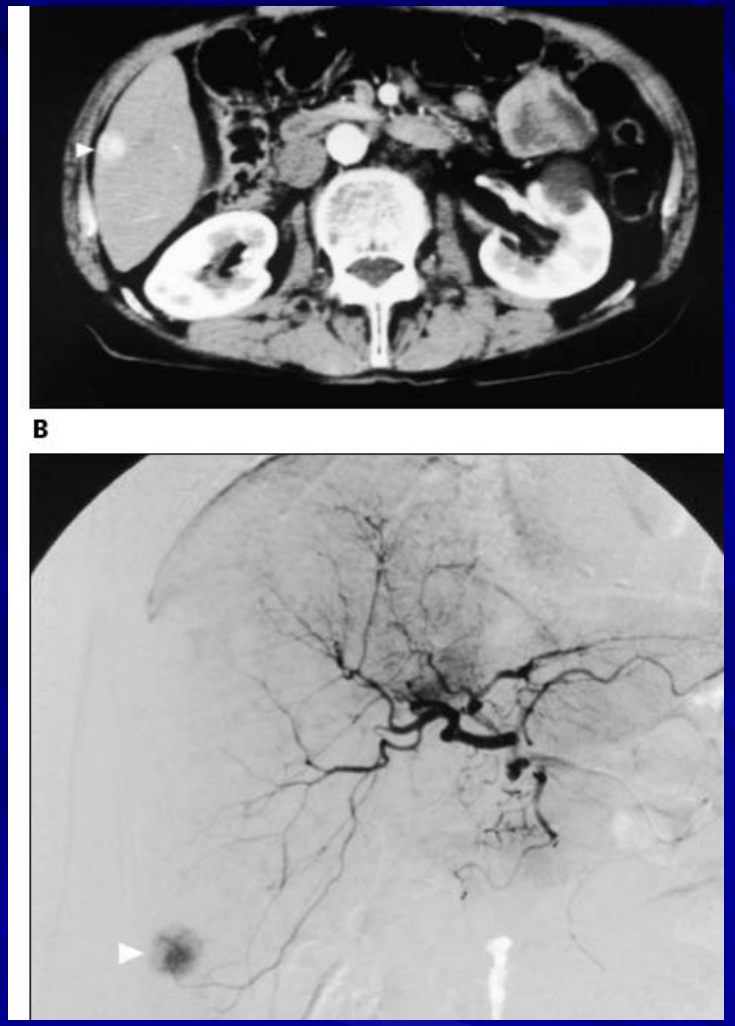
Ex. AFP>400 …　99%以上是HCC

- No evidence of severe liver necrosis within 2 months.
- Careful investigation should be done.
- Notice minor changes in abdominal CT and angiography

有機會找到Small HCC







Small Hepatocellular Carcinoma Therapeutic Effectiveness of Percutaneous Radio Frequency Ablation Therapy With a LeVeen Needle Electrode
Kazuhito Shirato, MD, et al J Ultrasound Med 21:67–76, 2002

36. Normal AFP HCC

- **Prognosis evaluation in alpha-fetoprotein negative hepatocellular carcinoma after hepatectomy: comparison of five staging systems.** Zhang XF[1] et al)西安交大丿:Eur J Surg Oncol. 2010 Aug;36(8):718-24.
- The data of 306 in total and 98 AFP negative patients
- AFP negative patients tended to have intact tumor capsule and earlier staged tumor by TNM, CLIP and BCLC. The independent risk factors worsening overall survival of AFP negative patients were absence of tumor capsule, Child-Pugh classification B, hepatitis B surface antigen positive and BCLC stage B-C.
- Normal AFP level implies earlier staged tumors. BCLC has the strongest potential in prognosis evaluation in AFP negative patients.

神經突生長促進因子2（NEGF2）Midkine

Midkine Increases Diagnostic Yield in AFP Negative and NASH-Related Hepatocellular Carcinoma.

- Roslyn Vongsuvanh et al (Sudney Univ. Australia) PLOS, May 24, 2016.
- **serum midkine (MDK**), dickkopf-1 (DKK1), osteopontin (OPN) and AFP for HCC diagnosis in 86 HCC patients matched to 86 cirrhotics, 86 with chronic liver disease (CLD) and 86 healthy controls (HC).
- More than half of HCC patients had normal AFP. In this AFP-negative HCC cohort, 59.18% (n = 29/49) had elevated MDK, applying the optimal cut-off of 0.44 ng/ml.
- Using AFP ≥ 20 IU/ml or MDK ≥ 0.44 ng/ml, a significantly greater number (76.7%; n = 66/86) of HCC cases were detected
- **Conclusion:** AFP and MDK have a complementary role in HCC detection. MDK increases the diagnostic yield in AFP-negative

- **Serum Midkine and Osteopontin Levels as Diagnostic Biomarkers of Hepatocellular Carcinoma.**
- Hodeib H[1],et al (Egypt): Electron Physician. 2017 Jan 25;9(1):3492-3498.
- Midkine (MDK) is a 13-kDa small heparin-binding growth factor.
- mean serum levels of OPN and MDK were significantly elevated in HCC patients either by comparing HCC patients vs. HCV patients without cirrhosis, HCC patients vs. HCV patients with cirrhosis or HCC patients vs. healthy subjects. Serum MDK levels had better **sensitivity and specificity** than OPN and AFP levels in the diagnosis of HCC (98.4 %, 97.1% and 97%) and (96.2%, 95.3% and 95%) for MDK, OPN and AFP respectively.

New Biomarkers for Hepatocellular Carcinoma

Roongruedee Chaiteerakij, MD, Benyam D. Addissie, MD,
Lewis R. Roberts, MD, PhD
Mayo Clinic
Rochester, MN

World J Gastroenterol. 2015 Oct 7; 21(37): 10573–10583.
Published online 2015 Oct 7. doi: 10.3748/wjg.v21.i37.10573
PMCID: PMC458807
PMID: 2645701

Biomarkers for the early diagnosis of hepatocellular carcinoma

Nobuhiro Tsuchiya, Yu Sawada, Itaru Endo, Keigo Saito, Yasushi Uemura, and Tetsuya Nakatsura

Nobuhiro Tsuchiya, Yu Sawada, Itaru Endo, Department of Gastroenterological Surgery, Graduate School of Medicine, Yokohama City University, Yokohama 236-0027, Japan
Nobuhiro Tsuchiya, Keigo Saito, Yasushi Uemura, Tetsuya Nakatsura, Division of Cancer Immunotherapy, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center, Kashiwa 277-8577, Japan

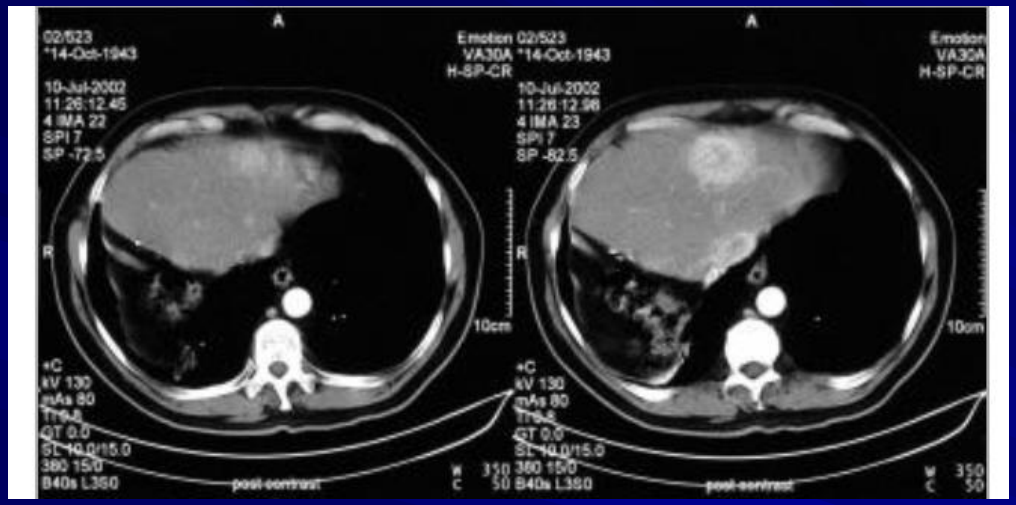
Advances in genomics and proteomics platforms and biomarkers assay techniques over the last decade have resulted in the identification of numerous novel biomarkers and have improved the diagnosis of HCC. The most promising biomarkers, such as glypican-3, osteopontin, Golgi protein-73 and nucleic acids including microRNAs, are most likely to become clinically validated in the near future.

New Treatments in Liver Disease

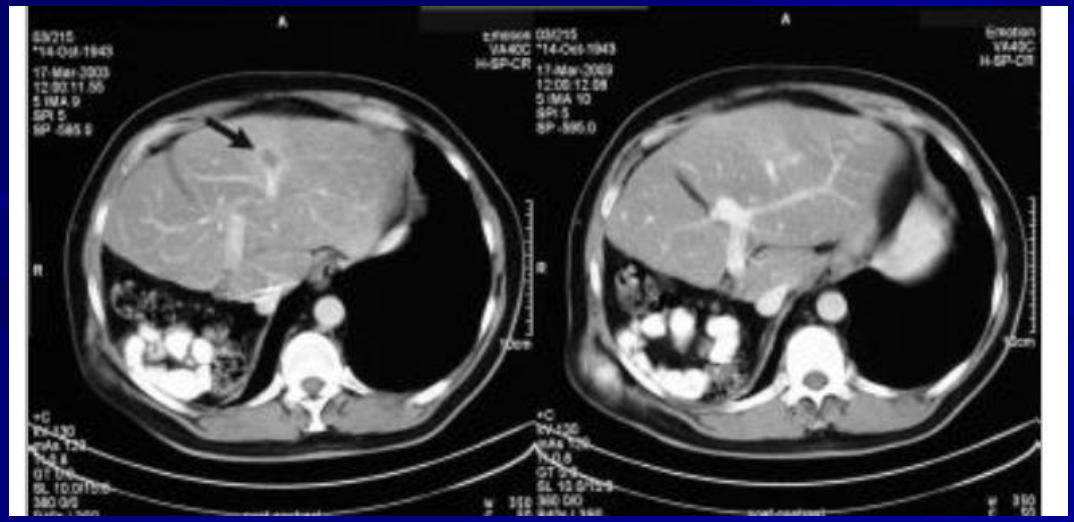
American Association for the Study of Liver Diseases

HCC biomarkers are used for predicting risk for HCC development, screening and surveillance, diagnosis, stratifying patients for targeted therapy, monitoring treatment response, and predicting HCC recurrence and patient survival. A number of SNPs have been identified as new biomarkers for HCC risk prediction. For HCC diagnosis, the serum AFP remains a useful biomarker, with a higher sensitivity than AFP-L3 and DCP. The combination of AFP with AFP-L3 or DCP may be better than using AFP alone as a biomarker for HCC diagnosis. Recent findings suggest that the combination of AFP with other variables, such as ALT, or patient and tumor characteristics (e.g. the MESIAH score), improves performance of AFP for early HCC detection and

37. Check Imaging in Metastatic cancer



CT scans taken in the portal venous phase show a hypervascular metastatic deposit from a renal cell carcinoma. The patient had a previous right hepatectomy for an earlier renal cell solitary metastatic deposition.



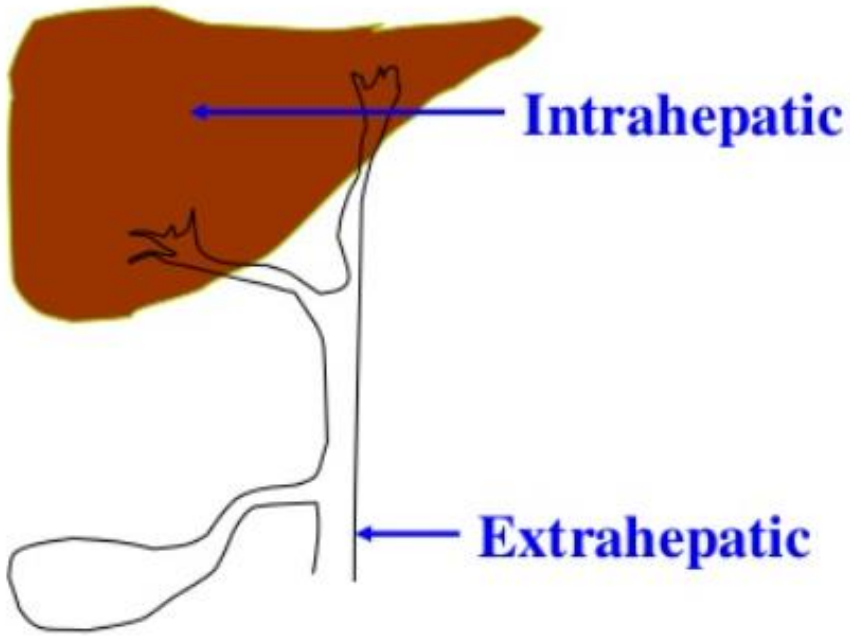
CT scan in the same patient as in the previous image following immunotherapy. Note the considerable reduction in the size of the liver lesion.

38. Cholestasis

- **Cholestasis** is a condition where bile cannot flow from the liver to the duodenum. The two basic distinctions are an obstructive type of cholestasis where there is a mechanical blockage in the duct system that can occur from a gallstone or malignancy, and metabolic types of cholestasis which are disturbances in bile formation that can occur because of genetic defects or acquired as a side effect of many medications.

Cholestasis (Greek-bile stoppage)

Reduction or absence of bile flow into duodenum

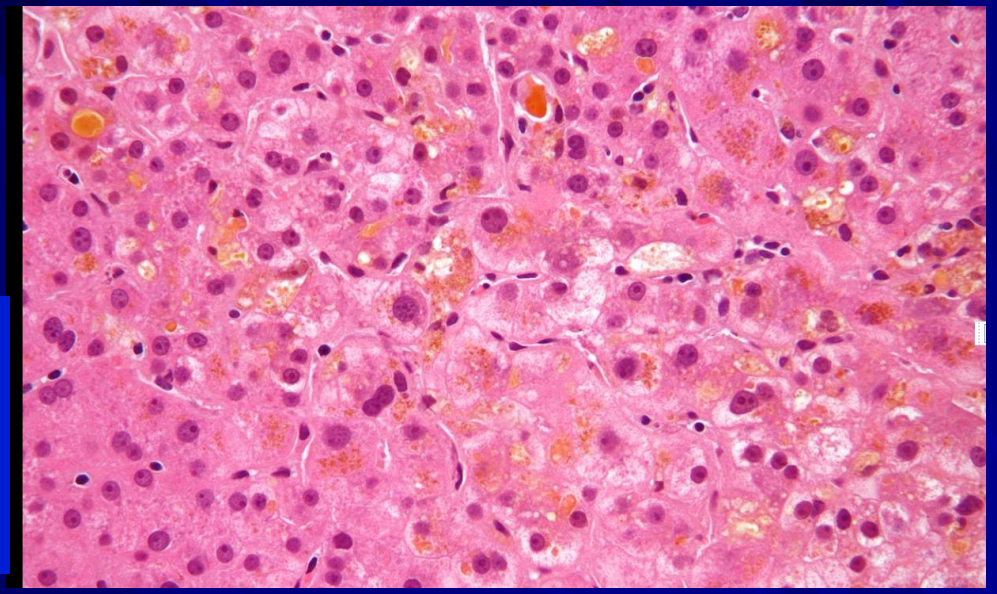


- Impairment of bile secretion at the level of bile ductules (ductular cholestasis)
- Functional defect in bile formation at hepatocyte level (hepatocellular chlestasis)

Chronic if > 6mo duration
Etiology: differs across ages
Alkaline phosphatase >1.5ULN, GGT> 3ULN*

Cholestasis

the individual hepatocytes will have a brownish-green stippled appearance within the cytoplasm, representing bile that cannot get out of the cell. Canalicular bile plugs between individual hepatocytes



- Cholestasis can be suspected when there is an **elevation of both 5'-nucleotidase and ALP enzymes**. With a few exceptions, the optimal test for cholestasis would be elevations of serum bile acid levels. However, this is not normally available in most clinical settings. **The gamma-glutamyl transferase (GGT) enzyme was previously thought to be helpful in confirming a hepatic source of ALP**; however, GGT elevations are markedly sensitive and lack the necessary specificity to be a useful confirmatory test for ALP. Normally GGT and ALP are anchored to membranes of hepatocytes and are released in small amounts in hepatocellular damage.

- **Abnormal liver enzyme levels may signal liver damage or alteration in bile flow. Liver enzyme alteration may be either the accompanying biochemical picture in a patient with symptoms or signs suggestive of liver disease or an isolated, unexpected finding in a patient who has undergone a wide range of laboratory tests for a** nonhepatic disease or for minor, vague complaints. The latter situation is a common clinical scenario today because of the routine incorporation of hepatic tests in automated blood chemistry panels. Isolated alterations of biochemical markers of liver damage in a seemingly healthy patient often represent a challenge even for the experienced clinician and usually set off a battery of further, costly tests[1] and consultations that may ultimately prove unnecessary.

CMAJ. 2005 Feb 1; 172(3): 367–379.
doi: 10.1503/cmaj.1040752

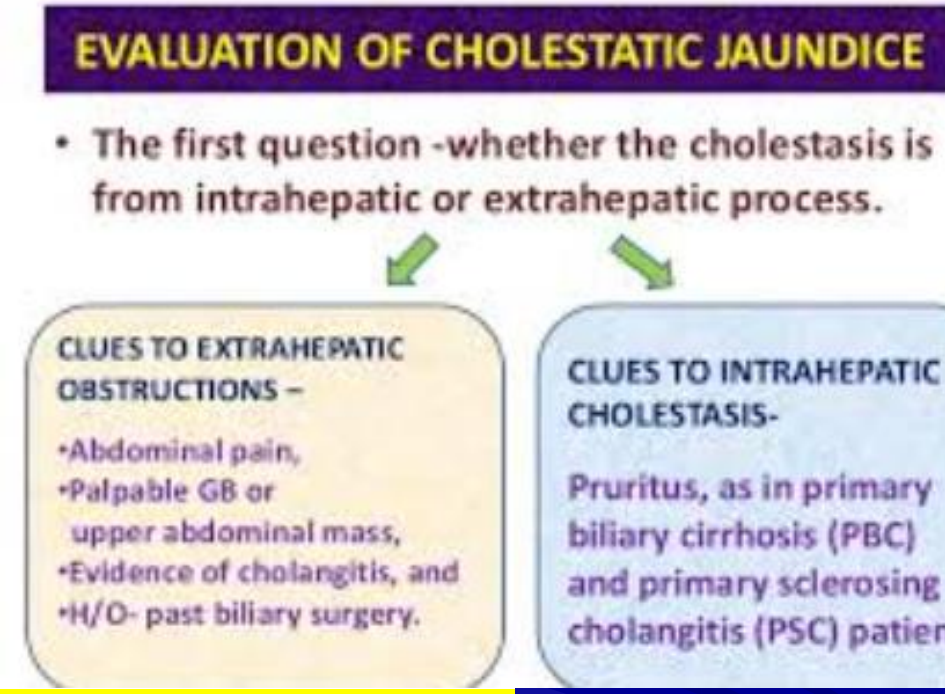
Liver enzyme alteration: a guide for clinicians

Edoardo G. Giannini, Roberto Testa, and Vincenzo Savarino

Cholestasis, intrahepatic

Intrahepatic cholestasis occurs inside the liver. It can be caused by:

- Alcoholic liver disease
- Amyloidosis
- Bacterial abscess in the liver
- Being fed exclusively through a vein (IV)
- Lymphoma
- Pregnancy
- Primary biliary cirrhosis
- Primary or metastatic liver cancer
- Primary sclerosing cholangitis
- Sarcoidosis
- Serious infections that have spread through the bloodstream (sepsis)
- Tuberculosis



1.Itching→intrahepatic
2. CBD dilatation-
→extrahepatic.

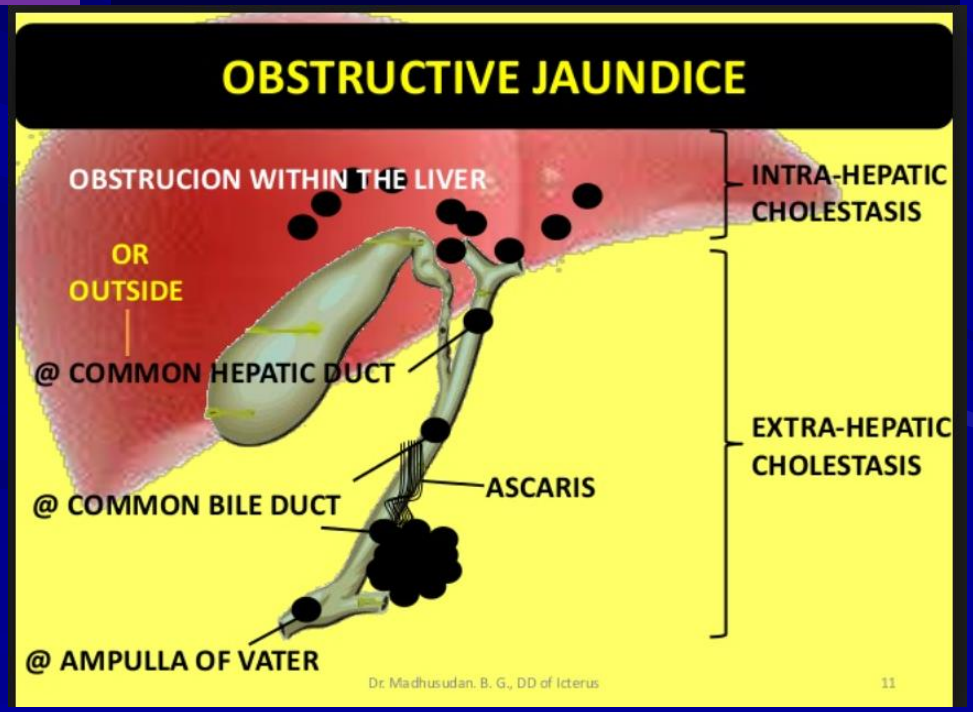
intrahepatic cholestasis of pregnancy

- Intrahepatic cholestasis of pregnancy is a liver disorder that occurs in pregnant women. Cholestasis is a condition that impairs the release of a digestive fluid called bile from liver cells. As a result, bile builds up in the liver, impairing liver function. Because the problems with bile release occur within the liver (intrahepatic), the condition is described as **intrahepatic cholestasis**. Intrahepatic cholestasis of pregnancy usually becomes apparent in the third trimester of pregnancy. **Bile flow returns to normal after delivery** of the baby, and the signs and symptoms of the condition disappear. However, they can return during later pregnancies. This condition causes severe itchiness (pruritus) in the expectant mother. The itchiness usually begins on the palms of the hands and the soles of the feet and then spreads to other parts of the body.

Obstructive JAUNDICE

- Gall stone with obstructive jaundice due to impacted stone at CBD
- Obstructive jaundice due to pancreatic head cancer

US
Abdominal CT
ERCP
MRCP
Tests.bilirubin/GGT
Tumor markers
PTC



39. Within 72 hours
找出阻塞性黃疸的原因並處理之,達到減黃之目的

- Dx of obstructive jaundice
- Evaluation
- Check site of obstruction
- Check causes , **benign or malignant**
- Relief of obstruction at least reduction of jaundice.(biliary stents, PTCD, or surgery)

40. CEA值可供手術─切除與否之參考

- **注意不同方法之CEA值不可比較**
- **不同之lab 之檢查結果可供參考，不宜比較其大小**
- CEA值可供手術─切除與否之參考

CEA in Colorectal cancer 大腸癌 40-44 % (+)

<5…(正常值) …100%可切

5~10…(稍高) … 90%仍可開刀

10-20…(相當高) …50%可開

>20…(很高) … 1/7(14-15%)可開

41. Electrolyte abnormalities
hypokalemia,

Serum K : <3.2 m Eq/L.

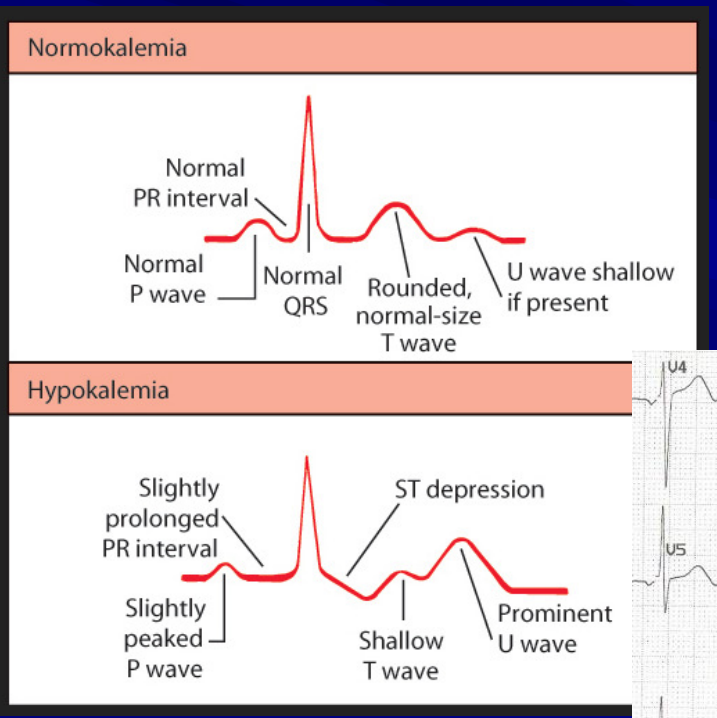
Severe hypokalemia : <2.5 mEq/L.

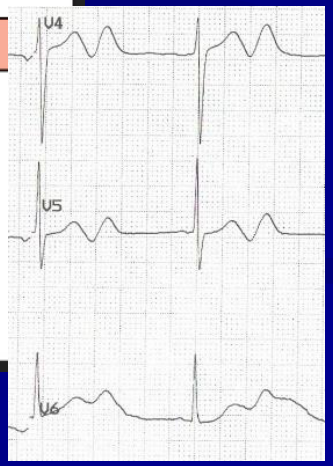
內科學誌 2010：21：31-39

低血鉀的診斷與治療

李忠政[1] 黃文德[1] 林石化[2]

[1]國軍左營總醫院 內科部
[2]三軍總醫院 腎臟內科





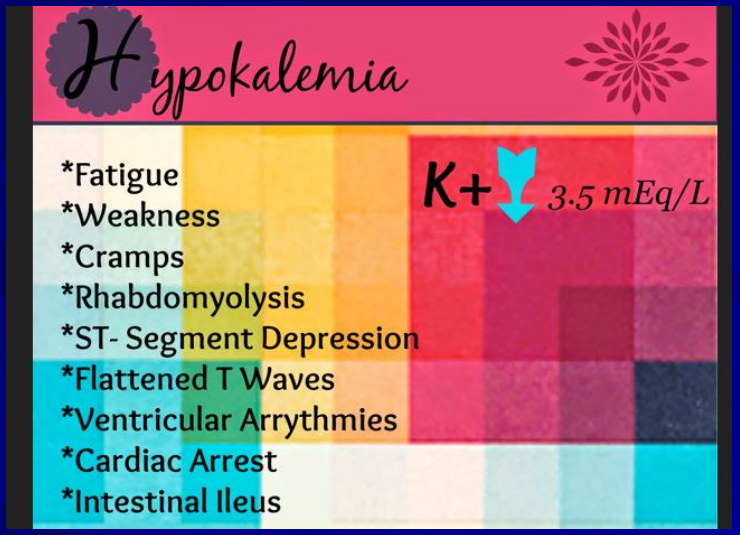
低血鉀可能會增加心臟血管疾病患者的罹病率及死亡率，導致 心律不整 (cardiac arrhythmias)、肌肉癱瘓甚至呼吸停止，因此如何快速的診斷與治療低血鉀 是本篇探討的主題。其病因可以依尿液鉀離子的排泄量 (potassium (K+) excretion)、血中酸鹼 值、血壓高低、血漿腎素活性(renin activity)、醛固酮 (aldosterone)濃度、皮質類固醇(cortisol) 濃度，及尿液中鈉離子與氯離子的濃度而進一步鑑別診斷。低尿液鉀離子排泄可為鉀離子急 性往細胞內移動，腸道鉀離子流失或之前腎臟過度排泄所引起。而高尿液鉀離子排泄則通常 合併有酸鹼異常。低血鉀的治療，主要取決於低血鉀的程度、造成低血鉀的快慢、臨床症狀、 潛在病因及其他相關的潛在危險因子。

hypokalemia

表三：低血鉀的治療

1. Medical emergency	Cardiac arrhythmia, respiratory insufficiency
2. Avoid risks of K^+ shift into cells	Do not give glucose, insulin and $NaHCO_3$
3. Magnitude of K^+ deficit	Large vs. small does of K^+
4. Route of K^+ administration	Central, peripheral or oral
5. K^+ preparations	KCl vs. $KHCO_3$ (K^+ citrate) vs. K^+ phosphate
6. Adjuncts to therapy	K^+-sparing agents, ACEI, AIIA
7. Associated settings	HPP, chronic hyponatremia, hypomagnesemia, volume depletion, severe metabolic acidosis, low muscle mass

ACEI: angiotensinogen converting enzyme inhibitor, AIIA: angiotensin II antagonist, HPP: hypokalemic periodic paralysis.



一、K^+ 補充量：在病人沒有 K^+ 往細胞內移動的狀況下，K^+ 濃度由 4 mmol/L 下降到 3 mmol/L 需要流失 350 mmol，如果降到 2 mmol/L 則需流失 750 mmol 的 K^{+1}。

二、K^+ 補充途徑：如果聽不見腸音，口服補充 K^+ 則不可行；周邊靜脈補充濃度不可超過 40 mmol/L；補充速度除非在緊急狀況下，否則不可超過 60 mmol/hour。

42. HB markers

Test	Result	Interpretation
HBsAg anti-HBc anti-HBs	negative negative negative	Susceptible (vaccinate)
HBsAg anti-HBc anti-HBs	negative positive positive	Infected but resolved. Resolved HBV infection
HBsAg anti-HBc anti-HBs	negative negative positive	Vaccinated **Anti HBc (-)**
HBsAg anti-HBc anti-HBs	positive positive negative	Active HBV infection (usually chronic) *If anti-HBc IgM present, may represent acute infection.
HBsAg HBcAb HBsAb	negative positive negative	Various possibilities: distant resolved infection (most common) recovering from acute infection false positive occult hepatitis B

43.找出檢驗異常的原因

- Severe anemia
- Hyperbilirubinemia
- Liver cell necrosis—
  SGOY and SGPT > 300
- Abnormal alkaline phosphatase and GGT
- =bone growing—alkaline phosphatase
- =biliary obstruction and cholestasis-both
- Alcoholic ---GGT
- Neoplastic—both GGT and ALP

Search for the causes of anemia, even mild

- Hgb: less than 12.
- Low Fe intake/chronic blood loss(due to menstruation)
- Chronic blood loss from the Gi tract

  Colon cancer, gastric cancer
- Episodes of bleeding(acute) resulted in moderate-severe anemia.
- BM function : impaired Pernicious anemia

  -- uremia, cancer with marrow metastases. Others

What are the causes of liver cell necrosis?

- Hepatitis
- Heart failure
- Drugs
- Fatty liver
- Alcohol and
- or other liver toxins
- Marijuana (cannabis) smoking
- leptospirosis
- ---

recognised causes of acute liver cell necrosis:

The following are recognised causes of acute liver cell necrosis:
(i) paracetamol overdose
(ii) severe heart failure
(iii) human papilloma virus
(iv) leptospirosis
(v) cannabis smoking

Sonia, 2008.

44.Physical check up健檢

- 早期發現問題:
- Abnormal ? 紅字
- -→是 acute change 還是 chronic
- --->調整生活方式/治療之效果
- **Data 之分析會比較嚴格,以求改善**
- **改變生活習慣:運動**
- Diet. Change
- 要Follow up.

- 注意所訂之 normal range.

Normal ranges是人設定的
電腦處理是死的

- Serum cholesterol : up to 200 (normal range)
- **201: abnormal**
- Lab cv ratio <5 % good quality
- 200X0.05=10
- 210=190 ---故 201 仍是正常

- *the **coefficient of variation (CV)**, also known as **relative standard deviation (RSD)***

摘要(2024.03.01.)

- 1. 一般常用的檢驗項目要熟悉 Normal ranges, clinical significance.思考不正常所代表的意義.與主要疾病有無關連.
- 2. 很多檢驗數據因Lab. 品質不良, Lab error大,會影響判斷
- 3. Lab data 可作疾病變動的指標(信號), 必須參考症狀及徵象之變動.
- 4. 要好好紀錄在病歷之上, 而且至少要在一週內Follow up.(主要變化時要 QD or Q2D)