

Case discussion

Fever + acute liver failure and Illness Scripts

Fever + Acute liver failure
Causes and management

Cheng-Yi WANG
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Case history

- A 26-year-old nonalcoholic female presented to the emergency department with a history of 4 days fever which was intermittent; the maximum temperature recorded was 102°F, associated with headache, retroorbital pain, and myalgia but without chills and rigor.

Q1, 一個年輕的女性發高燒(high fever) 4天在病史上
你還想知道一些什麼來解決發燒的原因

102°F = 38.9°C

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1. There was no history of mucocutaneous bleeding or bruises.
- 2. There was a history of multiple episodes of nausea and vomiting along with diffuse abdominal pain and distension, loss of appetite, and the generalized weakness associated with acute shortness of breath.
- 3. There was no history of chest pain, palpitation, orthopnea, dizziness, loss of consciousness, abnormal body movements, or altered sensorium. There was no similar history in the past.
- 4. Gyn-Obs history---病人否認有任何性關係,LMP: 3天前OK
- 5. 有沒有被蟲咬或被蚊子咬的病史.

Q2, Physical examination 要特別注意哪一些變化?

Physical examination 要特別注意哪一些變化?

- On examination, her blood pressure was 100/60 without a significant postural drop, pulse was 106 beats/min, oxygen saturation at room temperature was 98%, respiratory rate was 20/min, and the temperature was 101.4°F. **She was well-oriented to time, place, and person.** On abdominal examination, it was grossly distended with dull percussion with decreased bowel sound. There was the presence of crackles over the lower surface of both lung fields. Her heart sound was normal.

- 1.體溫與脈搏的變化有沒有相對性的脈搏緩慢(relative bradycardia)
- 2.有無皮膚出血的徵象破文整叮咬的傷口或紅腫
- 3.有無肺炎注意兩邊肺的呼吸聲.
- 4.血氧濃度:室溫氧飽和度為 98%，呼吸頻率為 20/分，
- 4.腹部檢查有無腹膜炎的徵象,特別注意疼痛的位置在何處確定是否需要找 婦科做內診

抽血檢查要特別注意哪一些事項?

Table 1

Investigations done on the day of admission

Investigations	Results	Reference range
Total leukocyte count (cells/mm ³)	11 950	4000–11 000
Differential count (%)	Neutrophils: 60.90, lymphocytes: 34.30	Neutrophils: 40–70, lymphocytes: 20–45
Hemoglobin (g%)	12.4	11.9–14.6
Packed cell volume (%)	35.20	40–50
Platelets (cells/mm ³)	78 000	150 000–450 000
Alanine transaminase (U/l)	2202	9.0–52
Aspartate transaminase (U/l)	74 160	14–36
Total bilirubin (mg/dl)	4.70	0.2–1.3
Conjugated bilirubin (mg/dl)	1.40	0–0.3
Unconjugated bilirubin (mg/dl)	1.20	0.01
Alkaline phosphatase (U/l)	311	30–126
Prothrombin time (s)	19.50	11.0–16
Control (s)	14	
Random blood glucose (mg/dl)	60	80–140
C-reactive protein (mg/l)	87	0–10
Creatinine (mg/dl)	0.60	0.52–1.04
Urea (mg/dl)	19	15–45
Total protein, serum (g/dl)	5.30	6.3–8.2
Albumin, serum (g/dl)	2.20	3.5–5.0
Serum lactate (mmol/l)	5.1	0.7–2.0

Q3請問血液檢查有什麼異常？

- 1.白血球增加
- 2.中性球增加
- 3.血小板明顯減少
- 4.AST很高
- 5.ALT很高
6. AST>>ALT
- 7.ALK-P-tase不正常
- 8.血膽色素不正常
- 9.非結合性膽色素很高
10. Prothrombin time
延長
- 11.血糖稍低
12. CRP明顯增高
13. Cr:正常
- 14.Serum Albumin很低
15. Serum lactate增高

這些結果代表什麼意義。

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Q4,這些結果代表什麼意義.

- 1.感染發炎,
- 2.極嚴重肝細胞壞死
- 3.血清白蛋白偏低可能是肝功能萎縮造成
- 4.Metabolic acidosis.



Acute liver failure

Blood examination

- 1.瘧疾、肝炎病毒、恙蟲病和鉤端螺旋體的血液檢查結果為陰性。◦ malaria, hepatitis viruses, scrub typhus, and leptospira were negative.
- 2,但在她的血液中檢測到登革熱病毒抗原非結構蛋白1
- dengue viral antigen nonstructural protein 1 was detected in her blood.

Q5.dengue viral antigen nonstructural protein 1,這是什麼?

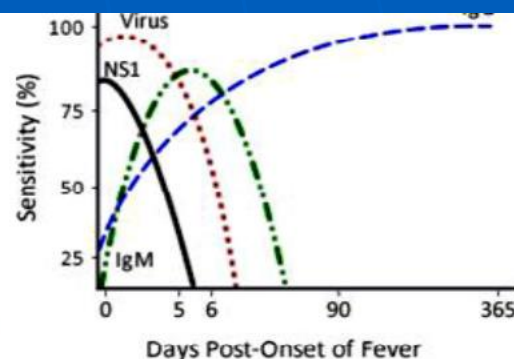
Hong-Ru Chen, Yen-Chung Lai & Trai-Ming Yeh

Dengue virus non-structural protein 1: a pathogenic factor, therapeutic target, and vaccine candidate *Journal of Biomedical Science J Biomed Sci* 25, 58 (2018).

Dengue virus (DENV) infection is the most common mosquito-transmitted viral infection. DENV infection can cause mild dengue fever or severe dengue hemorrhagic fever (DHF)/**dengue shock syndrome (DSS)**. Hemorrhage and vascular leakage are two characteristic symptoms of DHF/DSS. However, due to the limited understanding of dengue pathogenesis, no satisfactory therapies to treat nor vaccine to prevent dengue infection are available, and the mortality of DHF/DSS is still high. **DENV nonstructural protein 1 (NS1)**, which can be secreted in patients' sera, has been used as an early diagnostic marker for **dengue infection** for many years. However, the roles of NS1 in dengue-induced vascular leakage were described only recently. In this article, the pathogenic roles of DENV NS1 in hemorrhage and vascular leakage are reviewed, and the possibility of using NS1 as a therapeutic target and vaccine candidate is discussed.

Q6.登革熱確定診斷的依據

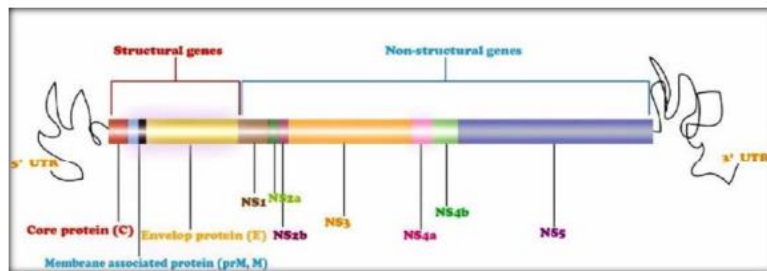
- (一)臨床檢體(血液)分離並鑑定出登革病毒。
- (二)臨床檢體分子生物學核酸檢測陽性。
- (三)血清學抗原(登革病毒的非結構蛋白**non-structural protein 1**，簡稱**NS1**)檢測陽性。



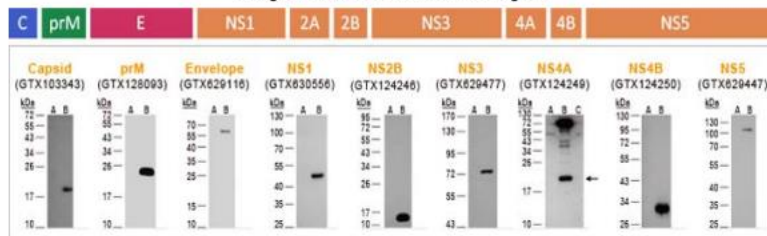
- (四)急性期(或初次採檢)血清中，登革病毒特異性**IgM**或**IgG**抗體為陽性者。
- (五)成對血清(恢復期及急性期)中，登革病毒特異性**IgM**或**IgG**抗體(二者任一)有陽轉或 ≥ 4 倍上升。

Q6, 登革熱確定診斷之依據

~登革病毒的結構包括**3種結構蛋白(structural protein)**和**7種非結構蛋白(nonstructural protein)**，其中非結構蛋白**NS1 antigen**在感染初期可於感染者血清中偵測到，所以用來研發登革熱快速診斷試劑。目前市售的快速診斷試劑可用人體血清、血漿或全血來進行定性檢測，操作方法簡便，約**20–30分鐘**可知道檢驗結果。目前市售登革熱**NS1**抗原快速診斷試劑有些可檢驗**NS1**抗原；有些並可合併**IgM**、**IgG**抗體檢測。

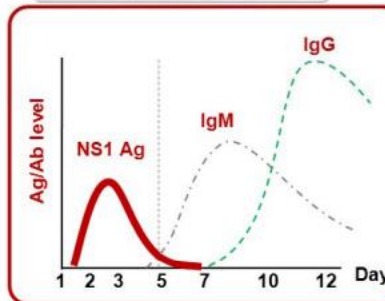


Dengue Virus Protein Schematic Diagram



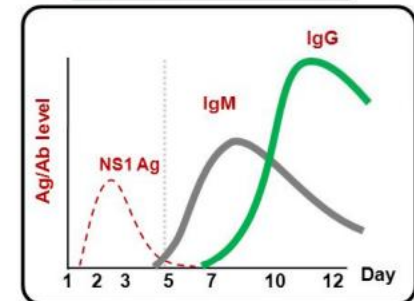
NS1 Ag

3 drops (110 µl) of plasma or serum for early acute phase samples (day 1 ~5)



IgG/IgM Ab

10 µl of plasma or serum for early convalescence phase samples (after day 5 ~ 14)



Slide courtesy of Dr. Subhamoy Pal

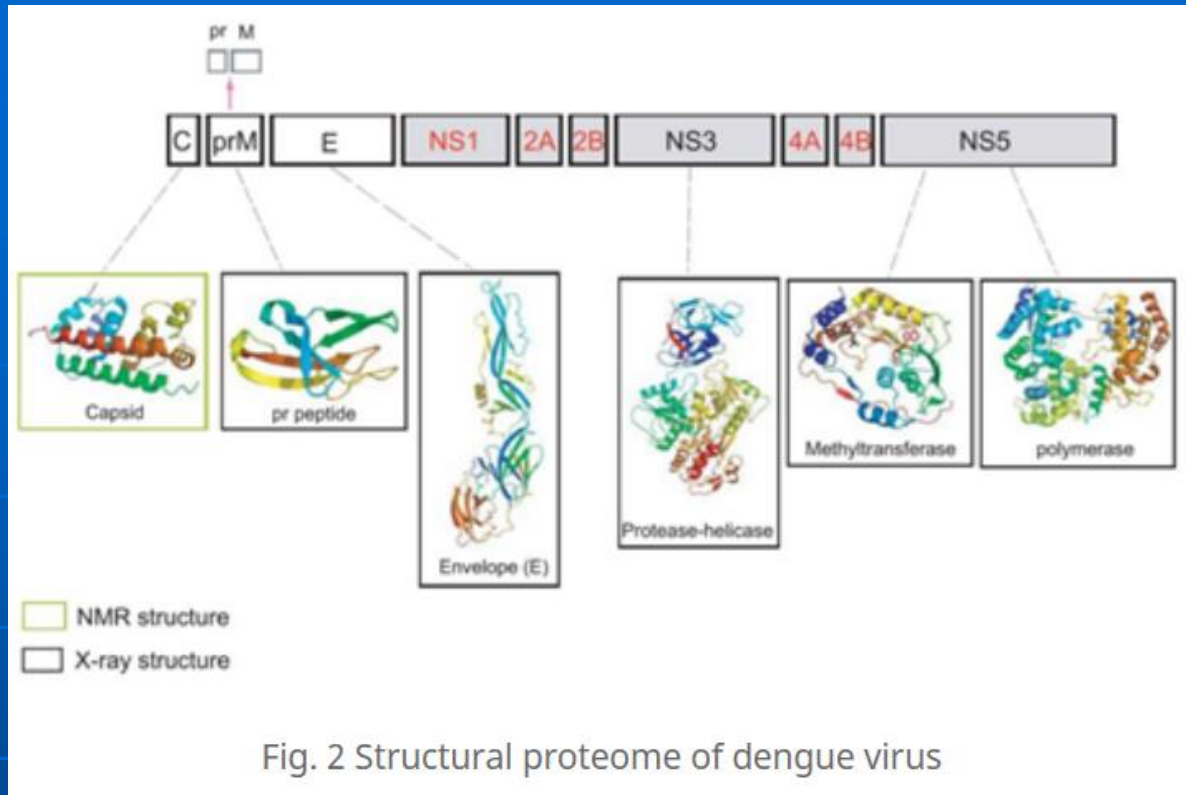
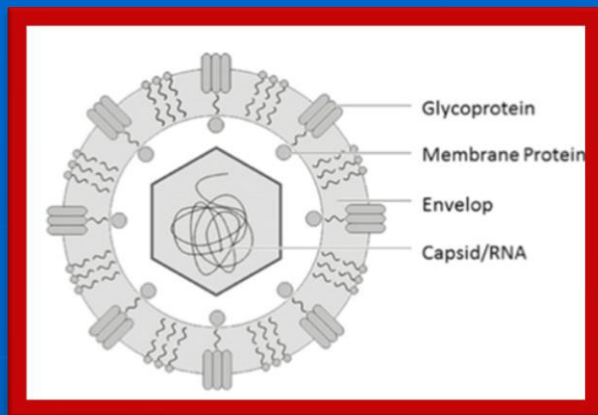


Fig. 2 Structural proteome of dengue virus

Dengue Fever virus is a RNA virus and homogeneous to West Nile virus, Japanese encephalitis virus and yellow fever virus. Genome of the dengue virus contains about 11,000 nucleotide bases, which code three different types of protein molecules (C, prM and E) that form the virus particle and seven other types of protein molecules that are found in infected host cells only and are required for life cycle of the virus.

1. **Capsid proteins (C)** Capsid protein (12 kDa) of mature DENV is highly basic
2. **Membrane protein (prM/M)** prM, also termed as precursor-membrane protein,
3. **Envelope protein (E)** Envelope protein is a glycoprotein belonging to class II viral membrane fusion protein
4. **Non-structural protein (NS)** The seven non-structural proteins include NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5. NS1 plays important role in structural stability and secretion of NS1 in dimeric

一定要了解

全國登革熱本土病例及境外移入病例统计表-依发病日

最近一例發病日	臺灣 2018 年-2022 年登革熱之疫情	2024/02/04																														
2024年5週 (上週累計數)	<table><tr><th>發病年份</th><th>確定病例</th><th>本土登革重症</th><th>主要流行地區 (本土病例數)</th><th>備註</th></tr><tr><td>2018</td><td>533</td><td>1</td><td>臺中市(113)、新北市(44)、高雄市(12)、彰化縣(8)、臺北市(2)、嘉義縣(2)、桃園市(1)、臺南市(1)</td><td>本土(183)、境外(350)</td></tr><tr><td>2019</td><td>640</td><td>0</td><td>高雄市(58)、臺南市(31)、新北市(7)、臺北市(2)、桃園市(1)、臺中市(1)</td><td>本土(100)、境外(540)</td></tr><tr><td>2020</td><td>137</td><td>0</td><td>新北市(50)、桃園市(23)</td><td>本土(64)、境外(73)</td></tr><tr><td>2021</td><td>12</td><td>0</td><td>-</td><td>本土(0)、境外(12)</td></tr><tr><td>2022</td><td>88</td><td>0</td><td>高雄市(18)、臺中市(2)</td><td>本土(20)、境外(68)</td></tr></table>	發病年份	確定病例	本土登革重症	主要流行地區 (本土病例數)	備註	2018	533	1	臺中市(113)、新北市(44)、高雄市(12)、彰化縣(8)、臺北市(2)、嘉義縣(2)、桃園市(1)、臺南市(1)	本土(183)、境外(350)	2019	640	0	高雄市(58)、臺南市(31)、新北市(7)、臺北市(2)、桃園市(1)、臺中市(1)	本土(100)、境外(540)	2020	137	0	新北市(50)、桃園市(23)	本土(64)、境外(73)	2021	12	0	-	本土(0)、境外(12)	2022	88	0	高雄市(18)、臺中市(2)	本土(20)、境外(68)	10
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2024年02月 (本月累計數)		5																														
2024年 (今年累計數)		125																														
2023年(去年總數)		26703																														
上週與前三週平均數比較 (病例數)		@@@																														
上週與過去三年同期平均數比較 (病例數)		▽16.33																														
今年累計死亡數		△8.67																														
		0																														



Clinical course-1

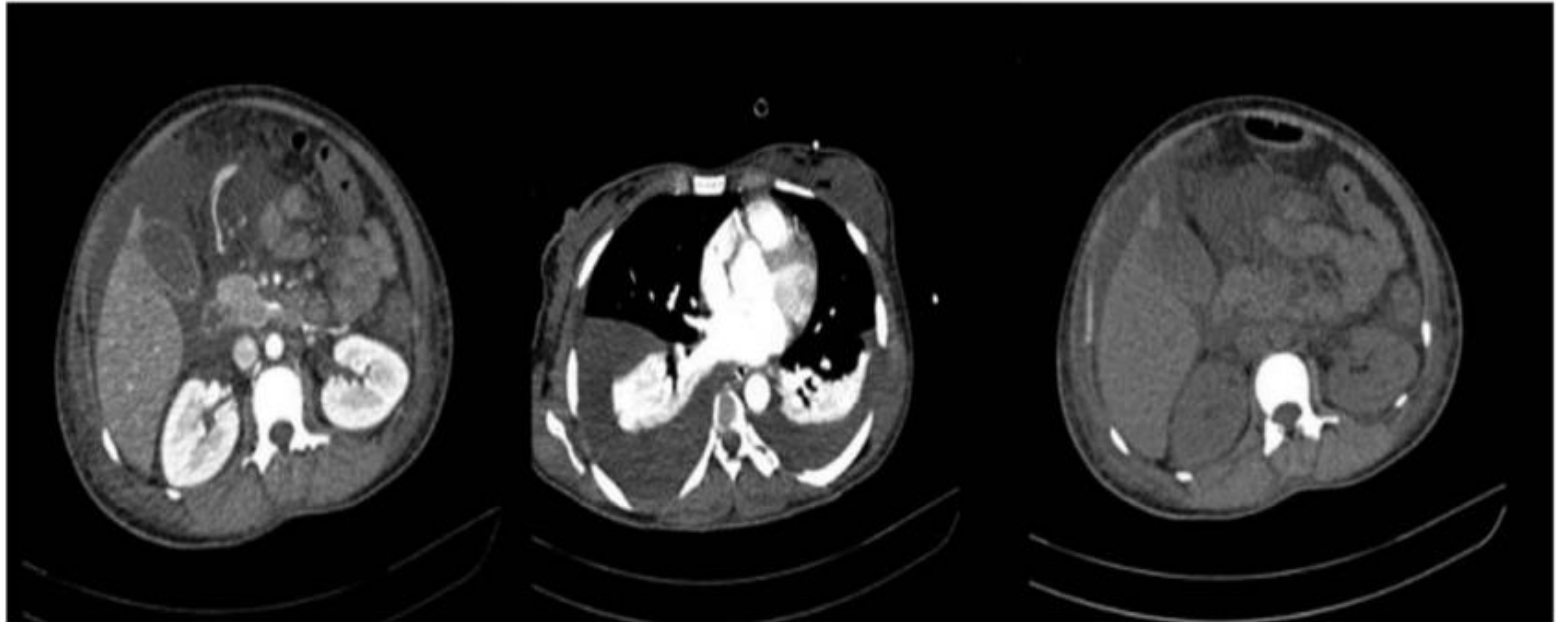


Figure 1. Computed tomography scan of whole abdomen: Gross ascites with large amount of bilateral pleural effusion with bilateral lower lobe atelectasis.

The ultrasound of the abdomen and pelvic done on the day of admission showed moderate ascites with bilateral pleural effusion. The following day after the admission, she had four to five episodes of nausea and vomiting, for which she was kept nil per oral. She was started on intravenous fluids and antiemetic due to worsening lactate levels and persistent tachycardia; later that day, she complained of severe abdominal pain and respiratory difficulty, for which she was shifted to the ICU.

- Q8, Medical images 提示很多臨床狀況.很可能是照顧上的重點所以要好好的注意看有哪些變化.又代表臨床什麼意義
- bilateral pleural effusion→
- →hypoalbuminemia
- -→respiratory problems.--<tachypneic

Clinical course-2

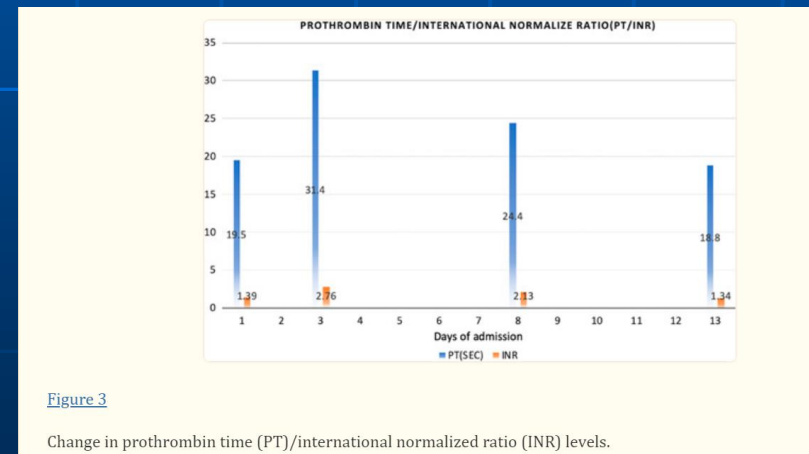
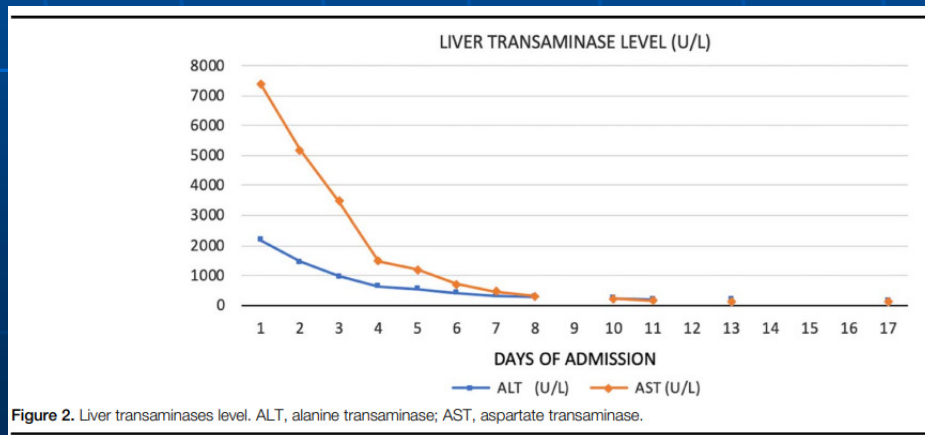
- During the third day, her abdominal distension progressively increased, and she became tachypneic, confused, drowsy, and restless. She was subsequently **diagnosed with Dengue shock syndrome with ALF and grade III Hepatic Encephalopathy** evidenced by altered liver biochemistry with coagulopathy, severe lactic acidosis, and altered level of the sensorium.

Clinical course-3

- She was started on antibiotics, enema, diuretics, proton pump inhibitors, methylprednisolone, lactulose, 20% albumin infusion, N-acetylcysteine, and was kept on total parenteral nutrition. Hepatotoxic medications were avoided. She was intubated due to altered level of consciousness to protect her airway. The computed tomography scan of whole abdomen was done on the third day of hospital admission (Fig. 1). Therapeutic tapping of ascitic fluid was done to provide relief to the patient. Over time, her deranged transaminases (Fig. 2) level was improved. Her coagulopathy which was deranged (Fig. 3), was appropriately managed with fresh frozen plasma and vitamin K. Slowly her clinical status as well as biochemical profiles was improved.

Clinical course-4

- She was completely weaned off the ventilator on the fifth day of intubation. After 20 days, she was discharged from the hospital. Later during a follow-up visit, her transaminase levels were within normal range.



Q9, Clinical course:要看出臨床經過的變化是否改善或惡化常需要依據一些評估指標(assessment parameters).

- 這個案例的指標是放在肝功能上,還有肝昏迷的相關指數.
- The most common definition of ALF involves any degree of mental deterioration (encephalopathy) in a patient without underlying cirrhosis and an illness lasting less than 26 weeks¹⁰. **Evidence of coagulation irregularity**, often an international normalized ratio of 1.5, is also included.
- Degree of encephalopathy
- Coagulation irregularity.
- Blood ammonia. Serum bilirubin

Cause of hepatic coma

1. Dengue hemorrhagic fever is diagnosed by the presence of fever with signs of hemorrhages, thrombocytopenia, and plasma leakage⁴. Dengue shock syndrome is the most severe form of dengue, which can affect several organs, including the liver, brain, and kidney, and result in fatal outcomes.
2. Liver involvement in dengue is a crucial (關係重大) feature, and the effect ranges from an asymptomatic rise in liver enzymes to the development of ALF
3. 何時要思考肝臟受到影響
 - (a) Dengue patients who presented with abdominal pain, nausea, vomiting, and anorexia should be evaluated for liver involvement¹¹.
 - (b) Liver function test and coagulopathy
4. Mechanism of ALF:
 - The exact pathophysiology behind liver failure in dengue is not clear. The possible hypothesis includes T-cell-mediated host immunity and the underlying cytokine storm, which is also known as cytokine “Tsunami”^{4,12,13}. Interleukin-22 and interleukin-17 are particularly responsible for liver injury
 - ALF often results in multiorgan dysfunction including hemodynamic instability, renal failure, cerebral edema, and even death because of shock

Dengue shock syndrome and ALF

- Dengue shock syndrome is the most severe form of dengue, which can affect several organs, including the liver, brain, and kidney, and result in fatal outcomes [Samanta and Sharma, 2015].
- Liver involvement in dengue is a crucial feature, and the effect ranges from an asymptomatic rise in liver enzymes to the development of ALF.

Samanta J, Sharma V. Dengue and its effects on liver. World J Clin Cases 2015;3:125. (Department of Gastro-enterology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India.)

登革熱已成為一種重要的蟲媒病毒疾病，對熱帶國家人口的疾病負擔產生重大影響。登革熱通過伊蚊叮咬傳播。該病毒似乎具有一些肝毒性作用。肝功能檢查中紊亂形式的肝臟疾病很常見，可能包括血清膽紅素輕度升高、轉氨酶升高和血清白蛋白紊亂。雖然在大多數情況下無癥狀，但黃疸和急性肝衰竭（ALF）等臨床表現偶爾會使臨床表現複雜化。事實上，在流行國家，登革熱被認為是ALF的重要病因。

- ALF often results in multiorgan dysfunction including hemodynamic instability, renal failure, cerebral edema, and even death because of shock[4,12]. **Souza et al.[14] found that 74.2% of patients with serologically confirmed dengue had significantly elevated transaminase.** Many studies have point that the elevation of AST is more than alanine aminotransferase (ALT). The change in the ratio of aspartate aminotransferase (AST)/ALT is rarely observed in hepatitis A, B, or C viruses–induced acute hepatitis but only in Dengue fever[4]. Later Kuo et al.[15] and Nguyen et al.[16] found that the level of AST was higher than that of ALT.

如何去找引發急性肝衰竭之原因

- Infection?
- Dengue virus ?

找到登革熱病毒感染的證據就可以判斷這是急性肝衰竭的原因

- Q8,在疾病劇本裡好好敘述登革熱發生的肝臟變化—看看幾篇報告就可以了解
 - Souza *et al.* 14 found that 74.2% of patients with serologically confirmed dengue had significantly elevated transaminase. Many studies have point that the elevation of AST is more than alanine aminotransferase (ALT). The change in the ratio of aspartate aminotransferase (AST)/ALT is rarely observed in hepatitis A, B, or C viruses–induced acute hepatitis but only in Dengue fever4.
 - Later Kuo *et al.* 15 and Nguyen *et al.* 16 found that the level of AST was higher than that of ALT. Damaged striated muscle, cardiac muscle, and erythrocytes release the AST, which could be the reason for the high level of AST as compared with ALT17,18.
 - The prothrombin time and activated partial thromboplastin time are prognostic variables used to evaluate the degree of liver damage and serve as indicators of bleeding in individuals with ALF19.
 - Severe coagulopathy-like disseminated intravascular coagulation, severe sepsis, renal impairment, increased intracranial pressure resulting in cerebral edema, and cardiopulmonary collapse resulting in multiple organ failure are all complications of ALF20,21.

Q10,急性肝衰竭處理的幾個重點-1

1. Severe coagulopathy-like disseminated intravascular coagulation, severe sepsis, renal impairment, increased intracranial pressure resulting in cerebral edema, and cardiopulmonary collapse resulting in multiple organ failure are all complications of ALF^{20,21}.
 - Coagulations disorders should be addressed as well.
2. During ALF, complications like metabolic abnormalities, either due to infections or electrolyte abnormalities, should be corrected.
3. Hepatic encephalopathy is usually corrected by restricting protein intake along with the administration of lactulose and antibiotics like rifamixin and neomycin (nephrotoxic). However, lactulose is frequently prescribed to patients who have hepatic encephalopathy as a result of chronic liver illness. However, its utility in cases of sudden liver failure is debatable. According to one study, receiving lactulose helped patients with ALF live a small increase in survival time²²

- 4 Other treatment principles include the administration of N-acetyl cysteine, which has a crucial role in preventing free radicals-mediated hepatocyte damage and prevention of hypoperfusion, dengue shock syndrome, or dengue hemorrhagic fever. Although this plays a specific role in mitigating the process, none is proven beneficial in all cases.
- 5. The last resort is a liver transplant in the case of ALF; however, it is not that feasible due to a limited number of donors.
- 6. Future: Preventive measures:
 - new methods should be developed to prevent as the dengue virus spread and new drugs should be discovered to prevent hepatotoxic injury^{23,24}.

Q11,登革熱的死亡率,有疫苗嗎

治療

- 典型登革熱致死率低於1%
- 依據WHO資料，登革熱重症若無適當治療，**死亡率可能超過20%**，早期診斷並加以適當治療，死亡率可低於**1%**
- 登革熱沒有特效藥物可積極治療，一般採行支持性療法

■ 2015年12月上市之活性減毒疫苗，可保護4種血清型

- 法國Sanofi Pasteur藥廠生產，商品名為Dengvaxia® (CYD-TDV)，目前已在墨西哥、菲律賓、印尼、泰國及新加坡等20多個國家核准上市，在台灣尚未上市
- 適用年齡為9-45歲的兒童及成人
- 感染過登革熱病毒的人接種疫苗有效且安全；但未曾感染過登革熱病毒的人於接種後倘自然感染登革熱，則發生登革熱重症風險增加。
- 針對接種前血清抗體陽性者，接種3劑 (0/6/12個月) 後之疫苗保護力約81.9% (95%CI : 67.2-90.0%)

Q12,找幾篇相關的臺灣報告了解過去我們在這一方面有多少認識

- 這是作業.

Dengue fever with liver problems in Taiwan

3 cases died of acute liver failure.(1992)

Total cases: 270

- 在1987年11月至1988年12月的疫情期間，通過生化測試對125名男性和145名女性患者進行了登革熱對肝功能的影響。天冬氨酸轉氨酶（AST）、丙氨酸轉氨酶（ALT）、膽紅素、鹼性磷酸酶、γ-谷氨酰轉肽酶（G-GT）水平分別為93.3%、82.2%、7.2%、16.3%和83.0%。在大多數情況下，轉氨酶的升高為輕度至中度，但在11.1%和7.4%的患者中，轉氨酶的升高分別是AST和ALT正常上限的10倍。最初，AST水平高於ALT，在癥狀出現後9天增加到最高水準，然後在兩周內降至正常水準。生化檢查結果在有和沒有乙型肝炎或丙型肝炎病毒感染的病例之間沒有顯著差異，但在出血發作的患者中觀察到AST、ALT和G-GT的升高顯著升高。2例患者的肝活檢顯示小葉性肝炎的特徵。在五例死亡病例中，三例死於肝衰竭。結論是，登革熱可能引起與常規病毒性肝炎患者相似的肝損傷和轉氨酶升高。在流行或流行地區，在肝炎的鑒別診斷中應考慮登革熱感染。

Chung-Huang Kuo et al (CGMH, Kaoshiung) 肝臟生化檢查和登革熱 . Kuo CH, Tai DI, Chang-Chien CS, et al. Liver biochemical tests and dengue fever. Am J Trop Med Hyg 1992;47:265-270 (L1127)

Abnormal liver functions in Dengue fever (Taiwan, 1992)

■ Liver functions) % abnormality

■ 天冬氨酸轉氨酶 (AST)	93.
■ 丙氨酸轉氨酶 (ALT)	82,2
■ 膽紅素	7.2
■ 鹼性磷酸酶、	16.3
■ γ-谷氨醯轉肽酶 (G-GT)	83.0

Remarks : 10-fold greater than the normal upper limit for AST and ALT in 11.1%
and 7.4%

Acute liver failure---3 cases

Mortality-----5/270 ☹1.1%)

Chung-Huang Kuo et al (CGMH, Kaoshiung) Liver biochemical tests and dengue fever. Am J Trop Med Hyg 1992;47:265-270 (L1127)

Conclusion

■ Q12,好好寫下這一篇這個討論的心得感想/或結論.

1. Dengue fever has been a significant burden in countries with poor resources. Since most dengue cases are better with conservative treatment, few develop serious complications.
2. Although liver involvement is mild in many cases, there are ALF cases associated with high morbidity and mortality due to complications such as encephalopathy, severe bleeding, renal failure, and metabolic acidosis.
- 3 People infected more than one time with different serotypes increase the risk of severe complications and mortality.
2. 4 To accurately diagnose dengue and prevent misdiagnosis as viral hepatitis in dengue-endemic areas, clinicians must be aware of the need for **early patient monitoring and measurement of suitable laboratory data**. The afflicted patient's health, bleeding, and laboratory-determined markers such as complete blood count, serum transaminase levels, prothrombin time, and international normalized ratio should thus be constantly monitored while assuring adequate supportive care and treatment.疾病指標的重要性要案例個別考慮
3. 5. Resource-limited countries like many countries in Asia are facing an increasing case of dengue fever with increasing serious complications.

- 請完成登革熱發生肝衰竭之疾病劇本.
- 可以**2-5**人組成小組,寫一份報告但註明小組成員分擔的部分.
- 請在**1**周內交給總醫師/林醫師
- 下次上課時間是**3月1日**.老師也會帶乙份劇本給大家做參考