

The Role of Various Laboratory Parameters and Imaging Associated with Obstructive Jaundice in Cholangiocarcinoma

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ABSTRACT

Cholangiocarcinoma is the second most common primary liver malignancy with a global increase of incidence and mortality. The mean age at presentation is 50 years. Patients with cholangiocarcinoma usually will have symptoms of obstructive jaundice followed with supporting laboratory and imaging findings. The predominant clinical feature of extrahepatic cholangiocarcinoma is biliary obstruction resulting in jaundice; while intrahepatic cholangiocarcinoma causes symptoms of intrahepatic mass including abdominal pain in right upper quadrant and other tumor-related symptoms such as cachexia and malaise. The diagnosis and staging of cholangiocarcinoma require multidisciplinary approaches including laboratory, radiological, endoscopic approaches and analysis on pathology.

This case report describes a patient with a cholangiocarcinoma based on results of endoscopic retrograde cholangiopancreatography (ERCP) imaging. In addition to a diagnosis tool, ERCP can also be a therapeutic modality for placing stent to reduce symptoms of cholestasis. There were supporting laboratory findings such as increased bilirubin level, alkaline phosphatase (ALP) and gamma glutamyltransferase (GGT) levels as well as increased level of tumor markers such as carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9 and cytological examination.

Keywords: *cholangiocarcinoma, jaundice, obstructive, ERCP*

ABSTRAK

Kolangiokarsinoma merupakan keganasan hati primer kedua yang paling umum, dimana insiden dan mortalitasnya meningkat secara global. Usia rata-rata timbulnya gejala adalah 50 tahun. Pasien dengan kolangiokarsinoma pada umumnya mengalami gejala ikterus obstruktif disertai dengan hasil laboratorium dan pencitraan yang mendukung. Gambaran klinis yang dominan dari kolangiokarsinoma ekstrahepatik adalah obstruksi bilier yang menyebabkan ikterus, sedangkan kolangiokarsinoma intrahepatik menimbulkan gejala adanya massa intrahepatik yang menyebabkan nyeri kuadran kanan atas abdominal dan gejala terkait tumor lainnya yaitu kakeksia dan malaise. Diagnosis dan staging kolangiokarsinoma memerlukan pendekatan multidisipliner antara lain laboratorium, radiologis, endoskopi dan analisis patologi.

Pada kasus berikut ini seorang pasien didiagnosa kolangiokarsinoma yang ditegakkan berdasarkan pencitraan endoscopic retrograde cholangiopancreatography (ERCP). Selain untuk diagnosis, ERCP menjadi modalitas terapi dengan dilakukan pemasangan stent untuk mengurangi gejala kolestasis. Pemeriksaan laboratorium yang mendukung antara lain peningkatan bilirubin, alkalin fosfat dan gamma glutamil transferase (GGT), peningkatan penanda tumor seperti carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, dan pemeriksaan sitologi.

Kata kunci: *kolangiokarsinoma, ikterus, obstruktif, ERCP*

INTRODUCTION

Cholangiocarcinoma is a malignant cancer that arises from a neoplastic transformation of cholangiocytes, the epithelial cells that line intra- and extrahepatic biliary duct. Cholangiocarcinoma is the second most common primary liver malignancy with a global increase of incidence and mortality. It has specific characteristics with signs of obliterated ducts and vasculature. Biliary tract sepsis, liver failure and/or cachexia as well as malnutrition are the most essential causes of death associated with the tumor.¹

The mean age at presentation is 50 years. In western countries, the diagnosis of cholangiocarcinoma is made at 65 years or more and it is rarely diagnosed before 40 years of age. In general population, 52-54% of cholangiocarcinoma is found in men; however, higher mortality is found in women. Different prevalences of cholangiocarcinoma among various racial and ethnic groups have been reported. The Southeast Asia has the highest prevalence.²

Usually, the etiology of cholangiocarcinoma is unidentifiable; however, some risk factors can be estimated including the primary sclerosing cholangitis. Biliary tract cancer is correlated to ulcerative colitis with or without sclerosing cholangitis. Thirty percent of patients are diagnosed with cholangiocarcinoma within a year based on the abnormal results of liver function tests. The cancer-related clinical symptoms are epigastric pain, weight loss and increased CA 19-9 and carcinoembryonic antigen (CEA). Moreover, worm infection of hepatobiliary tract also a risk factor for cholangiocarcinoma and there is a strong correlation with liver fluke species of *Opisthorchis viverrini* and *Clonorchis sinensis*, particularly in East Asia, which has the highest prevalence of cholangiocarcinoma and it is an endemic area of liver fluke infection due to the habit of eating undercooked fish. The flukes are then getting into the biliary duct or inside the gall bladder. Another risk factor for cholangiocarcinoma, which is more typical in Asian countries than western countries is hepatolithiasis.^{2,3} The following case report will discuss about a 38-year-old patient with cholangiocarcinoma who presented with symptoms of cholestasis, i.e. obstructive jaundice with complications of anemia of chronic illness, sepsis and acute pancreatitis.

CASE ILLUSTRATION

A 38-year-old male patient presented with a symptom of worsening jaundice since three days

before hospital admission. There were also dark-colored urine and clay-colored stool. The patient complained about abdominal pain on the right upper quadrant and the abdomen was slightly enlarged. There was also a history of weight loss. Physical examination revealed that the patient had moderate illness with blood pressure of 120/80 mmHg, pulse rate of 84 beats per minute and body temperature at 36.8° C. His respiratory rate was 18 beats per minute and he had moderate nutritional status. Jaundiced sclera and hepatomegaly were found. Moreover, laboratory workup demonstrated increased bilirubin level including total bilirubin of 18.12 mg/dL, direct bilirubin of 16.32 mg/dL and indirect bilirubin of 1.80 mg/dL. There were also increased levels of alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT), i.e. the ALP was 539 U/L and the GGT was 169 U/L, which supported the presence of cholestasis. The patient was diagnosed with klastkin tumor and cholangiocarcinoma based on imaging results including ultrasonography, computerized tomography (CT) scan, esophagogastroduodenoscopy (EGD), particularly the ERCP, which showed intra- and extrahepatic obstruction and stenosis of coronary heart disease (CHD). The pathology anatomy examination did not find any evidence of malignant tumor and repeated exam was on schedule using brush cytology. To manage the symptom of obstructive jaundice, the patient was treated with low fat diet, medications for stomach problems such as omeprazole (OMZ), zomepsin, anti-nausea medicine (domperidone) and medicine for cholestasis (urda-falk) and anti-pruritus (cefrizin).

The patient also had other problems including anemia with hemoglobin (Hb) level of 12.6 g/dL and hematocrit (Ht) level of 37% as well as impaired synthesis in the liver, which was characterized by hemostasis disorder with prothrombin time (PT) of 19.2 seconds and activated partial thromboplastin time (APTT) of 52.7 seconds and low albumin level, i.e. 3.03 g/dL; there was also dyslipidemia with triglyceride level of 334 mg/dL, total cholesterol level of 242 mg/dL, high density lipoprotein (HDL) level of 6 mg/dL and low density lipoprotein (LDL) level 23 mg/dL. The dyslipidemia in this patient was treated with simvastatin and it showed improvement although the normal value had not been reached.

There was also hypokalemia with potassium level of 3.12 mEq/L, which might be due to lack of food intake since the patient had loss of appetite and only had once daily meal and the condition was worsened by diarrhea,

which occurred at the 16th day of hospitalization. The patient was treated with kalium chloride intravenous fluid drop (KCIIVFD).

During hospitalization, the patient also had experienced acute pancreatitis following his first ERCP, which was characterized by increased levels of amylase and lipase, i.e. the amylase was 544 U/L; while the lipase was 452 U/L. Moreover, the patient was treated with clear liquid gastric diet, injections of antibiotics (cefoperazone and levofloxacin), gastric medication (OMZ), anti-nausea (ondansetron) and oral gastric medication (inpepsa®). The patient also experienced sepsis, which might be caused by hospital-acquired pneumonia (HAP) infection. The patient was then treated with other antibiotics (meropenem and amikacin) and antipyretics (PCT). In 4-5 days the symptoms subsided.

DISCUSSION

Cholangiocarcinoma, which can be also defined as Klatskin tumor, is categorized according to its anatomical site, i.e. intra- and extrahepatic. The extrahepatic type involving the confluence of both the left and right hepatic duct is found in 80-90%; while the intrahepatic type is found in 5-10% in all of cholangiocarcinoma. The anatomical margins for differentiating intra- from extrahepatic cholangiocarcinoma are the order both biliary ducts. The extrahepatic cholangiocarcinoma is then can be into types I to IV. Type I: tumor involves common hepatic duct distal to the biliary duct; type II: tumor involves the biliary; type IIIa: tumor involves the biliary and the right hepatic duct; type IIIb: tumor involves the biliary and the left hepatic duct; type IV: multifocal or tumor involves both the right and left hepatic ducts. Histologically, adenocarcinoma is the most common pathological form, which accounts for 90% of cases. Others papillary adenocarcinoma, intestinal type adenocarcinoma, clear cell adenocarcinoma, signet-ring cell carcinoma, adenosquamous carcinoma, squamous cell carcinoma, dan oat cell carcinoma.²

The most common clinical symptom is jaundice followed with pruritus, which distinguishing it from primary biliary cirrhosis that usually has pruritus appearing the most early in the course of the disease. Jaundice may occur later when only one of hepatic duct is affected. Bilirubin serum level always increases, but jaundice may be subsided in 50% patients. The pain is usually mild and in the form of epigastric pain. Diarrhea may occur as steatorrhea. Weakness and

weight loss may also happen. Liver is smooth and enlargement is palpable at 5-12 cm below the costal margin. Spleen is not palpable and ascites rarely occurs. Cholangiocarcinoma is usually asymptomatic until it reaches advanced level. When symptoms appear, predominating clinical symptoms is determined by anatomical sites of the tumor. The predominant clinical presentation of extrahepaticcholangiocarcinoma is biliary obstruction, which results in jaundice; while intrahepatic cholangiocarcinoma causes symptoms of intrahepatic mass, which produces abdominal pain on the right upper quadrant and other tumor-associated symptoms such as cachexia and malaise.^{2,3}

The patient had some problems and the most dominant was obstructive jaundice supported by other clinical symptoms, such as worsening jaundice in approximately 3 months, bilirubinuria and clay-colored stool. There was also bilirubinemia, which was particularly characterized by increased levels of total, direct and indirect bilirubin; while increased ALP and GGT levels indicated the presence of cholestasis.

Cytological specimens obtained during ERCP procedure or percutaneous drainage showed a relatively significant results; however cytological expertise was required for interpretation. Brush cytology is better than analysis of bile aspiration and it has 60% sensitivity. Aspiration of fine needle biopsy obtained from suspected tumor can also be performed using ultrasonography or fluoroscopy. Endoscopic ultrasound-guided aspiration cytology is also significant, but the expertise for interpretation is rare.

The most studied serum tumor markers are carbohydrate antigen (CA) 19-9, carcinoembryonic antigen (CEA) and CA 125. CEA and CA-125 are not specific and can be increased in gastrointestinal or gynecologic malignancies or other bile duct pathologies, such as cholangitis and hepatolithiasis. CEA is increased in 30% of cholangiocarcinoma cases and it can also be increased in inflammatory bowel disease, biliary obstruction, other tumor and severe liver disease. The concentration of CA 19-9 serum tumor marker is usually increased in patients with biliary tract malignancies. The level may also be increased in cholangitis and cholestasis. Its sensitivity to detect cholangiocarcinoma in primary sclerosing cholangitis is 50-60%. CA 19-9 can not provide differentiation between cholangiocarcinoma and pancreatic or gastric malignancies. Moreover, it can also be increased in severe liver disease due to any causes. Combined examination using CA 19-9 and CEA do not improve the sensitivity.^{2,3,4}

The levels of CA 19-9, CEA and CA 125 serum tumor marker are increased 85%, 30% and 40-50% in patients with cholangiocarcinoma. However, none of these markers is specific for cholangiocarcinoma.⁵ The tumor marker evaluation performed in this patient indicated a normal CEA level, i.e. 4.08 ng/mL and increased CA 19-9 level, i.e. 29.9 U/mL. These findings supported the diagnosis of malignancy; however, CA 19-9 level can also be increased due to other causes such as severe liver disease.

The patient already had experienced synthesis dysfunction in the liver, which was characterized by hemostasis disorder with PT of 19.2 seconds and APTT of 52.7 seconds and low albumin level, i.e. 3.03 g/dL as well as confirmed reduced cholinesterase level, i.e. 2,490 U/L. Hemostasis disorder that occurred in this patient was caused by reduced synthesis of coagulation factors; moreover, the cholestasis in the patient also causes vitamin K deficiency. The patient was treated with fresh frozen plasma (FFP) transfusion, dexamethasone and vitamin K for two days; the symptoms of hemostasis disorder improved although normal value had not been reached. The laboratory workup of complete peripheral blood test indicated anemia and the profile of peripheral blood examination showed an isopoikilocytosis and target cells.

In patients with liver disease, an isocytosis can be found, i.e. a combination between micro- and macrocytosis. However, the patient did not show any sign and symptom of gastrointestinal bleeding and there was poikilocytosis and cell targets were observed due to altered ratio of cholesterol and phospholipid in the erythrocyte membrane. These findings are particularly found in patients with cholestasis. The patient had normocytic normochrome anemia with reduced serum iron (SI) and total iron binding capacity (TIBC) levels, i.e. SI of 24 ug/dL and TIBC of 182 ug/dL; while the transferrin saturation was 13%. Increased ferritin level, i.e. 1,680 ng/mL indicates the presence of acute phase protein of inflammatory process.

Anemia due to chronic disease usually manifests as a mild to moderate normocytic normochromic anemia. Patients with such condition have low reticulocyte count, which indicate low production of erythrocytes. An evaluation on anemia of chronic disease must include the determination of iron status in the body to exclude iron deficiency anemia, which has microcytic hypochromic characteristic. In anemia due to chronic disease and iron deficiency, the concentration of serum iron level and transferrin saturation are reduced, which suggests an absolute iron deficiency in iron deficiency

anemia and hypoferrremia due to iron intake in the reticuloendothelial system. In anemia due to chronic disease, reduced saturation of transferrin demonstrates the low iron level. In iron deficiency anemia, the saturation of transferrin can be even lower since the serum concentration of iron transporter, the transferrin, is increased; while the transferrin level is still normal or lower in anemia of chronic disease. Ferritin is used as a marker of iron storage, in patients with anemia of chronic disease. A normal or increased level of ferritin shows increased storage and iron retention in reticuloendothelial system.⁶

Target cells can be found in hepatocellular jaundice or cholestasis and they particularly will be obviously seen in cholestasis. Increased biliary acid can also be a contribution by inhibiting the activity of lecithin cholesterol acyl transferase (LCAT). The LCAT of erythrocyte membrane is reduced, which produces increased cholesterol and lecithin in the membrane.

Hemostasis disorder in patients with hepatobiliary disease is quite complicated due to various changes of coagulation pathway resulting in the formation of fibrin and also fibrinolysis at the same time. It causes reduced coagulation that requires interventional treatment when bleeding takes place. Hepatocytes are the main sites for synthesis of all proteins of coagulation factors except for von Willebrand factor and factor VII C. The proteins are vitamin K dependent, i.e. factor II, VII, IX and X, as well as factor V, VIII, XI and XII, fibrinogen and factor XIII. Vitamin K is a lipid soluble vitamin produced by intestinal bacteria. Its deficiency is usually caused by cholestasis, either intra- or extrahepatic. In cholestasis, parenteral vitamin K supplementation can rapidly correct the PT to normal value in 24-48 hours and it can be useful for diagnosis. If the coagulopathy is caused by liver disease, PT can be improved, but it can not reach normal level.⁷

Cholangiography is one of the most important tests in the evaluation of cholangiocarcinoma as it can provide earlier diagnosis and can help evaluate the proximal and distal extension of intraductal tumor. Cholangiography can be performed using endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP) or transcutaneous cholangiography (PTC). MRCP has the advantage as it is not invasive and there is a possibility of achieving additional information about intra- and extrahepatic anatomical structures; while ERCP and PTC have the advantage of allowing sampling of bile duct for diagnostic analysis and therefore, it can evaluate the presence

of biliary obstruction by inserting stents. The choice of using imaging modality also depends on tumor location. Distal extrahepatic cholangiocarcinoma can be optimally evaluated using ERCP. Sometimes, hilar cholangiocarcinoma can only be managed by placing percutaneous stent.²

An evaluation using ERCP is not always without complication. The incidence of acute pancreatitis following ERCP procedure varies approximately 2-9%. Abdominal pain can be a symptom of acute pancreatitis and it should be treated with hospital care for at least 2 days and serum amylase level can be increased at least 3 times above the normal value at 24 hours. The etiologies may include mechanical, chemical, thermal, hydrostatic injury as well as allergy and infection to pancreas. Usually, the patients at risk are female patients with young age, dysfunction of sphincter of Oddi, recurrent pancreatitis, pancreatic sphincterotomy, balloon dilatation in an intact biliary sphincter and difficult cannulation with or without access to sphincterotomy. Prevention measures include selecting patients carefully, recognizing risk factors and painstaking attention to technique and procedures of placing the pancreatic stents. Medications such as antibiotics, nitroglycerin, non-steroid anti-inflammatory drugs (NSAID), gabexate and somatostatin can be used as prophylaxis for preventing ERCP-induced pancreatitis.^{8,9}

Acute pancreatitis experienced by the patient was due to complication of the ERCP procedure that had been performed. The patient had epigastric pain, increased amylase and lipase levels of > 3 times on the following day and it was back to normal value 2 days later. The patient's condition was improved in 3 days later, particularly after intubation of nasogastric tube (NGT). Afterwards, the second ERCP was performed and plastic stent was placed and there were improved cholestasis symptoms.

The patient was diagnosed with HAP based on data that he had dyspnea during hospitalization and the physical examination revealed crackles and the chest X-ray suggested bronchopneumonia. It is concluded that the patient had experienced HAP since the pneumonia occurred within more than 48 hours after hospital admission without previous signs of infection prior to hospitalization. Pneumonia is one of the most common nosocomial infections that occur during hospitalization. HAP is defined as pneumonia that occurs 48 hours or more after hospital admission and the signs and symptoms of infection were not present at the time of admission. It is essential to differentiate

HAP with community-acquired pneumonia (CAP) since patients with HAP are susceptible for pneumonia caused by more virulent microorganisms. Pathogenesis of HAP is multifactorial including recurrent illness that causes the patient must be hospitalized, which increases the risk for nosocomial infection. Immune disorder may also allow pathogenic microorganisms to cause invasive infections, which are less likely to occur in healthy individuals. Moreover, hospitalized patients sometimes have poor nutritional status and therefore, it will increase the risk of infection. Aspiration of oropharyngeal secretion has an essential role in the development of HAP. About 45% of all healthy individuals can experience aspiration during their sleep. However, with a combination of low immune function, disrupted clearance of mucocilia of respiratory tract and more pathogenic microorganism, the oropharynx of hospitalized patients can be colonized by pathogenic Gram-negative bacteria. The risk factors for the pathogenic infection are hospital length of stay, smoking, elderly age, uremia, previous antibiotic exposure, alcohol consumption, endotracheal intubation, coma, major surgery, malnutrition, multiple organ failure and neutropenia. HAP can be divided into 2 categories, i.e. early onset HAP (develops in < 5 days since the time of hospital admission) and late onset (develops in 5 days or more since admission).

The most common Gram-positive cocci causing pneumonia in hospitalized patients are *Streptococcus pneumoniae* and *Streptococcus aureus*. *S. pneumoniae* is the most common cause of CAP; therefore, it is more likely to be correlated with early onset HAP than late onset CAP. Moreover, the early-onset HAP due to Gram-negative bacteria is commonly caused by *Hemophilus influenzae* and lactose fermenter such as *Enterobacteriaceae*. *Enterobacteriaceae* is Gram-negative bacteria that causes lactose fermentation, i.e. *Escherichia coli*, *Klebsiella spp.* and *Enterobacter spp.*^{10,11}

The patient also experienced fever, dyspnea and cough and his leukocyte count was 20,500/ μ L; therefore, a diagnosis of sepsis was made. Sepsis is a systemic inflammatory process induced by infection with various spectrums starting from systemic inflammatory response syndrome (SIRS) to multiple organ dysfunction syndrome (MODS). SIRS can be diagnosed when there are two of the following criteria: body temperature is $< 36^{\circ}\text{C}$ or $> 38^{\circ}\text{C}$, pulse rate is > 90 times per minute, respiratory rate is > 20 times per minute or pCO_2 is < 32 mmHg and leukocyte count is $< 4,000/\mu\text{L}$ or $> 12,000/\mu\text{L}$ or with the presence of $> 10\%$ immature neutrophils. Sepsis is SIRS accompanied

with infection, either confirmed or suspected. It is induced by body impairment, which may include ischemia, inflammation, injury or infection. In healthy individuals, neuroendocrine and immune system will eradicate them; however, if the control mechanism fails, the condition of patient can be worse and it turns into sepsis. The inflammatory process that takes place is very complicated involving cellular and humoral response, complements and cytokines. Some mediators are involved including platelet activating factor (PAF), tumor necrosis factor alpha (TNF α), interleukin 1,6,8 and 10. The most common cause of sepsis is bacterial infection; however, infections caused by virus, fungi and parasites also should be considered.¹² Urinalysis on the 2nd day of hospitalization indicated bilirubinuria. Afterwards, on the 17th and 22nd day, there was proteinuria of positive 1 result and trace blood / Hb. The proteinuria that occurred in the patient may be a transient proteinuria since the patient had a fever.

The blood gas analysis showed acid pH, low pO₂, low HCO₃ and negative base excess. The measured anion gap was 22.7 mmol/L. The results indicated that the patient had metabolic acidosis with increased anion gap, which suggests that there was unmeasured anion, in this case, the lactate, that may occur in patients who experience sepsis. Bile fluid culture was performed to find out the source of sepsis, which revealed results of *Pseudomonas sp.* Infection caused by *Pseudomonas sp.* is usually an opportunistic infection, other possibility includes contaminant of ERCP instruments. *Pseudomonas sp.* can be found naturally in water and it can be the cause of contaminant on surgical instruments, which are introduced into the body.

The pathology anatomy (PA) examination did not reveal the presence of malignant tumor and repeated brush cytology was on schedule. It may occur since it might not be a representative sampling. In addition, negative results of tumor cells in PA examination do not exclude the possibility of malignancy as there is still a possibility that the tumor is undetected. The patient was discharged from hospital after his cholestasis symptoms had been managed and other problems such as sepsis and acute pancreatitis improved. Afterwards, the patient was scheduled for outpatient care.

REFERENCES

- Gatto M, Bragazzi MC, Semeraro R, Napoli C, Gentile R, Torrice A, et al. Cholangiocarcinoma: update and future perspective. *Dig Liver Dis* 2010;42:253-60.
- Blechacz BRA, Gores GJ. Cholangiocarcinoma. *Clin Liver Dis* 2008;12:131-50.
- Sherlock S, Dooley J. Tumours of the gallbladder and bile ducts. *Disease of the liver and biliary system*. 11th ed. Milan: Blackwell Sci 2002.p.647-56.
- Khan SA, Davidson BR, Goldin R, Pereira SP, Rosenberg WMC, Taylor-Robinson SD, et al. Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document. *Gut* 2002;51:vi1-vi9.
- Boberg KM, Scrumpf E. Diagnosis and treatment of cholangiocarcinoma. *CurrGastroenterol Rep* 2004;6:52-9.
- Weiss G, Goodnough LT. Anemia of chronic disease. *N Eng J Med* 2005;352:1011-23.
- Sherlock S, Dooley J. The haematology of liver disease. *Disease of the liver and biliary system*. 11th ed. Milan: Blackwell Sci 2002.p.47- 65.
- Cherian JV, Selvaraj JV, Natrayan R, Venkataraman J. ERCP in acute pancreatitis. *HepatobiliaryPancreat Dis Int* 2007;6:233-40.
- Pannu HK, Fishman EK. Complications of endoscopic retrograde cholangiopancreatography: spectrum of abnormalities demonstrated with CT. *Radiographics* 2001;6:1441-53.
- Kieninger AR, Lipsett PA. Hospital-acquired pneumonia: pathophysiology, diagnosis and treatment. *Surg Clin Am* 2009;89:436-61.
- Torres A, Ewig S, Lode H, Carlet J. Defining, treating and preventing hospital acquired pneumonia: European perspective. *Intensive Care Med* 2009;35:9-29.
- Griffiths B, Anderson ID. Sepsis, SIRS and MODS. *Surgery* 2009;10:446-9.

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