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**Dates:** Received: 14 November, 2016; Accepted: 05 December, 2016; Published: 06 December, 2016

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**Keywords:** Cholestasis; Jaundice; Pediatric; Pneumonia; ARDS

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### Case Report

## Isolated Conjugated Hyperbilirubinemia in Seriously Ill Children – Don't Forget Sepsis!

### Abstract

**Background:** Jaundice is frequently associated with extrahepatic systemic infections. The important causes include increased bilirubin levels due to hemolysis, hepatic dysfunction, reduced excretion and cholestasis. Sepsis induced cholestasis has a unique pathophysiologic basis. Although common in gram negative sepsis among neonates, the clinical features of sepsis induced cholestasis are not widely recognized older children.

**Case report:** We present a 6 year old, premorbidly asymptomatic boy with community acquired MRSA sepsis-pneumonia and ARDS (Acute respiratory distress syndrome) with isolated conjugated hyperbilirubinemia. A diagnosis of sepsis induced isolated cholestasis was considered after ruling out other possible causes of cholestasis. The hyperbilirubinemia improved with improvement in the primary pathology.

**Conclusion:** Early recognition of sepsis as a cause of isolated cholestatic jaundice would avoid unnecessary investigations and therapy would help in early institution of appropriate therapy.

### Abbreviations

TSB: Total Serum Bilirubin; DB: Direct Bilirubin (Conjugated Bilirubin); AST: Aspartate Transaminase; SAP: Serum Alkaline Phosphatase; GGT: Gamma Glutamyl Transpeptidase; INR: International Normalized Ratio; CRP: C Reactive Protein; PCT: Procalcitonin; MODS: Multiple Organ Dysfunction Syndrome; HAV: Hepatitis A Virus; HEV: Hepatitis E Virus; Hbsag: Hepatitis B Surface Antigen; LFT: Liver Function Test; MRSA: Methicillin Resistant *Staphylococcus Aureus*

### Introduction

Cholestatic jaundice in a sick newborn always reminds of sepsis to a pediatrician. But the differential diagnosis of conjugated hyperbilirubinemia in the pediatric age group focuses mainly on primary hepatobiliary disease and genetic syndromes [1]. Though, jaundice has been known to be associated with sepsis in all age groups since 18<sup>th</sup> century [2], it is indeed rare. Therefore, severe jaundice may be misdiagnosed as a sign of primary hepatic or biliary tract disease and divert attention from the underlying infection and lead to inappropriate treatment [3]. Hepatic dysfunction can occur directly by bacterial products or as a result host response to infection. There are certain infections which cause direct

hepatocellular injury and result in hepatic dysfunction. Hepatic dysfunction in sepsis may be part of multiple organ dysfunction syndrome (MODS), can also be a result of ischemia sustained during septic shock (ischemic hepatitis/ shock liver), or may be complicated by cholestasis [4]. Sepsis induced cholestasis as a cause for jaundice, particularly in the critically ill children continues to be overlooked with very few detailed reports in this age group. Here we present an interesting case of fulminant sepsis with isolated conjugated hyperbilirubinemia without any other feature of hepatic dysfunction and also discuss the relevant literature along with possible therapeutic options. The case is presented to highlight this entity for our fellow pediatricians who are expected to encounter such patients in their clinical practice.

### Case Report

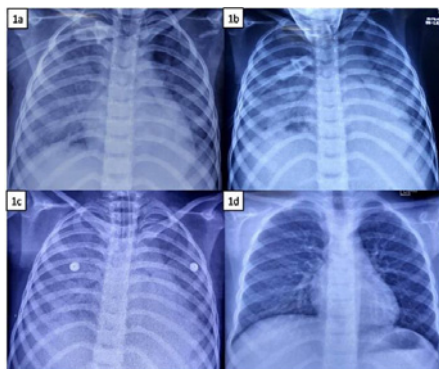
A 6 year old male previously normal male child presented with history of continuous, high grade fever with chills and nonproductive cough for 3 days, vomiting for 2 days and difficulty in breathing for 1 day. There was no history suggestive of viral prodrome, pain abdomen, loose stools, jaundice, rash and joint pain, bleeding from any site, decreased urine output, altered sensorium or seizure. He was immunized as per national immunization schedule till 5 years of age and did not

receive pneumococcal vaccine. Development was appropriate for age and there were no co-morbidities. On examination, there was tachycardia and evidence of respiratory distress with tachypnea and chest retraction. He was also hypoxemic (SpO<sub>2</sub> 90% in room air) but no pallor, icterus or lymphadenopathy. He was normally built. Systemic examination revealed bilateral crepitation in all lung fields with clinical evidence of right sided pleural effusion. There was no organomegaly and examination of other systems was also within normal limits. Investigations revealed neutrophilic leucocytosis with normal biochemical parameters (Table 1). Chest x-ray confirmed bilateral pneumonia with right sided mild pleural effusion (Figure 1a). He was started on intravenous antibiotic (Inj. Cefotaxime) and simultaneously workup was done to find out the etiology (Table 1).

Clinical status of patient worsened by day two of admission in the form of septic shock and required inotropes to maintain

**Table 1:** Initial investigations of the child.

Investigations	Result	Investigations	Result
Hemoglobin (gm/dl)	11.7	Malaria antigen test	Negative
Total leukocyte count (/mm <sup>3</sup> )	29600	Dengue NS1 antigen	Negative
Differential leukocyte count	N78 L16 E1 M5	Dengue IgM antibody	Negative
Platelet count (/mm <sup>3</sup> )	189000	Hepatitis A (HAV) IgM	Negative
Urea (Mg/dl)	35	Hepatitis E (HEV) IgM	Negative
Creatinine (Mg/dl)	0.56	Hepatitis B antigen (HBsAg)	Negative
TSB/ DB (mg/dl)	0.9/0.5	Leptospira microscopic agglutination test	Negative
AST (U/L) (0-35 U/L)	21	Scrub typhus serology (IgM)	Negative
ALT (U/L) (0-35 U/L)	18	PCR for Mycoplasma pneumoniae	Negative
Total protein (gm/dl)	6.5	H1N1 PCR	Negative
Albumin (gm/dl)	3.5	Antinuclear antibody (ANA)	Negative
SAP (U/L)	249	Immunoglobulin (Ig) G (mg/dl)	264
GGT (U/L)	36	CRP (mg/dl)	65
Prothrombin time (seconds)/ INR	13.5/ 1.17	PCT (ng/mL)	88



**Figure 1:** 1a – Chest x-ray (CXR) of the child at presentation showing bilateral infiltrates and mild right sided pleural effusion; 1b – CXR on D2 showing worsening pulmonary infiltrates; 1c - CXR on D4 showing almost complete whiteout of both lungs with endotracheal tube in situ; 1d – CXR on D14 showing complete resolution of pulmonary infiltrates.

the blood pressure and perfusion to vital organs. There was also increasing respiratory distress and worsening infiltrates in CXR (Figure 1b). The patient developed clinical jaundice on day 3 of admission, which worsened over the next 24 hrs. There was no pruritis. Liver function tests revealed conjugated hyperbilirubinemia with normal transaminases, normal serum alkaline phosphatase (SAP) and gamma glutamyl transpeptidase (GGT) (Table 2).

Appropriate investigations ruled out possible causes of jaundice (Table 1). Hemolysis was ruled out by appropriate investigations (corrected reticulocyte count 1.5%, serum lactate dehydrogenase 113 U/L and no evidence of hemolysis on peripheral smear). Ultrasound (USG) revealed a normal sized liver with slightly altered echo texture and also ruled out any biliary tract obstruction. Inflammatory markers {C reactive protein (CRP) and Procalcitonin (PCT)} were dramatically elevated. The child also developed ARDS (Acute respiratory distress syndrome) requiring mechanical ventilation (Figure 1c). In the meantime blood culture grew methicillin resistant *Staphylococcus aureus* (MRSA) which was sensitive only to vancomycin, lizolid and teicoplanin. Thus, antibiotic was changed to vancomycin. After next 48 hours the bilirubin levels showed a persistent declining trend concordant with the clinical improvement and declining serum inflammatory markers (CRP and PCT) (Table 2). The repeat hemoglobin levels showed a non-significant decline (Hb 10.9 gm/dl on D3 and 10.5 gm/dl on D7). The child was off all inotropes by D8 and could be weaned off mechanical ventilation by D9. On D14 of hospital stay, the child completely recovered from jaundice, his CXR normalized (Figure 1d) and he was discharged. On Currently on follow up after 6 months, he is completely asymptomatic and the liver functions have also normalized.

## Discussion

The child in our case had MRSA sepsis with pneumonia, ARDS and septic shock with isolated conjugated hyperbilirubinemia. The work failed to reveal any etiology and normal transaminases made infectious hepatitis, acetaminophen overdose, Reye's syndrome and ischemic hepatitis extremely unlikely [5]. Therefore, a diagnosis of sepsis induced conjugated hyperbilirubinemia was considered. It was further supported by the trend of the hyperbilirubinemia which first increased with worsening of clinical features and laboratory markers of sepsis and then showed a dramatic response after appropriate antibiotic therapy in conjunction with them even in the absence of any other specific intervention.

Cholestasis of sepsis is defined as hepatocellular cholestasis during or following a septic process, generally extrahepatic, and results from impairment in bile transport [6]. Hyperbilirubinemia in sepsis can be due to any of the three following basic mechanisms, i.e. hemolysis, hepatic dysfunction or cholestasis [4]. In addition to the increased bilirubin load in sepsis, hyperbilirubinemia results from decreased bilirubin uptake by the hepatocytes, decreased intrahepatic processing of bilirubin, decreased canalicular transport of bilirubin and finally decreased clearance of conjugated bilirubin [5]. Direct invasion of bacteria by liver is not the major cause for cholestasis

**Table 2:** Serial values of liver function test (LFT) and inflammatory markers (CRP and PCT).

Day of admission	TSB/ DB (mg/dl)	AST (U/L) (0-35 U/L)	ALT (U/L) (0-35 U/L)	SAP (U/L)	GGT (U/L)	CRP (mg/dL)	PCT (ng/mL)
Day 3	8.8/5.2	15	14	288	35	56	138
Day 4	12/10.8	14	17	252	38	88	>200
Day 7	8.0/7.0	11	13	236	34	32	71
Day 9	5.0/3.6	10	12	270	28	16	23
Day 14	2/1.2	13	18	233	29	8	1

in sepsis [7]. Various cytokines especially TNF (Tumor necrosis factor)-and IL (Interleukin)-6 are released as a response to endotoxemia. The interplay among these cytokines along with the lipopolysaccharide [LPS] released by the bacteria play a central role in the genesis of cholestatic liver disease in sepsis [8]. Cholestasis predominately results from decreased basolateral and canalicular transport of bile acids as a result of down-regulation of various hepatocellular transporters and receptors [4,5]. Adenosine triphosphate (ATP)-dependent bile salt export pump (BSEP) requires a special mention here. The passage of bile salts into biliary canaliculi is the rate-limiting step in bile metabolism and at this level bile acids are excreted mainly by this pump. TNF-and IL-1 modulate gene expression of BSEP at both the transcriptional and the post-transcriptional levels [9].

There is no established diagnostic criteria of sepsis induced cholestasis and the diagnosis is based upon historical, clinical and laboratory parameters [6]. The patients with sepsis induced cholestasis present with jaundice & clinical features of infection; however occasionally they may present with jaundice alone. Pruritus and pain abdomen are conspicuously rare and the same was also seen in our case. There may be hepatomegaly; transaminases and SAP levels are usually moderately elevated with conjugated bilirubin in the range of 2-10 mg/dl [4,6]. The unique feature in our case was isolated conjugated hyperbilirubinemia without any rise of transaminases, SAP or GGT. Most commonly cholestasis in sepsis is associated with intra-abdominal sepsis with Gram negative organisms but cases with Staph sepsis [10] and pneumonia [2] are also reported. Other risk factors associated with sepsis induced cholestasis include prematurity, severity and duration of sepsis, total parenteral nutrition, and concurrent liver disease [6]. Liver biopsy, if done, shows little or no inflammation with intrahepatic cholestasis being the most prominent histological feature. However, it is seldom required for the diagnosis of sepsis induced cholestasis [4,6].

There are no specific pharmacological therapies for the cholestatic process which alter the outcome. The emphasis is therefore on eradication of infection by aggressive antimicrobial therapy and surgical drainage if required coupled with appropriate supportive care [4,5]. Drugs potentially inducing cholestasis or hepatocellular, e.g. acetaminophen, non-

steroid antiinflammatory drugs, sodium valproate, rifampicin, etc. should be avoided or at least used with caution [9]. Therapeutic approaches having anecdotal evidence of benefit include: enteric nutrition, Ursodeoxycholic acid, glycine, nitric oxide (NO) donors (e.g. molsidomine), N-Acetyl Cysteine, corticosteroids, anti-TNF-agents, Extracorporeal liver support {e.g. the Molecular Adsorbents Recirculating System (MARS)} and orthotopic liver transplantation [4-6,9].

Prolonged cholestasis reflects the severity of the infection or the presence of other hepatobiliary pathology and in presence of sepsis, is it a predictor of mortality [4-6]. In general, cholestasis of sepsis has no long-term consequences, with the exception of TPN-dependent patients, particularly infants. In these patients recurrent sepsis has an important impact on the progression of cholestasis to end-stage liver disease [6].

## Conclusion

Sepsis associated cholestasis is probably an under recognized entity and should always be considered in the differential diagnosis of jaundice in the critically ill patients, especially when there is a disproportionate rise in direct bilirubin compared to the serum alkaline phosphatase and transaminases levels. Exclusion of other pathology (e.g. biliary obstruction), elimination of confounding or potentially contributing factors (e.g. drugs) and careful evaluation of the response to treatment of sepsis forms the mainstay of management in the absence of a specific therapy.

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