

# **Hyperbilirubinemia in a Neonatal Intensive Care Unit: Incidence and Etiology**

Thesis

**Submitted for fulfillment of  
master degree (M.Sc.) in pediatrics**

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**2009**

# Abstract

Although most newborns develop some degree of jaundice, bilirubin levels high enough to put a newborn at risk of bilirubin encephalopathy and kernicterus are rare but still occur in Egypt.

The aim of current study was to assess the magnitude of neonatal jaundice and detect possible etiologies. This study included retrospective analysis of the data of all jaundiced cases admitted to NICU of Cairo University Pediatric Hospital during the period from the first January to the end of December 2007 and the data of the referred neonatal cholestatic cases in hepatology unit at the same hospital.

In the study period, there were 808 patients having neonatal jaundice who were admitted to neonatal intensive care unit with a mean age of  $5.74 \pm 4$  days and a mean weight of  $2658.6 \pm 710$  grams. They represented 72.9% of all cases admitted in the year 2007. Neonatal jaundice alone as a cause of admission represented 54.1% of all cases admitted. The mean total bilirubin level at day of presentation was  $23.1 \pm 9.87$  mg/dl. It was found that ABO incompatibility, Rh incompatibility and sepsis (18.7%, 5.8% and 12.5% respectively) are the main causes of indirect hyperbilirubinaemia. In 56% of cases the cause was unknown. It was found that 325 (40%) studied cases had extreme hyperbilirubinemia with peak of total bilirubin  $\geq 25$  mg/dl. Phototherapy was the only therapy in 68.4% of cases while 29.9% required exchange transfusion. Eleven (1.4%) cases were discharged with frank kernicterus. Among 23 referred cholestatic cases, it was found that inspissated bile syndrome then neonatal sepsis and extrahepatic biliary atresia are the main causes of neonatal cholestasis.

From this study, we concluded that, neonatal jaundice is still a major problem in our community. The main causes are ABO incompatibility, Rh incompatibility and sepsis especially in extreme hyperbilirubinemia which shows high prevalent in the NICU population. Any infant with direct hyperbilirubinemia should be diagnosed to rule out cholestatic liver disease.

**Key words:** Neonatal jaundice, hyperbilirubinemia, kernicterus, cholestasis, neonates.

# Acknowledgement

First of all, thanks to ALLAH the most beneficial and merciful for helping me to complete this study.

I would like to express my sincere appreciation to **Prof. Dr. Ismail Mohamed Bahie-El-Din El-Hawary**, Assist. Professor of pediatrics ,Cairo University, for his generous support and guidance to help me to complete this work. It was indeed an honor to work under his supervision.

It is my pleasure to express my unlimited gratitude and deepest thanks to **Prof. Dr. Mona El Said El Raziky**, Assist. Professor of pediatrics, Cairo University, for her continuous supervision and vast experience she offered me to complete this study. No words of gratitude can equal her help and support.

I also wish to thank **Prof. Dr. May Ahmed Khairy**, Assist. Professor of pediatrics Cairo University, for her great help, guidance and valuable advice through this work.

I would like to express my thankfulness to my best friend **Hanan** for her help and support throughout the entire period of the study.

I am very grateful to all my family especially **Mom**, my brother, my daughters and my husband **Ahmed** who are a gift from ALLAH and I would like to thank them for their patience and support, ALLAH bless them.

Finally, I would like to dedicate this effort to my **Dad's soul**, ALLAH have mercy him.

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# List of Abbreviations

<b>AAP</b>	American Academy of Pediatrics
<b>AAT</b>	Alpha-1-antitrypsin
<b>ABC</b>	ATP-binding cassette
<b>ABE</b>	Acute bilirubin encephalopathy
<b>ABR</b>	Auditory brainstem responses
<b>AGS</b>	Alagille syndrome.
<b>ALT</b>	Alanine transferase
<b>AN/AD</b>	Auditory neuropathy/auditory dys-synchrony
<b>AST</b>	Aspartate transferase
<b>ATP</b>	Adenosine triphosphate
<b>B/A ratio</b>	Bilirubin/albumin ratio
<b>BA</b>	Biliary atresia
<b>BASD</b>	Bile acid synthetic defect
<b>BBi</b>	Blood–brain interface
<b>Bf</b>	Free bilirubin
<b>BIND</b>	Bilirubin-induced neurologic dysfunction.
<b>BSA</b>	Body surface area
<b>BSEP</b>	Bile salt export pump
<b>CBC</b>	Complete blood count.
<b>cMOAT</b>	Canalicular multispecific organic anion transporter
<b>CMV</b>	Cytomegalovirus
<b>CN-1</b>	Crigler-Najjar syndrome type 1
<b>CN-2</b>	Crigler-Najjar syndrome type 2
<b>CNS</b>	Central nervous system
<b>CO</b>	Carbon monoxide
<b>COHb</b>	Carboxyhemoglobin
<b>CP</b>	Cerebral palsy
<b>CRP</b>	C-Reactive protein
<b>CSF</b>	Cerebrospinal fluid
<b>CUPH</b>	Cairo University Pediatrics Hospital

<b>DAT</b>	Direct antiglobulin test
<b>DCT</b>	Direct Coombs' test
<b>DMSO</b>	Dimethyl sulfoxide
<b>DNA</b>	Deoxyribonucleic acid
<b>ET</b>	Exchange transfusion
<b>ETCO<sub>c</sub></b>	End- tidal concentration of CO corrected for the ambient CO
<b>G-6-PD</b>	Glucose-6-phosphate dehydrogenase.
<b>GGT</b>	Gamma glutamyl transpeptidase
<b>HCT</b>	Hematocrit
<b>IBS</b>	Inspissated bile syndrome
<b>IDM</b>	Infant of diabetic mother
<b>IgG</b>	Immunoglobulin G
<b>IgM</b>	Immunoglobulin M
<b>INH</b>	Idiopathic neonatal hepatitis
<b>ISBT</b>	Ileal Na <sup>+</sup> -dependent bile salt transporter
<b>IVIG</b>	Intravenous immune globulin
<b>LBW</b>	Low birth weight.
<b>LPS</b>	Lipopolysaccharide
<b>MDR1</b>	Multidrug resistance-1 P-glycoprotein
<b>MDR3</b>	Multidrug resistance-3 P-glycoprotein
<b>MRI</b>	Magnetic Resonance Imaging
<b>mRNA</b>	Messenger ribonucleic acid
<b>MRP1</b>	Multidrug resistance-associated protein-1
<b>MRP2</b>	Multidrug resistance-associated protein-2
<b>MRP3</b>	Multidrug resistance-associated protein-3
<b>NADPH</b>	Reduced form of nicotinamide adenine dinucleotide phosphate
<b>NCS</b>	Neonatal Cholestasis Syndrome
<b>NICU</b>	Neonatal intensive care unit
<b>NISD</b>	Neonatal iron storage disease
<b>NTCP</b>	Na <sup>+</sup> -taurocholate transporter
<b>OATP</b>	Organic anion transporting polypeptide

<b>OATP1B1</b>	Organic anion transporter polypeptide 1B1
<b>OH</b>	Heme oxygenase
<b>PBC</b>	Primary biliary cirrhosis
<b>PCV</b>	Packed cell volume
<b>PFIC</b>	Progressive familial intrahepatic cholestasis
<b>PH</b>	Concentration of hydrogen ion.
<b>PSC</b>	Primary sclerosing cholangitis
<b>RBCs</b>	Red blood cells
<b>T4</b>	Thyroid hormone, Thyroxine
<b>TC</b>	Triangular cord
<b>TcB</b>	Transcutaneous bilirubin
<b>Torch</b>	Toxoplasmosis, other viruses, rubella, cytomegalovirus, herpes (simplex) viruses
<b>TPN</b>	Total Parenteral Nutrition
<b>TSB</b>	Total serum bilirubin.
<b>TSH</b>	Thyroid stimulating hormone
<b>UCB</b>	Unconjugated bilirubin
<b>UDCA</b>	Ursodeoxycholic acid
<b>UGT (UDPGT)</b>	Uridine diphosphoglucuronate glucuronosyltransferase
<b>UGT1A1(UDP-GT1A1)</b>	Uridine diphosphate glucuronosyl transferase 1A1
<b>US</b>	Ultrasonographic
<b>USA</b>	United States of America
<b>UTI</b>	Urinary tract infection
<b>UV</b>	Ultraviolet
<b>VDRL</b>	Venereal Disease Research Laboratory
<b>VeCO</b>	Pulmonary excretion rate of CO
<b>VLBW</b>	Very low birth weight

## Introduction

Jaundice is the most common condition that requires medical attention in newborns. The yellow coloration of the skin and sclera in newborns with jaundice is the result of accumulation of unconjugated bilirubin (**Hansen, 2009**). Alterations in the equilibrium between bilirubin production, conjugation, and excretion cause this transitional elevation during the neonatal period. The pathophysiology of this condition may vary according to the etiology. Different clinical entities presenting with neonatal jaundice include physiological jaundice, blood group iso-immunization, immaturity, or genetic deficiency of enzyme systems among others. Common clinical risk factors associated with neonatal jaundice include prematurity, low birth weight, neonatal sepsis, Asian race, bruising, previous sibling with a history of jaundice, breast feeding, epidural anesthesia, instrumental delivery and oxytocin use during labor (**Tioseco et al, 2005**).

Early discharge of the healthy newborn infant, particularly those in whom breastfeeding may not be fully established, may be associated with delayed diagnosis of significant hyperbilirubinemia (**Canadian Paediatric Society, 2007**).

Discriminating between benign and serious causes of jaundice is a common task faced by most pediatricians and neonatologists in their daily practice (**Karpen, 2002**).

In many cases, a causal etiology for hyperbilirubinemia will not be found and performing a battery of laboratory tests will in most cases not shed further light on the cause of the jaundice. Save for TSB monitoring, only a few laboratory tests, summarized in CBC, reticulocyte count, red-cell morphology, blood group, DAT (Direct antiglobulin test) and G-6-PD test are actually indicated for the average hyperbilirubinemic neonate. Liver function tests and direct bilirubin fractionation add little information in the first days of life and should be performed only in cases of persistent or unexplained prolonged jaundice, or in the presence of evidence of disease (**Kaplan et al, 2008**).

The principal issue facing the clinician is the ability to distinguish between hyperbilirubinemia resulting from a variety of causes and those with underlying liver disease. This is critical because the earlier an infant is recognized as having serious cholestatic liver disease, the more likely a correct diagnosis can be made, and institution of appropriate therapy begun. In general, if a patient is developing progressive jaundice soon after birth, is still jaundiced at 2 weeks of life, or develops jaundice within the first month of life, a work-up for neonatal cholestasis should begin (**Karpen, 2002**).

Regardless of the cause of indirect hyperbilirubinemia, the goal of therapy is to prevent indirect-reacting bilirubin related neurotoxicity while not causing undo harm.

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## **Introduction and Aim of the study**

Phototherapy and, if unsuccessful, exchange transfusion remain the primary treatment modalities used to keep the maximal total serum bilirubin below the pathologic levels (**Piazza and Stoll, 2007**).

Although neonatal jaundice is usually a self limiting condition, in exceptional circumstances, extreme hyperbilirubinaemia, with its devastating potential of irreversible brain damage due to bilirubin encephalopathy or kernicterus, may occur (**Kaplan and Hammerman, 2005**).

Cholestatic jaundice in early infancy is an important clinical condition that results from diminished bile flow and/or excretion, and can be caused by a number of disorders. Idiopathic neonatal hepatitis (INH) and biliary atresia (BA) are two main causes (**Dehghani et al, 2006**).

## **Aim of the study**

The aim of this study is to assess, retrospectively, the magnitude of jaundice and its possible etiologies in-patients attending the Neonatal Intensive Care Unit (NICU) of Cairo University Pediatrics Hospital (CUPH).

# Chapter 1

## Bilirubin Metabolism

Neonatal jaundice refers to the accumulation of the yellow-orange pigment, bilirubin, in the skin and sclerae of the newborn, some degree of hyperbilirubinemia invariably occurs in the human newborn after birth. The syndrome of neonatal jaundice can be best understood by analogy to a temporarily and partially clogged sink. In this example, the spigot represents the processes of bilirubin production and the drain represents the processes of bilirubin elimination. When the rate at which bilirubin is produced exceeds (spigot “on”) the rate at which bilirubin can be eliminated (drain “clogged”), the level of bilirubin in the circulation and body (sink) increases as a result. Therefore, the relative imbalance of these processes determines the pattern and degree of neonatal hyperbilirubinemia, which vary for a variety of reasons and represent the known risk factors ( **Stevenson et al, 2001**).

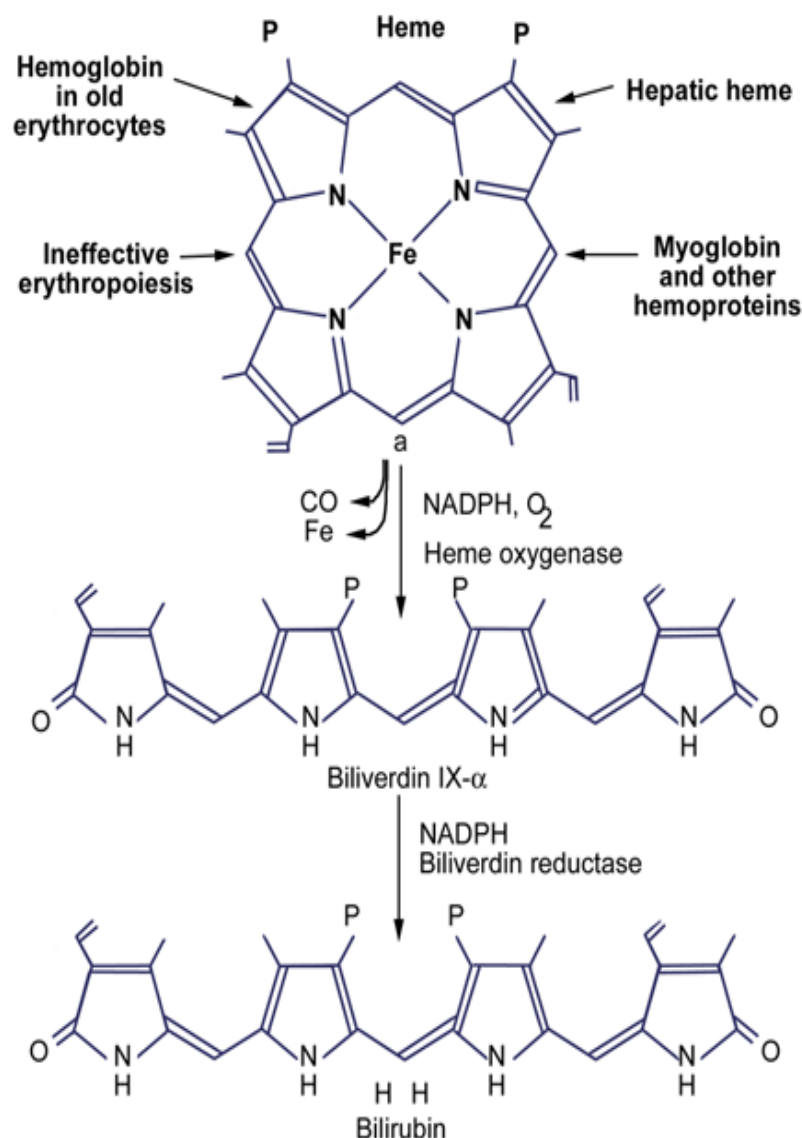
### Bilirubin formation: ( Figure 1)

Eighty to ninety percent of bilirubin is derived from the breakdown of hemoglobin from senescent or hemolyzed red blood cells. The proportion of bilirubin arising from hemoglobin varies with the pathologic condition, and may increase greatly in the circumstance of hemolysis or ineffective erythropoiesis. A smaller proportion of total bilirubin formation comes from the degradation of the heme from other heme-containing proteins, such as myoglobin, cytochromes, guanylyl cyclase, nitric oxide synthase, and others. ( **Stevenson et al, 2001**).

#### ➤ The first step:

Heme from erythropoietic and other origins is degraded by heme oxygenase enzyme complex to equimolar amounts of carbon monoxide (CO) and biliverdin ( **Stevenson et al, 1994**).

Heme oxygenase (HO), the rate - limiting enzyme in bilirubin production, has been identified from the late 1960s. This enzyme allows for the degradation of heme from hemoglobin or other heme- containing proteins to form biliverdin. This process is energy requiring because NADPH donates electrons through the cytochrome cP450 system and molecular oxygen is consumed for the liberation of iron from the porphyrin ring of heme, the release of carbon monoxide (CO), as well as the formation of biliverdin ( **Dennerly et al, 2001 b**).



**Figure 1: Production of Bilirubin. (Mukherjee, 2008)**

Heme oxygenase is found in several tissues, with significant activity in the liver, spleen, and erythropoietic tissue. HO activity is inducible by heme and other metalloporphyrins, hormones, starvation, stress, toxins, and xenobiotics. Heme oxygenase induction is generally considered to be the result of an increased protein synthesis and gene transcription. This hypothesis is supported by studies of the heme oxygenase gene. In the developing fetus and neonate, hepatic HO activity and mRNA levels are elevated above that of the adult. This suggests that the elevated heme catabolism observed in neonates may be associated with an increased transcription of the heme oxygenase gene. The apparent induction of hepatic HO during the neonatal period is probably the result of tissue-specific and time-dependent transcriptional