In The Name Of God

Islamic Azad University

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Prevalence of urinary tract infection among newborns admitted with jaundice in Booali Hospital during 2007

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LIST

Prevalence of urinary tract infection among newborns admitted with jaundice in Booali Hospital during 2007

Background: Neonatal jaundice is clinically presented in 60% of full-term newborns. Urinary tract infection (UTI) is one of the suggested etiologic factors for jaundice. In present study we evaluated prevalence of UTI in newborns admitted with jaundice.

Methods: One-hundred newborns with jaundice who had been admitted in Booali hospital, Tehran, during 2007 were studied for prevalence of UTI.

Results: Mean age of neonates was 5.9±3.05 days. Forty seven percent were male and 53% were female. UTI was present in 8 newborns (8%). Escherichia Coli was contributing germ in 5 newborns (62.5%) and Klebsiella in 3 neonates (37.5%).

Conclusion: The frequency rate of urinary tract infection among newborns with jaundice in this study (8%) was similar to other reports from Iran and other regions of the world.

Keywords: Frequency, Jaundice, Newborns, UTI

Introduction

Urinary tract infection (UTI) is the most common disease of the urogenital system and one of the most important bacterial infections in the pediatric age group its incidence varies from 0.1 to 1% among neonates and from 5 to 11% among febrile infants aged less than 8 weeks. In the first 3 months of life, it is more prevalent in males especially in the uncircumcised ones.

In infants, the clinical presentations of UTI varies from non-specific sign and symptoms such as poor weight gain, vomiting , fever, poor feeding and jaundice to severe illness. The major clinical presentation of UTI among young infants is acute pyelonephritis. Between 30 to 55% of infants with UTI are reported to have urinary tract congenital abnormalities, of which vesicouretral reflux is the most common.

Some investigators have suggested that unexplained hyperbilirubinemia in newborns may be associated with bacterial infection especially UTI, but the current scientific guidelines, e.g. that of the American Academy of Pediatrics (AAP) do not recommend any evaluation for UTI among infants with late onset hyperbilirubinemia. This is study aimed to determine the prevalence and the associated parameters of UTI in neonates with jaundice in Booali Hospital.

Review of Literatures

Background

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. In most infants, unconjugated hyperbilirubinemia reflects a normal transitional phenomenon. However, in some infants, serum bilirubin levels may excessively rise, which can be cause for concern because unconjugated bilirubin is neurotoxic and can cause death in newborns and lifelong neurologic sequelae in infants who survive (kernicterus). For these reasons, the presence of neonatal jaundice frequently results in diagnostic evaluation.

Neonatal jaundice may have first been described in a Chinese textbook 1000 years ago. Medical theses, essays, and textbooks from the 18^{th} and 19^{th} centuries contain discussions about the causes and treatment of neonatal jaundice. Several of these texts also describe a lethal course in infants who probably had Rh isoimmunization. In 1875, Orth first described yellow staining of the brain, in a pattern later referred to as kernicterus.

Pathophysiology

Neonatal physiologic jaundice results from simultaneous occurrence of the following 2 phenomena:

- Bilirubin production is elevated because of increased breakdown of fetal erythrocytes. This is the result of the shortened lifespan of fetal erythrocytes and the higher erythrocyte mass in neonates.
- Hepatic excretory capacity is low both because of low concentrations of the binding protein ligandin in the hepatocytes and because of low activity of glucuronyl transferase, the enzyme responsible for binding bilirubin to glucuronic acid, thus making bilirubin water soluble (conjugation).

Bilirubin is produced in the reticuloendothelial system as the end product of heme catabolism and is formed through oxidation-reduction reactions. Approximately 75% of bilirubin is derived from hemoglobin, but degradation of myoglobin, cytochromes, and catalase also contributes. In the first oxidation step, biliverdin is formed from heme through the action of heme oxygenase, the rate-limiting step in the process, releasing iron and carbon monoxide. The iron is conserved for reuse, whereas carbon monoxide is excreted through the lungs and can be measured in the patient's breath to quantify bilirubin production.

Next, water-soluble biliverdin is reduced to bilirubin, which, because of the intramolecular hydrogen bonds, is almost insoluble in water in its most common isomeric form (bilirubin IXá Z,Z). Because of its hydrophobic nature, unconjugated bilirubin is transported in the plasma tightly bound to albumin. Binding to other proteins and erythrocytes also

occurs, but the physiologic role is probably limited. Binding of bilirubin to albumin increases postnatally with age and is reduced in infants who are ill.

The presence of endogenous and exogenous binding competitors, such as certain drugs, also decreases the binding affinity of albumin for bilirubin. A minute fraction of unconjugated bilirubin in serum is not bound to albumin. This free bilirubin is able to cross lipid-containing membranes, including the blood-brain barrier, leading to neurotoxicity. In fetal life, free bilirubin crosses the placenta, apparently by passive diffusion, and excretion of bilirubin from the fetus occurs primarily through the maternal organism.

Albumin is bound to a receptor on the cell surface when the bilirubin-albumin complex reaches the hepatocyte, and bilirubin is transported into the cell, where it binds to ligandin. Uptake of bilirubin into hepatocytes increases with increasing ligandin concentrations. Ligandin concentrations are low at birth but rapidly increase over the first few weeks of life. Ligandin concentrations may be increased by the administration of pharmacologic agents such as phenobarbital.

Bilirubin is bound to glucuronic acid (conjugated) in the hepatocyte endoplasmic reticulum in a reaction catalyzed by uridine diphosphoglucuronyltransferase (UDPGT). Monoconjugates are formed first and predominate in the newborn. Diconjugates appear to be formed

at the cell membrane and may require the presence of the UDPGT tetramer.

Bilirubin conjugation is biologically critical because it transforms a water-insoluble bilirubin molecule into a water-soluble molecule. Water-solubility allows conjugated bilirubin to be excreted into bile. UDPGT activity is low at birth but increases to adult values by age 4-8 weeks. In addition, certain drugs (phenobarbital, dexamethasone, clofibrate) can be administered to increase UDPGT activity.

Infants who have Gilbert syndrome or who are compound heterozygotes for the Gilbert promoter and structural mutations of the *UDPGT1A1* coding region are at an increased risk of significant hyperbilirubinemia. Interactions between the Gilbert genotype and hemolytic anemias such as glucose-6-phosphatase dehydrogenase (G-6-PD) deficiency, hereditary spherocytosis, or ABO hemolytic disease also appear to increase the risk of severe neonatal jaundice.

Once excreted into bile and transferred to the intestines, bilirubin is eventually reduced to colorless tetrapyrroles by microbes in the colon. However, some unconjugation occurs in the proximal small intestine through the action of B-glucuronidases located in the brush border. This unconjugated bilirubin can be reabsorbed into the circulation, increasing the total plasma bilirubin pool. This cycle of uptake, conjugation, excretion, unconjugation, and reabsorption is termed the enterohepatic

circulation. The process may be extensive in the neonate, partly because nutrient intake is limited in the first days of life, prolonging the intestinal transit time.

Certain factors present in the breast milk of some mothers may also contribute to increased enterohepatic circulation of bilirubin (breast milk jaundice). Data suggest that the risk of breast milk jaundice is significantly increased in infants who have genetic polymorphisms in the coding sequences of the *UDPGT1A1* or *OATP2* genes. Although the mechanism that causes this phenomenon is not yet agreed upon, evidence suggests that supplementation with certain breast milk substitutes may reduce the degree of breast milk jaundice.

Neonatal jaundice, although a normal transitional phenomenon in most infants, can occasionally become more pronounced. Blood group incompatibilities (eg, Rh, ABO) may increase bilirubin production through increased hemolysis. Historically, Rh isoimmunization was an important cause of severe jaundice, often resulting in the development of kernicterus. Although this condition has become relatively rare in industrialized countries following the use of Rh prophylaxis in Rh-negative women, Rh isoimmunization remains common in developing countries.

Nonimmune hemolytic disorders (spherocytosis, G-6-PD deficiency) may also cause increased jaundice, although increased hemolysis appears to

have been present in some of the infants reported to have developed kernicterus in the United States in the last 10-15 years. The possible interaction between such conditions and genetic variants of the Gilbert and *UDPGT1A1* genes is discussed above.

Frequency

United States

Neonatal hyperbilirubinemia is extremely common because almost every newborn develops an unconjugated serum bilirubin level of more than 30 µmol/L (1.8 mg/dL) during the first week of life. Incidence figures are difficult to compare because authors of different studies do not use the same definitions for significant neonatal jaundice. In addition, identification of infants to be tested depends on visual recognition of jaundice by health care providers, which is subject to great variability and depends both on observer attention and on infant characteristics such as race and gestational age.

With the above caveats, epidemiologic studies provide a frame of reference for estimated incidence. In 1986, Maisels and Gifford reported 6.1% of infants with serum bilirubin levels greater than 220 µmol/L (12.9 mg/dL).[1] In a 2003 study in the United States, 4.3% of 47,801 infants had total serum bilirubin (TSB) levels in a range in which phototherapy was recommended by the 1994 American Academy of Pediatrics (AAP)

guidelines, and 2.9% had values in a range in which the 1994 AAP guidelines suggest considering phototherapy.[2]

International

Incidence varies with ethnicity and geography. Incidence is higher in East Asians and American Indians and lower in African Americans. Greeks living in Greece have a higher incidence than those of Greek descent living outside of Greece. Incidence is higher in populations living at high altitudes. In 1984, Moore et al reported 32.7% of infants with serum bilirubin levels greater than 205 µmol/L (12 mg/dL) at 3100 m of altitude.[3] A study from Turkey reported significant jaundice in 10.5% of term infants and in 25.3% of near-term infants.[4] Significant jaundice was defined according to gestational and postnatal age and leveled off at 14 mg/dL (240µmol/L) at 4 days in preterm infants and 17 mg/dL (290 µmol/L) in the term infants.

Mortality/Morbidity

- Death from physiologic neonatal jaundice per se should not occur.
- Death from kernicterus may occur, particularly in countries with less developed medical care systems. Mortality figures in this setting are not available.

Race

- The incidence of neonatal jaundice is increased in infants of East Asian, American Indian, and Greek descent, although the latter appears to

apply only to infants born in Greece and thus may be environmental rather than ethnic in origin.

- African-American infants are affected less often than white infants. For this reason, significant jaundice in an African-American infant merits a closer evaluation of possible causes, including G-6-PD deficiency.
- In 1985, Linn et al reported on a series in which 49% of East Asian, 20% of white, and 12% of African American infants had serum bilirubin levels greater than 170 μmol/L (10 mg/dL).[5]

Sex

Risk of developing significant neonatal jaundice is higher in male infants. This does not appear to be related to bilirubin production rates, which are similar to those in female infants.

Age

The risk of significant neonatal jaundice is inversely proportional with gestational age.

CLINICAL

History

- Presentation and duration
  - Typically, presentation is on the second or third day of life.
  - Jaundice that is visible during the first 24 hours of life is likely to be nonphysiologic; further evaluation is suggested.

- Infants who present with jaundice after 3-4 days of life may also require closer scrutiny and monitoring.
- In infants with severe jaundice or jaundice that continues beyond the first 1-2 weeks of life, the results of the newborn metabolic screen should be checked for galactosemia and congenital hypothyroidism, further family history should be explored, the infant's weight curve should be evaluated, the mother's impressions as far as adequacy of breastfeeding should be elicited, and the stool color should be assessed.

- Family history
  - Previous sibling with jaundice in the neonatal period, particularly if the jaundice required treatment
  - Other family members with jaundice or known family history of Gilbert syndrome
  - Anemia, splenectomy, or bile stones in family members or known heredity for hemolytic disorders
  - Liver disease
- History of pregnancy and delivery
  - Maternal illness suggestive of viral or other infection
  - Maternal drug intake
  - Delayed cord clamping
  - Birth trauma with bruising

- Postnatal history
  - Loss of stool color
  - Breastfeeding
  - Greater than average weight loss
  - Symptoms or signs of hypothyroidism
  - Symptoms or signs of metabolic disease (eg, galactosemia)
  - Exposure to total parental nutrition

Physical

- Neonatal jaundice first becomes visible in the face and forehead. Identification is aided by pressure on the skin, since blanching reveals the underlying color. Jaundice then gradually becomes visible on the trunk and extremities. This cephalocaudal progression is well described, even in 19th-century medical texts. Jaundice disappears in the opposite direction. This phenomenon is clinically useful because, independent of other factors, visible jaundice in the feet may be an indication to check the bilirubin level, either in the serum or noninvasively via transcutaneous bilirubinometry.
- In most infants, yellow color is the only finding on physical examination. More intense jaundice may be associated with drowsiness. Brainstem auditory evoked potentials performed at this time may reveal prolongation of latencies, decreased amplitudes, or both.

- Overt neurologic findings, such as changes in muscle tone, seizures, or altered cry characteristics, in a significantly jaundiced infant are danger signs and require immediate attention to prevent kernicterus. In the presence of such symptoms or signs, effective phototherapy should commence immediately without the laboratory test results. The potential need for exchange transfusion should not preclude the immediate initiation of phototherapy.
- Hepatosplenomegaly, petechiae, and microcephaly may be associated with hemolytic anemia, sepsis, and congenital infections and should trigger a diagnostic evaluation directed towards these diagnoses. Neonatal jaundice may be exacerbated in these situations.

Causes

- Physiologic jaundice is caused by a combination of increased bilirubin production secondary to accelerated destruction of erythrocytes, decreased excretory capacity secondary to low levels of ligandin in hepatocytes, and low activity of the bilirubin-conjugating enzyme UDPGT.
- Pathologic neonatal jaundice occurs when additional factors accompany the basic mechanisms described above. Examples include immune or nonimmune hemolytic anemia, polycythemia, and the presence of bruising or other extravasation of blood.

- Decreased clearance of bilirubin may play a role in breast milk jaundice and in several metabolic and endocrine disorders.
- Risk factors include the following:
  - Race: Incidence is higher in East Asians and American Indians and is lower in African Americans.
  - Geography: Incidence is higher in populations living at high altitudes. Greeks living in Greece have a higher incidence than those living outside of Greece.
  - Genetics and familial risk: Incidence is higher in infants with siblings who had significant neonatal jaundice and particularly in infants whose older siblings were treated for neonatal jaundice. Incidence is also higher in infants with mutations in the gene that codes for the UDPGT promoter (Gilbert syndrome), as well as in the UDPGT-coding region and in infants with homozygous or heterozygous G-6-PD deficiency and other hereditary hemolytic anemias.
  - Nutrition: Incidence is higher in infants who are breastfed or who receive inadequate nutrition.
  - Maternal factors: Infants of mothers with diabetes have higher incidence. Use of some drugs may increase the incidence, whereas others decrease the incidence.
  - Birthweight and gestational age: Incidence is higher in premature infants and in infants with low birthweight.

- Congenital infection

DIFFERENTIALS

Biliary Atresia, Breast Milk Jaundice, Cholestasis, Cytomegalovirus Infection, Dubin-Johnson Syndrome, Duodenal Atresia, Galactose-1-Phosphate Uridyltransferase Deficiency (Galactosemia), Hemolytic Disease of Newborn, Hepatitis B, Hypothyroidism

Other Problems to be considered

Certain conditions may cause nonphysiologic jaundice. In these infants, a baseline physiologic jaundice most likely occurs, which is then exaggerated, for example, by increased enterohepatic circulation in bowel atresia, bile stasis in choledochal cyst, or increased bilirubin production in hemolytic anemias. Such conditions include the following: Bowel atresia, Choledochal cyst, Conjugated hyperbilirubinemia, Crigler-Najjar syndrome, Arias syndrome, Gilbert syndrome, Immune hemolytic anemia, Nonimmune hemolytic anemia

WORKUP

Lab Studies

- Bilirubin measurement may include the following:
  - Transcutaneous bilirubinometry can be performed using handheld devices that incorporate sophisticated optical algorithms. However, such devices cannot be used to monitor the progress of phototherapy.

- In infants with mild jaundice, transcutaneous bilirubinometry may be all that is needed to assure that total bilirubin levels are safely below those requiring intervention.
- In infants with moderate jaundice, transcutaneous bilirubinometry may be useful in selecting patients who require phlebotomy for serum bilirubin measurement.
- In infants with extreme jaundice, transcutaneous bilirubinometry may be a useful tool to fast-track such infants to early and aggressive therapy.
- Usually, a total serum bilirubin level is the only testing required in an infant with moderately jaundice who presents on the typical second or third day of life without a history and physical findings suggestive of a pathologic process.

• Additional studies may be indicated in the following situations:

- Infants who present with jaundice on the first or after the third day of life
- Infants who are anemic at birth
- Infants who otherwise appear ill
- Infants in whom serum bilirubin levels are elevated enough to trigger treatment
- Infants in whom significant jaundice persists beyond the first 2 weeks of life