# An Introduction to Anemia and Bilirubinemia

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## 1 Introduction

In this report, we provide an overview of two serious medical conditions, anemia and bilirubinemia (commonly known as jaundice), which are associated with changes in the contents of specific chromophores present in the blood stream. In general terms, anemia results from a decrease in the hemoglobin content, while jaundice results from an increase in the bilirubin content. Both of them have a significant impact on public health worldwide, with anemia being more prevalent among women of childbearing age, and janudice more common among neonates due their underdeveloped liver.

In the remainder of this report, we briefly address their causes, types, symptoms and treatment options. In Section 2, we examine these points with respect to anemia, and in Section 3 with respect to jaundice. This report closes with a summary and general observations about these two medical conditions.

## 2 Anemia

Anemia is a condition that arises due to a decrease in the number of hemoglobin-containing red blood cells (RBCs). Hemoglobin is an iron-containing transport protein that carries oxygen in the blood stream from respiratory organs (lungs) to the rest of the body [1]. Besides the depletion of RBCs, anemia can also result from a decrease in the oxygen-binding ability of hemoglobin molecules [2]. In this case, there may or may not be normal hemoglobin concentration in the blood. According to Chang *et al.* [3], the depletion of RBCs can result from a number of pathologies and risky situations:

- ulcers;
- cancer;
- faulty bone marrow[1];
- infections (malaria in rural areas [5]);
- menstruation;
- surgery;

[1] RBCs are produced in the bone marrow. Anemia can result from a serious bone marrow disorder, which is more commonly caused by a lack of vitamin $B_{12}$ [4].

- medications or antibiotics (which may cause delays in immune reactions); and
- malnutrition.

The most common form of anemia is the iron deficiency anemia (IDA) which is caused by the premature or excessive destruction of red blood cells before they can be properly repleted [4]. It is worth noting that iron deficiency may not always lead to anemic conditions [6] and the average hemoglobin concentration for healthy individuals differs across race, gender and age. For example, amongst adult individuals characterized by darkly pigmented skin, the average concentration is 8 $g/l$ lower than that of other ethnic groups [6]. Almost all studies about anemia consider four focus groups: infants, children, non-pregnant women and pregnant women. Table 1 provides lower bound values for hemoglobin concentration and hematocrit[2] in nonanemic individuals belonging to these groups.

| Group | Hemoglobin ($g/l$) | Hematocrit (%) |
|---|---|---|
| infants | 110 | 33 |
| children | 115 | 35 |
| women (non-pregnant) | 120 | 36 |
| women (pregnant) | 110 | 33 |

Table 1: Lower bound values for hemoglobin concentration in nonanemic individuals [6].

Another form of anemia, known as pernicious anemia, occurs as a result of vitamin $B_{12}$ deficiency in the liver [8, 9]. It usually occurs when IDA is already in place, and it is often detected at a later stage when the iron deficiency is well established. Once it is detected, it can be treated by administering vitamin $B_{12}$. Pernicious anemia is most commonly found in older women [10].

Abnormal or severe below-normal hemoglobin contents associated with the onset of anemia can hamper the oxygen supply to various organs [11]. Table 2 gives an indication of what can be considered as mild, moderate and severe cases of anemia associated with these contents. Studies have shown that anemic patients have 41% higher chance of suffering a heart attack than nonanemic individuals [12]. In some cases, it may lead to death since parts of the heart are not receiving enough oxygen, and this, in turn, may cause artery blockages. In these cases, transfusions are necessary to raise hemoglobin contents to normal, and consequently reduce significant symptoms of anemia. It is worth noting that an increased degradation of hemoglobin and a consequent reduction of its content in the blood stream may also lead to bilirubinemia [13].

| Severity | Hb Range ($g/l$) |
|---|---|
| mild | $110 - 129$ |
| moderate | $80 - 109$ |
| severe | $< 80$ |

Table 2: Hemoglobin (Hb) contents associated with different levels of anemia severity in men (15 years of age and above) [14].

[2]Hematocrit is the ratio of volume of RBCs to the volume of blood, and it is rounded off to the nearest percent [7].

| Segment/Organ | Symptoms and Signs (mild to intermediate levels) | Additional Symptoms (severe level) |
|---|---|---|
| eyes | yellowness | |
| skin | paleness<br>coldness<br>yellowness | |
| respiratory organs | shortness of breath | |
| muscles | weakness | |
| intestine | changed stool color | |
| spleen | enlargement | |
| heart | palpitations<br>chest pain<br>angina<br>heart attack | rapid heart rate |
| blood vessels | low blood pressure | |
| central nervous system | fatigue<br>dizziness | fainting |

Table 3: Symptoms and signs associated with normal to severe levels of anemia [15]. Symptom is a feeling that a person experience with a disease or conditions (*e.g.*, chest pain), while a sign is an evidence of such a disease or condition that someone else can observe or measure (*e.g.*, yellowish skin) [4].

In order to avert or mitigate the serious consequences of anemia, it is of the utmost importance to detect it in its early stages. A complete blood count (CBC) analysis or an iron content test can be conveniently used as laboratory tests to detect IDA. Apart from these, physical examinations by the medical practitioner, such as inspections of the eyes, skin or general queries about diet and anemic background in the family, can also help in diagnosing this condition [15]. Table 3 summarises anemia symptoms with respect to the different parts of the body where they are manifested [15]. In addition, anemia can lead to different types of physiological and psychological impairments whose observation can be used to complement its diagnosis [3, 16]:

- fearfulness - anemic children are more prone to being fearful and anxious;
- functional isolation - anemic children were observed to be markedly less active than nonanemic children when it came to exploring their environment and moving around;
- cognitive and developmental deficiency;
- impaired visual potential - anemic children have shown longer delay when it comes to visually evoked

potential;

- fatigue, tiredness and dizziness;
- poor concentration and malaise;
- headaches and restless leg syndrome.

According to a survey conducted by the World Health Organization (WHO) [17] in 2000, nine out of ten anemia sufferers live in developing countries, and this medical condition contributes to 20% of maternal deaths each year. However, it has been noted that cases of anemia are not just confined to developing countries. Besides malnutrition, poor eating habits can also lead to the onset of this condition [17]. Hence, awareness and the promotion of proper guidelines to deal with these nutrition issues are, therefore, central for the prevention of anemia. In infants, these efforts include promoting breastfeeding and proper complementary foods. For anemic infants, supplemental iron should be provided at regular intervals and their condition monitored for improvement. For children, periodic screenings are not required once they have been scanned as infants, unless they are prone to risky conditions such as those stated earlier. In such cases, they need to be rescreened. Non-pregnant women between 15-25 years of age must be screened at least once for anemia. If the woman has a positive result, then the clinician should rescreen every 1.5 months after providing supplements or other forms of dietary treatments. In the case of pregnant women, they should be screened during their first prenatal visit and at each subsequent trimester [6].

## 3 Bilirubinemia

Bilirubinemia, or jaundice, refers to the yellowish pigmentation of skin and sclera caused by the presence of excess bilirubin in the blood stream [18]. Bilirubin is formed in the body and subsequently broken down by the liver through a process composed of three stages, termed pre-hepatic, hepatic and pos-hepatic [19, 20]. Jaundice can be pre-hepatic, hepatic or post-hepatic, *i.e.*, it can take place at any of these stages, which are described as follows [19, 20]:

1. Pre-hepatic (occurring prior to the liver) - The breakdown of red blood cells yields bilirubin as a byproduct. RBCs can break down either after their normal cycle completion of 120 days or as an aggravation due to anemia or genetic diseases such as Gilbert's syndrome[3] and thalassemia[4]. Bilirubin is produced once the RBC cell membrane disintegrates or ruptures releasing it into the blood stream. This form of bilirubin is referred to as "free", "unconjugated" or "indirect" bilirubin.

2. Hepatic (occurring within the liver) - The unconjugated bilirubin is made conjugated (water soluble) by biochemical processes in the liver. This conjugated bilirubin is then excreted as bile from the liver.

3. Post-hepatic (post conjugation of bilirubin in the liver) - This comprises of drainage of bile in the biliary system or the bile duct.

The majority of the reported jaundice cases are for neonates. One of the main reasons why this medical condition is more prevalent among neonates is that they produce more red blood cells than adults. Since

[3]Gilbert's syndrome affects 3-7% of the population [21], and it is caused by a degradation in activity of the enzyme present in liver that is responsible for conjugating the insoluble bilirubin, *i.e.*, making it water soluble [22].

[4]Thalassemia is an inherited disorder where body does not produce enough hemoglobin due to the weakening and premature destruction of the RBCs [23].

a neonate's liver is not fully developed, it may not be completely successful in removing adequate amounts of bilirubin from the body [24]. The common types of neonatal jaundice include [24]:

- "normal" jaundice - characterized by the slow processing of bilirubin by the neonate's liver;
- prematurity jaundice - in premature neonates, jaundice occurs more frequently since their liver is even less developed; and
- breast milk jaundice/blood group incompatibility jaundice - characterized by a sudden buildup of bilirubin in the neonate's blood either due to substances produced in the breast milk or due to a different blood type of the mother.

The bilirubin contents for neonates (as shown in Table 4) are different from that of adults [25]. In fact, it differs even from premature to full term neonates [26]. In adults, jaundice can result from the inflammation of liver caused by viruses, known as hepatitis. The most generic forms of this disease are hepatitis A, B and C [27]. Hepatitis A is transmitted through contaminated food or water. The virus is excreted in the faeces of an infected person, and thus, transmission is enhanced under poor hygiene conditions [27]. Hepatitis B is more likely to be passed at an infantile stage via exposure to infected maternal blood. In addition to this, it can be transmitted by sexual contact or ensued as a result of drug abuse [28, 29]. Hepatitis C is more likely to be transmitted through blood transfusions [30]. Although vaccines for hepatitis A and B are available, there is no vaccine for protecting against hepatitis C [30]. Jaundice can also be a consequence of obstructive cholestasis[5], which, in turn, may result from genetic disorders such as Gilbert's syndrome [22]. Crigler-Najjar, Dubin-Johnson and Rotors syndromes are other genetic disorders that cause abnormal secretion of bilirubin into bile, which ultimately leads to jaundice [22]. It is worth noting that jaundice is caused by a higher bilirubin content in elderly patients than in younger ones [32]. Moreover, a recent study has shown that, for patients suffering from chronic hepatitis, the bilirubin contents tend to be slightly higher in males than females [33]. In that study, groups of male and female patients suffering from chronic hepatitis were divided in the age bands of 31-40 years, 41-50 years, 51-60 years and 61-76 years, in order to allow a more detailed analysis of the variance of total bilirubin.

| Age/Time | Premature | Full Term |
|---|---|---|
| $<$ 24 hours | $<$ 8.0 $mg/dl$ (below 137 $mmol/l$) | $<$ 6.0 $mg/dl$ (below 103 $mmol/l$) |
| $<$ 48 hours | $<$ 12.0 $mg/dl$ (below 205 $mmol/l$) | $<$ 10.0 $mg/dl$ (below 170 $mmol/l$) |
| between 3 and 5 days | $<$ 15.0 $mg/dl$ (below 256 $mmol/l$) | $<$ 12.0 $mg/dl$ (below 205 $mmol/l$) |
| 7 days and older | $<$ 15.0 $mg/dl$ (below 256 $mmol/l$) | $<$ 10.0 $mg/dl$ (below 170 $mmol/l$) |

Table 4: Average normal range of bilirubin for neonates [26].

After a preliminary physical examination by a medical practitioner, the diagnosis of jaundice may require bilirubin, liver function and CBC tests [4]. These tests are done more than once in neonates to keep track of altering counts and condition. An elevated bilirubin content in a neonate may resolve itself within a few days to two weeks, and therefore, periodic testing is conducted. For adults, depending on the initial results, additional tests may be conducted. Urinalysis [4], which is an analysis of the urine, is a useful test that may give a fair indication of the presence of bile in urine.

[5]Cholestasis is a condition where the liver cannot successfully secrete bile into a tube-like structure called the bile duct [31].

Similar to anemia, jaundice may be treated by administering blood transfusions or medications [26]. When jaundice occurs in neonates, it can be treated by phototherapy [24]. Phototherapy consists in the use of ultraviolet light to help the neonate's body to eliminate bilirubin. In certain cases, blockages in and around the liver have to removed by surgery using a process called ERCP (endoscopic retrograde cholangiopancreatography) [34].

Severe cases of jaundice may result in the failure of important organs such as pancreas, kidneys and liver [35, 36, 13]. They may also lead to certain types of cancer, particularly in older individuals where a blockage in the excretion of bilirubin may result in the formation of a tumor [35]. Among neonates, severe cases of the disease may lead to kernicterus [18], a damage to the central nervous system that may result in death [37].

The measurement of unconjugated bilirubin content, known as serum bilirubin concentration, can be used to determine the jaundice risk levels, notably for neonates [38]. Figure 1 represents the various risk levels associated with varying serum bilirubin concentrations among neonates. Those in the high risk zone may be treated using phototherapy.

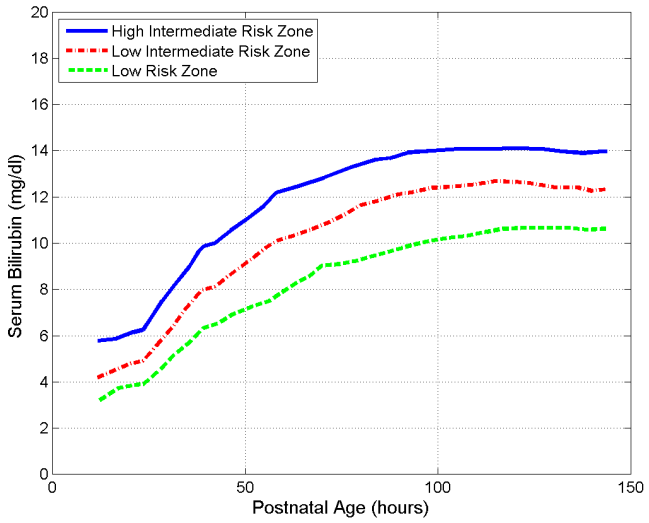


Figure 1: A percentile-based predictive bilirubin nomogram, also known as the Bhutani graph [26]. Redrawn from [26].

When jaundice results from the presence of ductal stones in the bile duct or carcinoma of the head of the pancreas (CAHOP), its treatment may require surgery [39]. Irabor [40] analysed the fall of serum bilirubin contents after operative relief was performed on seven adult patients with this type of obstructive jaundice [40]. The observed pattern of reduction or fall in the bilirubin serum content was that in all seven patients there was an initial precipitous drop of roughly 2/3 of the original value (before operation) by the 2nd post-operative day. There was then a gradual decline up to the 7th post-operative day when the measured contents were one-thirds of the original value. By the 14th day, the serum bilirubin was roughly one-fifths of the original value.

# 4 Summary

Both anemia and jaundice mainly result from an excessive breakdown of red blood cells at a rate higher than the body can produce. Hemoglobin comprises of 73% of the body's essential iron and thus, best reflects iron status [6]. Women lose more iron in their childbearing years than men. This is primarily because of menstrual blood loss which explains why most studies consider low hemoglobin concentration only in women apart from infants and children. Continual prevalence of anemia can result in jaundice. However, the latter can be a result of other contributing factors as well. Jaundice is observed most commonly among neonates.

While jaundice can be diagnosed in its early stages due to the characteristic yellowish pigmentation of the skin and eyes, anemia can go unnoticed for a long time [41]. It can usually be corrected by suggestive dietary changes or by blood transfusions in severe cases. An exception would be the sickle cell anemia where the red blood cells of a patient are sickle-shaped or crescent-shaped by birth [42].

While much research has been done on studying the causes, effect and treatment of jaundice in neonates, not many studies feature its occurrence in adults. This can be a possible topic for future research which can help us understand the various facets of this condition. Moreover, although several studies talk about severe anemia leading to jaundice [4, 13, 43], to the best of our knowledge, the time frame and stages associated with their interplay are still unknown. As future work, we plan to investigate variations in hemoglobin and bilirubin contents resulting from the simultaneous onset of both conditions.

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