NON-IMMUNE HYDROPS

INTRODUCTION
In 1943 Potter¹ differentiated non-immune hydrops (NIH) from immune hydrops due to fetal-maternal blood incompatibilities. Since the incorporation of Rh-immune globulin into antepartum care for Rh-negative women, 90% of hydropic cases are non-immune in origin².

DEFINITION
There are a number of definitions of NIH. The most common definition of NIH includes anasarca (a generalized increase in subcutaneous fluid [Fig 1a-c]) and the presence of free fluid in at least one serous cavity (e.g. pleural, pericardial or abdominal)³. The presence of fluid in two body cavities without anasarca has also been considered by some sufficient to qualify as NIH. Placentomegaly (Fig. 2) and polyhydramnios are frequently associated with non-immune hydrops⁴, but are not required to make a diagnosis.

Fig 1a. Fetal profile illustrating scalp edema due to non-immune hydrops. Click for larger image.
Fig 1b. Cross-section of the fetal chest. There is marked anasarca (markers), as well as a pleural effusion and polyhydramnios. Click for larger image.

Fig 1c. Autopsy specimen of a fetus with non-immune hydrops and anasarca. Click for larger image.
PREVALENCE
NIH has been reported in approximately 1 in every 1,500 to 1 in every 4,000 pregnancies. However, the prevalence varies based upon the population scanned and the gestational age at which the ultrasound examinations are performed. In a high-risk referral practice the prevalence of NIH may approach 1 in every 250 deliveries. The first trimester diagnosis of NIH is becoming more frequent.

PATHOPHYSIOLOGY
Non-immune hydrops is due to an abnormal distribution of fluid between the intravascular system and interstitial space. The return of lymphatic fluid to the venous system is impaired by one of several mechanisms, resulting in a back-up of fluid within the lymphatic system. The accumulation of fluid within the interstitial space may be due to either a fetal or placental etiology. Any, or a combination of, the following etiologies have been proposed for NIH:
1. Cardiac failure secondary to congenital heart disease
2. Increased cardiac output (e.g. secondary to a large placental chorioangioma)
3. Impaired venous return
4. Increased capillary permeability
5. Decreased colloidal osmotic pressure
6. Obstruction to normal lymphatic flow

The first site of fluid accumulation will occasionally provide clues that can narrow the differential diagnosis. For example, a fetal tachycardia initially gives rise to ascites, followed by a pleural effusion and, lastly, anasarca. Fetuses with anemia as the etiology for NIH only rarely will develop a pleural effusion.

ETIOLOGY
The pathophysiology of NIH indicates that its underlying etiology is multifactorial. The exact prevalence of specific conditions varies from one series to the next. Approximately 65% of NIH cases are due to one
of six general causes:
1. Chromosomal abnormalities/genetic syndromes
2. Cardiovascular defects or abnormalities of function
3. Anemia
4. Thoracic abnormalities
5. Infection
6. Twinning

In earlier studies a specific etiology for NIH could be determined in only 50 to 60% of cases. More recently, between 80% and 90% of cases could be given a specific diagnosis.

CHROMOSOMAL ABNORMALITIES
Trisomy 13, 18, 21, as well as triploidy and Turner syndrome (Fig. 3, 4) have all been associated with non-immune hydrops. The prevalence of chromosomal abnormalities increases as the gestational age at detection decreases. All of the mechanisms referred to in the section on pathophysiology have been implicated in fetuses with chromosomal abnormalities. The resolution of fetal hydrops as gestational age advances does not exclude a possible chromosomal abnormality. There are several genetic syndromes (Table I) with an increased recurrence risk that may present with NIH.

Fig 3. Fetus with Turner's syndrome and a posterior cystic hygroma. Click for larger image.
TABLE I. GENETIC SYNDROMES ASSOCIATED WITH NON-IMMUNE HYDROPS

- Noonan syndrome
- Fryns syndrome
- Arthrogryposis multiplex congenita
- Lethal Pterygium syndrome

CARDIOVASCULAR DEFECTS OR ABNORMALITIES OF FUNCTION

Structural cardiac defects may give rise to NIH (Table II). There is a higher incidence of congenital defects of the left side of the heart. However, right sided lesions are more likely to result in non-immune hydrops\(^{15}\). Severe tricuspid regurgitation (Fig. 5) results in an elevated right atrial pressure, impaired venous return, and subsequent hydrops. Ebstein's anomaly has an abnormally low insertion of the tricuspid valve. Severe tricuspid regurgitation with this anomaly has also been associated with NIH in 15 to 20% of cases\(^{10}\). Premature closure of the foremen ovale or ductus arteriosis can also result in NIH\(^{10}\).

TABLE II. CARDIOVASCULAR ETIOLOGIES OF NON-IMMUNE HYDROPS.

- Ebstein's anomaly
- Pulmonary stenosis
- Tachyarrhythmias
- Cardiac/pericardial tumors
Significant tachyarrhythmias (> 200 beats/minute) gives rise to poor ventricular filling, subsequent increased venous pressure, and reduced lymphatic flow. Neurologic outcome is generally good when NIH secondary to a tachyarrhythmia is successfully treated in utero and delivery occurs at term\textsuperscript{17}. Complete heart block with its frequently associated congenital heart defects (e.g. an incompetent AV value with regurgitation) can result in hydrops. Fetuses with heart block secondary to an autoimmune disease generally have a structurally normal heart. As a result, the likelihood of hydrops is low\textsuperscript{18}. Fetal hyperthyroidism secondary to maternal thyroid stimulating globulin G crossing the placenta can result in a goiter, fetal tachycardia, high output failure and subsequent hydrops\textsuperscript{19}. Causes of fetal hypothyroidism include the maternal administration of medications (propylthiouracil). Percutaneous umbilical blood sampling is required to confirm fetal thyroid status\textsuperscript{20}. Intrapericardial teratomas\textsuperscript{21}, as well as the rhabdomyomas\textsuperscript{22} associated with tuberous sclerosis may occasionally give rise to hydrops. The former results in hydrops secondary to compression, while the latter may cause a rhythm disturbance, an obstruction, or regurgitation. Arterio-venous malformations (liver hemangiomas\textsuperscript{23}, aneurysm of the vein of Galen\textsuperscript{24}) can, if large enough, result in hydrops.

ANEMIA
In Asian women, alpha thalassemia is a common etiology for NIH\textsuperscript{3}. Alpha chains are not produced in the
homozygous form. Since adequate oxygen cannot be supplied to fetal tissues, high-output failure results in hydrops.

A chronic fetal-maternal hemorrhage with resulting anemia can result in NIH. However, in most cases of severe fetal-maternal hemorrhage, fetal death may occur suddenly or within days - an insufficient amount of time for sonographic evidence of NIH to develop.

Fetal middle cerebral artery peak systolic velocity can be used to identify those fetuses that have severe anemia as a component of their NIH, regardless of cause. There is a direct correlation between the velocity of fetal blood and hematocrit - the lower the hematocrit, the higher the velocity. A peak velocity of 1.5 SD above the mean will detect 96% of severely anemic fetuses with a 14% false positive rate.

THORACIC ABNORMALITIES

The chest compression associated with severe skeletal dysplasias (Fig. 6) may cause NIH due to impaired venous return. A similar mechanism has been proposed for NIH associated with hydrothorax (Fig. 7), severe cystic adenomatoid malformation (Fig. 8), extra lobar pulmonary sequestration, and laryngeal atresia. In the latter cases, a small heart size (< 20% of the chest area) is due to external compression by the thoracic mass. In fetuses with cystic adenomatoid malformation and hydrops, pericardial effusions are rare, suggesting that the compression by the large mass does not permit expansion of the pericardial space. Severe polyhydramnios may result from esophageal compression.

Fig 6. Anasarca and shortened upper extremity due to short rib polydactyly syndrome. Click for larger image.
CONGENITAL INFECTION

A number of different bacterial and viral infections (Fig. 9) have been associated with NIH (Table III). A systemic infection involving multiple organs (heart, liver, sepsis with secondary endothelial damage, etc)
is the final common pathway resulting in NIH.

Fig 9. Liver calcification (arrows) secondary to a CMV infection. Fetal ascites and a pleural effusion are also illustrated. Click for larger image.

TABLE III. CONGENITAL INFECTIONS ASSOCIATED WITH NON-IMMUNE HYDROPS.

- **Bacterial**
  - Syphilis
  - Listeria
- **Parasitic**
  - Toxoplasmosis
- **Viral**
  - Cytomegalovirus
  - Parvovirus
  - Varicella
  - Herpes simplex
  - Adenovirus
  - Coxsackie
  - Rubella

Of the infections listed in Table III, parvovirus is by far the most commonly associated with NIH. Depending upon the series, parvovirus has been reported to cause up to 10% of NIH cases. Hence, the mother of any fetus with NIH should be tested for parvovirus infection. There is a reported 2.9% risk of hydrops associated with a parvovirus infection between 9 and 20 weeks' gestation. In the first trimester myocarditis and in the second trimester red cell hemolysis and secondary anemia can produce hydrops in the fetus affected by a parvovirus infection. The anemia associated with parvovirus is transient. As a result, an affected pregnancy need only be followed with middle cerebral artery Doppler studies for 12 weeks.
If severe NIH should result from a parvovirus infection, percutaneous umbilical blood sampling and transfusion are therapeutic. The goal of intrauterine transfusion is to maintain an appropriate fetal hemoglobin until the fetal infection resolves and red cell production returns to normal. Despite the presence of a systemic infection and secondary hydrops, adverse outcome in survivors of NIH due to parvovirus is rare.

Although CMV has been reported in between 0.5% and 2.5% of all newborns, the frequency of associated hydrops is far less than with parvovirus. However, CMV is the most common infectious cause of severe long-term neonatal sequelae. The absence of any sonographic findings after CMV exposure does not exclude a serious congenital infection with significant neurologic sequelae. In contrast to parvovirus infection, the presence of hydrops secondary to CMV indicates a severe infection with significant long-term sequelae.

With the onset of widespread testing, the prevalence of congenitally acquired syphilis has been markedly reduced. Certain organs are more susceptible to spirochete infection. While hepatosplenomegaly is common, involvement of the leptomeninges and bowel is less frequent. Placentomegaly is due to villous edema and/or hyperplasia. Septicemia with its resultant capillary damage and anemia secondary to hepatic damage may give rise to hydrops. In general, the anemia associated with CMV, toxoplasmosis, treponema pallidum, and other infections is milder than with parvovirus.

**TWINS**

Twin-to-twin transfusion syndrome (Fig. 10) occurs in 10% to 17% of monochorionic twins. Hydrops has been described either in the donor or the recipient. The etiology of hydrops in twin-to-twin transfusion syndrome is either severe anemia in the donor twin or high-output failure in the recipient. A thickened nuchal translucency in the first trimester has been associated with severe twin-to-twin transfusion later in gestation.
Acardiac twins of sufficient size can result in a hydropic pump twin. Radiofrequency ablation of the abdominal umbilical cord of the acardiac twin has been used to stop perfusion of the acardiac twin and return the blood volume of the pump twin to normal\(^{45}\).

**MISCELLANEOUS ETIOLOGIES OF NON-IMMUNE HYDROPS**

Sacrococcygeal (Fig. 11), mediastinal, pericardial\(^{46}\), or intracranial teratomas have been associated with NIH. Predominantly solid sacrococcygeal teratomas have a higher blood flow than cystic teratomas. As a result, the likelihood of high-output failure with secondary hydrops is significantly increased\(^{47}\). Hemorrhage into the tumor may result in anemia, compounding the risk of hydrops.

![Fig 11. Sacrococcygeal teratoma at 24 weeks' gestation. Click for larger image.](image)

Giant cavernous hemangiomas\(^{48}\), mesoblastic nephromas\(^{49}\), intracerebral arteriovenous malformations\(^{50}\), and large vascular placental chorioangiomas\(^{51}\) may also result in NIH. Other unusual causes of NIH are in Table IV. Poorly controlled maternal diabetes mellitus has been associated with NIH\(^{16}\). The altered in utero metabolic environment of poorly controlled diabetes mellitus results in significant myocardial stiffening, reduced ventricular filling, impaired venous return and eventually hydrops\(^{52}\).

**TABLE IV. UNUSUAL CAUSES OF NON-IMMUNE HYDROPS.**

- Lethal Pterygium syndrome\(^{59}\)
- Klippel-Trenaunay-Weber syndrome
- Lysosomal storage diseases\(^{21,60}\)
  - Gaucher
  - Neiman-Pick
- Smith-Lemli-Optiz syndrome\(^{61}\)
- Congenital diaphragmatic hernia\(^{62}\)

Spontaneous resolution of severe NIH has been reported\(^{53}\).
PROGNOSIS
Since NIH is the end stage presentation of multiple distinct and unrelated etiologies, prognosis varies markedly. Severity and gestational age at presentation, as well as etiology, affects long-term survival. The presence of a congenital anomaly or a chromosomal abnormality with NIH worsens the prognosis\textsuperscript{54}. While an overall perinatal mortality of 63.4\% was reported in one series, etiology specific mortality varied from 0\% to 90.9\%. Hence, patient counseling must be based on a specific diagnosis. If the cause of NIH cannot be determined, the perinatal mortality is approximately 50\%\textsuperscript{55}. In some cases the pathophysiology of NIH is multifactorial, resulting in a poorer overall prognosis\textsuperscript{15}.

EVALUATION AND MANAGEMENT
The wide spectrum of maternal, fetal and placental etiologies for NIH require an orderly diagnostic approach to optimize the clinician's success in not only diagnosing, but also in treating fetuses with this frequently lethal condition. A complete maternal history followed by appropriate blood work can go a long way towards narrowing the differential diagnosis. Fetal assessment can be categorized as indirect and invasive. A thorough 2-D ultrasound examination that includes echocardiography provides a detailed "physical exam" of the fetus. 3-D ultrasound will occasionally add additional important information. In order to evaluate the fetus for heart failure, a multi-vessel Doppler study that includes the umbilical artery, umbilical vein, middle cerebral artery and ductus venosus is required\textsuperscript{56}. An amniocentesis and/or fetal blood sampling completes the evaluation of the hydropic fetus. The latter tests permit an evaluation of fetal karyotype; PCR (polymerase chain reaction) for infection; fetal liver function; and metabolic testing, if indicated. Once the work-up has been completed, the possibility of etiology specific therapy should be assessed. As previously mentioned intravascular transfusion has been highly successful in the management of NIH secondary to parvovirus. Fetal drug therapy for fetal tachyarrhythmias\textsuperscript{57} or fetal hyperthyroidism\textsuperscript{19} may also be highly successful. Pleuro-amniotic shunting has been used in selected cases\textsuperscript{58}. If a surgically correctable etiology is identified, a carefully timed delivery can be life saving. An autopsy and placental evaluation in cases of stillbirth or neonatal death will help to delineate potential causes for NIH and provide information concerning recurrence risk. In one series the determination of an etiology for non-immune hydrops was increased from 50\% without to 80\% with an autopsy\textsuperscript{10}. In another series, this combined approach of a thorough antenatal assessment and necropsy when indicated was able to determine the cause of non-immune hydrops in over 90\% of cases\textsuperscript{10}.

REFERENCES


