

Transient Tachypnea of the Newborn

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Education Gaps

It can be challenging to diagnose and provide optimal treatment for transient tachypnea of the newborn.

Objectives After completing this article, readers should be able to:

1. Understand the pathophysiology of transient tachypnea of the newborn (TTN).
2. Identify risk factors, clinical symptoms, and radiographic findings in infants with TTN.
3. Appreciate the differential diagnoses for TTN.
4. Describe the typical clinical course of an infant with TTN.

INTRODUCTION

Fetal lungs are filled with liquid that is crucial for normal lung growth. After birth, this fetal alveolar fluid is cleared through pulmonary epithelial, vascular, and lymphatic channels. A delay in fluid clearance leads to ineffective gas exchange and results in respiratory distress. This impermanent condition of retained fetal lung fluid is known as transient tachypnea of the newborn (TTN). (1)(2)

TTN is one of the leading causes of neonatal respiratory distress and is therefore an important diagnosis to consider, identify correctly, and manage. (3) It is generally a benign, self-limited condition that presents shortly after birth and occurs in infants of any gestational age. Diagnosis of TTN is based on an infant's clinical presentation, physical examination findings, and classic chest radiographic findings. The management consists of supportive care, with symptoms generally resolving by 24 to 72 hours of age.

PATHOPHYSIOLOGY

As early as 6 weeks of gestation, the fetal lung epithelium begins to secrete alveolar fluid at 2 mL/kg per hour, increasing to a rate of 5 mL/kg per hour at term. (4) This liquid is crucial for normal lung growth and contributes to the volume of amniotic fluid that surrounds the fetus. A few days before the onset of spontaneous vaginal

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ABBREVIATIONS

| | |
|------------------|-------------------------------------|
| ABG | arterial blood gas |
| ALPS | Antenatal Late Preterm Steroids |
| CBC | complete blood cell |
| CPAP | continuous positive airway pressure |
| CRP | C-reactive protein |
| ENaC | epithelial sodium channel |
| FiO ₂ | fraction of inspired oxygen |
| IV | intravenous |
| TTN | transient tachypnea of the newborn |

delivery, fluid production decreases. (5) With the onset of labor, maternal hormones such as epinephrine and glucocorticoids stimulate the fetal lungs to begin absorption of alveolar fluid through activation of an amiloride-sensitive epithelial sodium channel (ENaC). (4) Animal studies of α -ENaC knockout mice have shown that when sodium transport is inactivated, alveolar fluid retention occurs, which leads to respiratory distress and death. (6)

The clearance of fetal lung fluid begins with passive sodium transport across ENaC proteins, which are found on the apical membrane of alveolar type II pneumocytes. After sodium enters the type II cell, it is actively transported into the pulmonary interstitium via a basolateral sodium-potassium (Na^+/K^+) ATPase pump. This creates an osmotic gradient that allows chloride and water to follow and be absorbed into the pulmonary circulation and lymphatics (Fig 1). (1)(7) It is through this mechanism that most of the fetal lung fluid is cleared. Starling forces and the thoracic “squeeze” through the birth canal contribute minimally toward fluid elimination. (2)

INCIDENCE

TTN is one of the most common causes of neonatal respiratory distress. TTN occurs in $\sim 10\%$ of infants born between 33 and 34 weeks of gestation, $\sim 5\%$ of infants delivered at 35 to 36 weeks, and fewer than 1% of all term infants. (8)(9) Generally the rate of respiratory morbidity is inversely proportional to gestational age. In 2013, the American College of Obstetricians and Gynecologists published guidelines recommending avoidance of nonmedically indicated vaginal or cesarean deliveries at less than 39 weeks of gestation. (10)(11)

Recently, data from the Antenatal Late Preterm Steroids (ALPS) Trial examined whether betamethasone administration

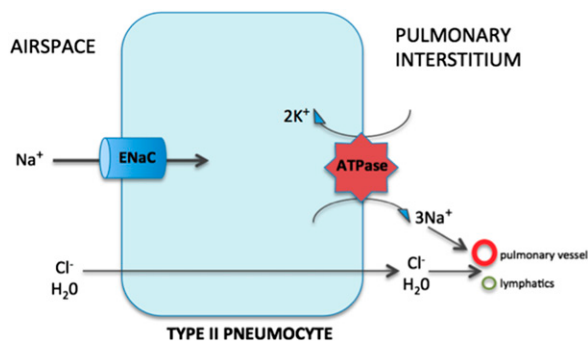


Figure 1. Mechanism of fetal lung fluid clearance. During maternal labor, epithelial sodium channels (ENaC) are activated and sodium (Na^+) is passively transported into type II pneumocytes. Na^+ then actively moves into the pulmonary interstitium, which is followed by the movement of chloride (Cl^-) and water (H_2O). This liquid is ultimately cleared into the pulmonary vasculature and lymphatics. (Reproduced with permission from *The Essential Guide to Clinical Neonatology*. New York, NY: Nova Biomedical Publishing Company. In press.)

in pregnant women at risk for late preterm delivery would affect neonatal respiratory morbidity. The ALPS Trial was a multicenter, double-blind, randomized controlled trial that included 2,831 infants born between 34 0/7 and 36 6/7 weeks’ gestation whose mothers received antenatal corticosteroids. The investigators found that late preterm neonates whose mothers received betamethasone had a decreased incidence of TTN and required less continuous positive airway pressure (CPAP) and fraction of inspired oxygen (FiO_2). (12) Administration of corticosteroids before delivery may improve TTN symptoms through induction of ENaC, which is involved in fetal fluid absorption. (13) How this new practice may affect the incidence of other neonatal morbidities is unclear.

RISK FACTORS

There are well-established risk factors that may contribute to the development of TTN (Table 1). These include male sex, birth asphyxia, maternal gestational diabetes, and cesarean section without labor or delivery before 39 weeks of gestation. (14)(15) Preterm infants are at an increased risk for TTN, which is inversely proportional to their degree of prematurity. Small- and large-for-gestational age infants are also at an increased risk of developing TTN. Although maternal asthma is a known risk factor, the mechanism is not well defined. (16)

CLINICAL PRESENTATION

Infants with TTN generally present within the first few minutes to hours after birth. They have signs of respiratory distress such as tachypnea (respiratory rate >60 breaths/min), nasal flaring, grunting, and intercostal, subcostal, and/or suprasternal retractions. On auscultation, breath sounds may be diminished, crackles may be appreciated, or lung fields may be clear. Tachycardia may often be associated. Newborns with TTN may also have cyanosis and need supplemental oxygen, but usually no more than an FiO_2 of 0.40.

If signs of respiratory distress resolve within the first few hours after birth, this may be due to a brief delay in lung fluid absorption, and is commonly referred to as “delayed transition.” However, if respiratory distress persists beyond a clinically acceptable period (eg, 2–6 hours) and continued support is needed, then all causes of neonatal respiratory distress should be considered, including TTN.

DIAGNOSIS

TTN is a diagnosis of exclusion, thus other causes of neonatal respiratory distress presenting soon after birth must be excluded (Table 2). The diagnosis is made based on an infant’s

TABLE 1. Neonatal Risk Factors for the Development of Transient Tachypnea of the Newborn (TTN)

- Delivery before completing 39 weeks of gestation
- Cesarean section without labor
- Prematurity
- Male sex
- Large for gestational age
- Small for gestational age
- Perinatal asphyxia
- Maternal asthma
- Maternal gestational diabetes

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clinical presentation, physical examination findings, and chest radiography findings. If symptoms persist beyond 72 hours after birth, alternative diagnoses to TTN must be examined. TTN cannot be confirmed until symptoms resolve completely.

Radiographic findings in TTN can include fluid in the interlobar fissure, bilateral alveolar and interstitial edema, prominent pulmonary vascular pattern with increased perihilar markings, and lung hyperinflation (Figs 2–4).

On initial chest radiography in a newborn with TTN, bilateral patchy alveolar edema may be difficult to differentiate from neonatal pneumonia. However, radiographic findings that clear after 24 hours are more consistent with TTN (Fig 5). In addition, preterm infants can have radiographic

evidence of retained fetal lung fluid and surfactant deficiency simultaneously.

Based on a newborn's clinical condition and infectious risk factors, laboratory tests may need to be performed. Blood tests to consider include a complete blood cell (CBC) count, C-reactive protein (CRP), arterial blood gases (ABG), lactate, and blood culture. In addition, empiric antibiotic therapy for early neonatal sepsis (eg, ampicillin and gentamicin) should be considered, because TTN may be difficult to clinically distinguish from neonatal sepsis or pneumonia.

ABG analysis may demonstrate mild hypoxemia and hypocapnia due to tachypnea. If hypercapnia is present, it may be a sign of fatigue or other complication such as an air leak. If

TABLE 2. Diagnoses to Consider When a Newborn Infant Presents With Respiratory Distress

- Respiratory distress syndrome
- Air leak (eg, pneumothorax)
- Congenital lung conditions (eg, congenital pulmonary airway malformation)
- Meconium aspiration syndrome
- Congenital diaphragmatic hernia
- Persistent pulmonary hypertension of the newborn
- Congenital heart disease
- Neonatal pneumonia
- Early-onset sepsis
- Inborn error of metabolism

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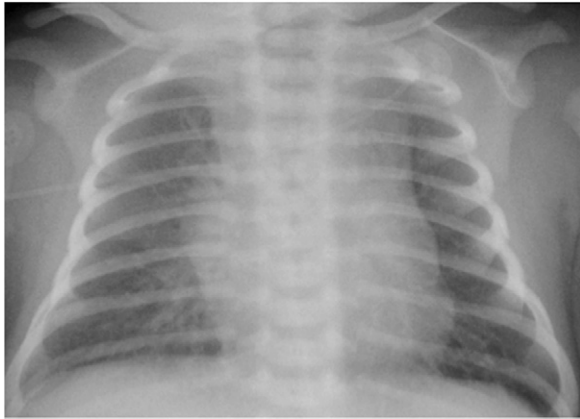


Figure 2. Chest radiograph of an infant with transient tachypnea of the newborn (TTN) demonstrating prominent perihilar pulmonary vascular markings in a “sunburst” pattern. (Reproduced with permission from *The Essential Guide to Clinical Neonatology*. New York, NY: Nova Biomedical Publishing Company. In press.)

persistent tachypnea is present in the setting of lethargy and metabolic acidosis, an ammonia level will help evaluate for an inborn error of metabolism. In the presence of hypoxia, pre- and postductal saturations will help to evaluate for differential cyanosis. If differential cyanosis is uncovered, then an echocardiogram should be obtained to rule out congenital heart disease or persistent pulmonary hypertension of the newborn. Echocardiography should also be performed to rule out congenital heart disease in neonates with presumed TTN who have tachypnea for more than 4 to 5 days. A reasonable approach in the care of a term neonate with respiratory distress is the “rule of 2 hours.”⁽¹⁷⁾ Two hours after the onset of neonatal respiratory distress, if an infant’s condition has not improved or has worsened, if the infant is requiring FiO_2 greater than 0.4, or chest radiography findings are abnormal,



Figure 3. Chest radiograph of an infant with transient tachypnea of the newborn (TTN) demonstrating hyperinflated lungs and increased perihilar interstitial markings. (Reproduced with permission from *The Essential Guide to Clinical Neonatology*. Nova Biomedical Publishing Company, New York. In press.)

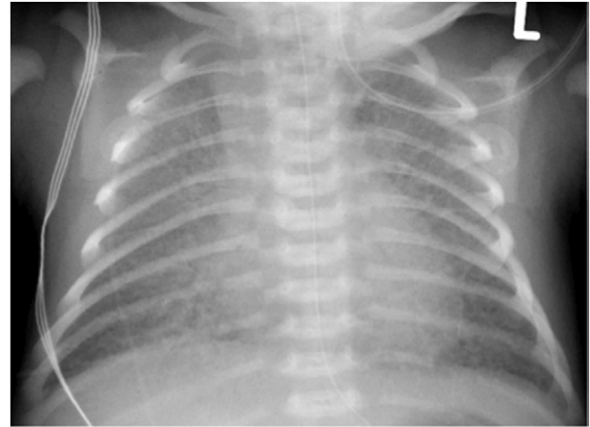


Figure 4. Chest radiograph of an infant with severe transient tachypnea of the newborn (TTN) demonstrating indistinct pulmonary vessels and diffuse pulmonary edema. (Reproduced with permission from *The Essential Guide to Clinical Neonatology*. New York, NY: Nova Biomedical Publishing Company. In press.)

practitioners should consider transferring the infant to a center that can provide a higher level of neonatal care.

MANAGEMENT

Given that TTN is a self-limited condition, the mainstay of treatment is supportive care. Routine NICU support should be provided, including continuous cardiopulmonary monitoring, maintenance of a neutral thermal environment, optimizing fluid balance, checking blood glucose levels, and observation for signs of infection.

Securing intravenous (IV) access should be considered in neonates with suspected TTN, given the high likelihood of requiring IV fluids or IV nutrition, because many infants with tachypnea and respiratory distress will likely have a delay in advancement of enteral feeding. If an infection is highly suspected, the infant will also require IV access for antibiotic therapy. Generally, an arterial line is not required for the management of TTN. If frequent ABG measurements are required or the infant needs arterial monitoring for hypotension, other causes should be considered.

Respiratory

Neonates with TTN may require noninvasive respiratory support (eg, nasal cannula, nasal CPAP) and may need supplemental oxygen to maintain normal oxygen saturation levels. If a newborn is requiring FiO_2 greater than 0.40 or endotracheal intubation, there is increased likelihood of another cause of the child’s distress. The clinical picture should be reevaluated, presence of differential cyanosis assessed, and additional testing considered. This includes repeat laboratory tests, such as a CBC count, CRP, ABG,

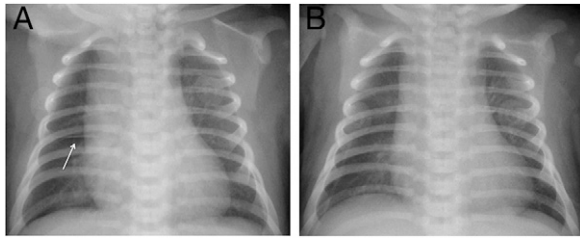


Figure 5. A. First chest radiograph after birth shows bilateral pulmonary edema. The arrow points to the classic appearance of “fluid in the right horizontal fissure”. B. Repeat radiograph obtained 24 hours after birth shows improved pulmonary edema and interval resolution of the fluid previously seen in the fissure. (Reproduced with permission from *The Essential Guide to Clinical Neonatology*. New York, NY: Nova Biomedical Publishing Company. In press.)

lactate, ammonia level, and imaging, such as chest radiography and/or echocardiography.

Nutrition/Hydration

An infant’s respiratory condition is the determining factor for receiving enteral or IV nutrition. Often the clinical status and degree of tachypnea make it unsafe for an infant to receive oral feeds and instead the infant can receive nutrition via gavage feeding, IV solution, or a combination of both. When an IV solution (eg, dextrose-containing electrolyte fluid, peripheral or total parenteral nutrition) is administered, electrolytes should be monitored closely. Central line placement may be indicated to meet nutritional or electrolyte requirements.

A single-center, randomized, controlled trial involving 67 neonates demonstrated a possible role for fluid restriction in newborns with severe TTN, defined as infants requiring respiratory support for 48 hours or more. In the first 24 hours after birth, total fluid intake was restricted to 40 mL/kg per day in term infants and 60 mL/kg per day in preterm infants. In both groups, total fluids were advanced by 20 mL/kg per day. Fluid restriction decreased the duration of respiratory support, decreased the cost of hospitalization, and did not cause dehydration. (18) However, this is not currently considered standard practice and further multicenter, randomized, controlled trials are needed.

Medications

Currently, strong data to support the routine use of medications in the treatment of TTN are lacking. Medications studied include diuretic therapy, inhaled racemic epinephrine, and inhaled β_2 -agonists. A recent systematic review analyzed the usefulness of routine diuretic therapy for TTN and concluded that neither oral nor IV furosemide provided any benefit by improving symptoms or reducing duration of hospitalization. (19) A small study of 20 newborns looked at the safety and efficacy of inhaled racemic epinephrine as a potential

treatment for TTN. (20) The authors did not observe issues with medication safety, but the number of study patients was too small to determine efficacy or make any generalizable conclusions. Last, the inhaled β_2 -agonist salbutamol has been studied and may have promise as a possible treatment option to improve respiratory symptoms associated with TTN and decrease hospital length of stay. (21)(22) Nevertheless, recent systematic reviews have concluded that more evidence is needed to confirm the efficacy and safety of inhaled epinephrine and β_2 -agonists in the treatment of TTN. (23)(24) Further studies need to be conducted on a larger scale; therefore, these treatments are not currently recommended as standard therapy for TTN.

PROGNOSIS

Studies have demonstrated an association between TTN and subsequent development of asthma, suggesting an underlying genetic predisposition. (25)(26) The risk of asthma is further increased if a neonate is delivered via cesarean section. (27)(28) More studies need to be conducted to make definitive conclusions about a possible causative link between TTN and asthma. In addition, there have been reports of “malignant TTN,” in which affected children develop persistent pulmonary hypertension of the newborn. (29) Some suggest that early use of distending pressure (eg, nasal CPAP) may mitigate the course of this severe form of TTN. Nevertheless, the overall prognosis is generally excellent in neonates with TTN. In the vast majority of infants, the symptoms will resolve within 48 hours. Rarely, tachypnea may last for a week or more.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the pathogenesis, pathophysiology, and risk factors of transient tachypnea of the newborn infant
- Know the clinical, laboratory, and imaging features of transient tachypnea of the newborn infant and formulate a differential diagnosis
- Know the prevention and management of transient tachypnea of the newborn infant

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1. A male infant born at 39 weeks' gestational age has a birthweight of 4,200 g. His mother underwent scheduled cesarean section due to fetal breech position. The infant is noted to have tachypnea at 1 hour of age. Which of the following statements concerning the occurrence of transient tachypnea of the newborn (TTN) is correct?
 - a. Female infants are at higher risk of TTN than male infants.
 - b. Cesarean delivery at earlier gestational age (<37 weeks) can prevent TTN for large-for-gestational age infants.
 - c. Maternal gestational diabetes does not increase the risk of TTN.
 - d. Both small- and large-for-gestational age infants are at increased risk of developing TTN.
 - e. TTN occurs in 10% to 15% of infants born at term.
2. A female infant born at 39 weeks' gestational age who was diagnosed with TTN is now 2 days old and still in the NICU for continued tachypnea. Which of the following characteristics is most consistent with a diagnosis of TTN?
 - a. The symptoms will typically last for at least 72 hours and resolve on the fourth or fifth day after delivery.
 - b. Radiography will usually show unilateral infiltrative pattern.
 - c. In contrast to pneumonia, radiographic findings will usually clear after 24 hours.
 - d. Although tachypnea will be prominent, there are usually no retractions or other symptoms such as grunting or flaring.
 - e. A fraction of inspired oxygen (FiO₂) of 0.4 is almost always required to reduce symptoms.
3. An infant is delivered by cesarean section at 38 weeks' gestational age for nonreassuring fetal heart rate. The Apgar scores are 8 and 9. She is noted to be small for gestational age and develops tachypnea and is noted to have pulse oximetry readings of 80% to 85% 2 hours after delivery. She is thought to have TTN and given oxygen by nasal cannula, with oxygen saturation improving to 90%. However, over the next hour, to maintain this oxygen saturation and due to increased work of breathing, treatment is escalated to provide continuous positive airway pressure with FiO₂ of 1.0. Which of the following evaluations and treatments for this patient is most appropriate?
 - a. The patient should be placed on a cooling blanket to achieve therapeutic hypothermia.
 - b. Because this is a self-limiting condition, vascular access should be avoided.
 - c. There is increased likelihood of another cause for this patient's symptoms other than TTN and further evaluation should be undertaken.
 - d. If there is no need for intubation, a chest radiograph should be avoided to reduce radiation exposure.
 - e. Inhaled nitric oxide should be added as treatment by nasal cannula to assess the possibility of pulmonary hypertension.
4. An infant born at 38 weeks' gestational age is noted to have tachypnea and subcostal retractions 1 hour after delivery. Chest radiograph and clinical picture are consistent with TTN. Which of the following statements is correct regarding medications for the treatment of TTN?
 - a. A Cochrane systematic review has determined that intravenous furosemide can reduce the duration of tachypnea in TTN by 50% compared with placebo.
 - b. TTN is an approved indication for inhaled nitric oxide in the setting of NICU admission and need for respiratory support.
 - c. Caffeine has been shown in several randomized clinical trials to reduce length of stay and prevent readmissions for TTN.

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- d. Routine administration of hydrochlorothiazide in the first hour after birth to term infants after elective cesarean delivery has been shown to reduce the incidence of TTN.
 - e. Medications such as diuretics and inhalation agents are not currently recommended as standard therapy in the management of TTN.
5. A male infant born at 39 weeks' gestational age had TTN in the first day, which has resolved. The infant is being discharged from the hospital and will follow up with the pediatrician in the clinic. Which of the following statements regarding the outlook for patients with TTN is correct?
- a. An association between TTN and subsequent development of asthma has been described, with potentially increased risk if the delivery is by cesarean section.
 - b. About 50% of patients with TTN develop a malignant form that progresses to persistent pulmonary hypertension in the first or second week after birth.
 - c. Most patients with TTN will have intermittent tachypnea up to 1 month of age, but they will not require hospitalization for that whole duration.
 - d. Daily inhaled albuterol for the first month after discharge from the hospital has been shown to decrease the risk of hospitalizations in the first year.
 - e. Patients diagnosed with TTN who received oxygen for more than 4 hours should receive monthly palivizumab if they are discharged from the hospital between October and April.

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