Physiology, Pathophysiology, and Pathogenesis

OUTLINE

Physiology of Eustachian Tube Within its System
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- Protective function
- Flask model of protective function
- Clearance function
- Surface tension factors

Pathophysiology of Eustachian Tube Within its System
- Impairment of pressure regulation
  - Anatomic obstruction
  - Failure of opening mechanism (functional obstruction)
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Role of Eustachian Tube in Pathogenesis of Otitis Media
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Pathogenesis of Otitis Media and Related Conditions
  - Acute otitis media
  - Otitis media with effusion
  - Persistent middle-ear effusion
  - Eustachian tube dysfunction
  - Chronic suppurative otitis media

Conclusions and Treatment Implications

The etiology and pathogenesis of otitis media are multifactorial and include genetic, infectious (usually viral and bacterial), immunologic, allergic, environmental, and social factors and eustachian tube dysfunction (Figure 1). A functionally and structurally immature eustachian tube and an immature immune system are probably the most important factors related to the increased incidence of otitis media in infants and young children. A genetic predisposition is also critical in many infants and children.\textsuperscript{1-3} When they are exposed to upper respiratory tract infections, otitis media is a common complication.

The pathogenesis of otitis media is likely to have the following sequence of events in most children: the patient has an antecedent event (usually an upper respiratory tract viral infection) resulting in congestion of the respiratory mucosa of the nose, nasopharynx, and eustachian tube. Congestion of the mucosa in the eustachian tube obstructs the narrowest portion of the tube, the isthmus. This obstruction causes negative middle-ear pressure followed by a middle-ear effusion.\textsuperscript{4,5} The mucosal secretions of the middle ear have no way out and accumulate there. If the effusion is relatively asymptomatic, that is, without the signs and symptoms of acute infection, it is termed \textit{otitis media with effusion}. However, during an upper respiratory tract infection, the viruses causing the primary infection and the potentially pathogenic bacteria that colonize the nasopharynx can be \textit{refluxed, aspirated, or insufflated} into the middle ear through the eustachian tube and cause an \textit{acute otitis media (AOM)}. AOM is characterized by the signs and symptoms of acute infection—fever and otalgia.\textsuperscript{6} For children with recurrent episodes of AOM or otitis media with effusion, anatomic or physiologic abnormality of the eustachian tube appears to be one of the most important factors.
In this chapter, we review our current understanding of the physiology (function) of the middle-ear system, including the nasal cavities, eustachian tube, middle ear, and mastoid gas cells. We also present a new, simplified, and evidence-based classification of the pathophysiology (dysfunction) of the eustachian tube. Finally, we describe our current understanding of the pathogenesis of AOM and otitis media with effusion. Other features of physiology, pathophysiology, and pathogenesis are discussed in the chapters on anatomy (see Chapter 2), epidemiology (see Chapter 4), microbiology (see Chapter 5), and immunology (see Chapter 6). Many of the studies cited in this chapter were conducted at the Children’s Hospital of Pittsburgh during the past 35 years and have been summarized elsewhere.

One of the editors of this book authored Eustachian Tube: Structure, Function, Role in Otitis Media, which is an up-to-date, extensive review of the state of our knowledge of the physiology and pathophysiology of the eustachian tube, and pathogenesis of otitis media related to the eustachian tube. This new text also includes other aspects of the tube related to otitis media. For a more comprehensive understanding of the contents of this chapter, the reader is referred to this new text. An added feature of this book is the enclosed CD-ROM, which not only has many of the figures in color, but some of the key figures related to the physiology and pathophysiology of the tubal system are animated.

**PHYSIOLOGY OF THE EUSTACHIAN TUBE WITHIN ITS SYSTEM**

As described in Chapter 2, the eustachian tube is not just a tube but an organ that is part of a system of organs. The nasal cavities, palate, and pharynx are at the proximal end of the eustachian tube, and the middle ear and mastoid gas cell system are at its distal end (Figure 2). Thus, the functions of the eustachian tube must be assessed within this system because the normal eustachian tube will function most effectively when the systems at either end are also normal.

There are three physiologic functions attributed to the eustachian tube: (1) pressure regulation (ventilation) of the middle ear that equilibrates gas pressure in the middle ear with atmospheric pressure (Figure 3); (2) protection of the middle ear from nasopharyngeal sound pressure and secretions (Figure 4); and (3) clearance (drainage) of secretions produced within the middle ear into the nasopharynx (Figure 5). In the following section, the pathophysiology of the eustachian tube within its system is presented. Table 1 shows a classification of the physiology and pathophysiology of the tube.
Pressure Regulation (Ventilation) Function

Of the three physiologic functions of the eustachian tube, the most important is regulation of pressure (ventilation) within the middle ear because hearing is optimal when middle-ear gas pressure is relatively the same as air pressure in the external auditory canal (that is, tympanic membrane and middle-ear compliance is optimal). Normally, the intermittent active opening of the eustachian tube, which happens when the tensor veli palatini muscle contracts during swallowing, maintains nearly ambient pressures in the middle ear (see Chapter 2, “Anatomy”). The gas in the nasopharynx that ventilates the middle ear is 79.2% nitrogen, 14.7% oxygen, 1% argon, and 5.1% carbon dioxide. This is the same composition as the expiratory phase of the respiratory cycle.

Under physiologic conditions, fluctuations in ambient pressure are bidirectional (ie, either to or from the middle ear), relatively small, and not readily appreciated. These fluctuations reflect the rise and fall in barometric pressures associated with changing weather conditions and elevation. However, changes in middle-ear pressure show mass directionality, can achieve appreciable magnitudes, and can result in pathologic changes. This is because the middle ear and...
The mastoid gas cell system is a relatively rigid (ie, non-collapsible) gas pocket surrounded by a mucous membrane in which gases are exchanged between the middle-ear space and the mucosa. Differential pressure exceeds 54 mm Hg between the middle-ear space at atmospheric pressure and the microcirculation in the mucous membrane. This represents a diffusion-driven gradient from the middle-ear cavity to the mucosa that can produce an underpressure (relative to ambient pressure) in the middle ear of more than 600 mm H$_2$O during equilibration.

Some investigators have postulated that gases can pass to and from the middle ear through the tympanic membrane. Doyle and coinvestigators reported experiments revealing that there is no oxygen and carbon dioxide transtympanic membrane exchange from the external ear canal into the middle ear. There is an exchange of nitrogen, although not at physiologic rates.

In an effort to describe normal eustachian tube function by use of the microflow technique inside a pressure chamber, Elner and coworkers studied 102 adults with intact tympanic membranes and no apparent history of otologic disorders. Patients were divided into four groups according to their abilities to equilibrate static relative positive and negative pressures of 100 mm H$_2$O in the middle ear. Patients in Group 1 were able to completely equilibrate pressure differences across the tympanic membrane. Those in Group 2 equilibrated positive pressure, but a small residual negative pressure remained in the middle ear. Subjects in Group 3 equilibrated only positive pressure with a small residual remaining, but no negative pressure.
Those in Group 4 were incapable of equilibrating any pressure. These data probably indicate decreased stiffness (increased compliance) of the eustachian tube in the subjects in Groups 2, 3, and 4, compared to those in Group 1. This study also showed that 95% of normal adults could equilibrate an applied positive pressure, and that 93% could equilibrate applied negative pressure to some extent by active swallowing. However, 28% of the subjects could not completely equilibrate either applied positive or negative pressure or both.

Ghadiali and colleagues are using computational modeling to better understand the active function of the eustachian tube. Using these new investigative tools has shown that the engineering-based measure of function (eg, compliance) is more accurate than current summary parameters.

Children have less efficient eustachian tube function than adults do. By use of a pressure chamber, children and adults who were considered otologically normal were evaluated in Sweden, revealing that 35.8% of the children could not equilibrate applied negative intratympanic pressure by swallowing. Only 5% of the adults were unable to perform this function. Children between 3 and 6 years of age had worse function than those aged 7 to 12 years. In this study and a subsequent one reported by the same research team, children who had middle-ear negative pressure as evaluated by tympanometry had poor function.

These studies show that even in apparently otologically healthy children, eustachian tube function is not as good as in adults. However, eustachian tube function does improve with advancing age, consistent with the decreasing incidence of otitis media from infancy to adolescence. Because there are several differences in the anatomy of the child’s and adult’s eustachian tube, we also find functional differences in the ability to open the eustachian tube during swallowing activity to equilibrate pressure between the middle ear and the nasopharynx (see Chapter 2, “Anatomy”).

Another explanation for finding high negative middle-ear pressure in children is the possibility that some individuals who are habitual “sniffers” actually create underpressure within the middle ear by this act. However, this mechanism is uncommon in children.

Otoscopy and tympanometry have shown that many children with no apparent middle-ear disease have high negative middle-ear pressure. An inefficient active opening of the tube in children probably explains this frequent finding. Brooks studied the parameters of middle-ear pressure using tympanometry and determined that the resting middle-ear pressure in a large group of apparently normal children was between 0 and −175 mm H₂O. However, pressures outside this range have been reported as normal for large populations of apparently asymptomatic children. High negative middle-ear pressure does not necessarily indicate disease; it may indicate only physiologic obstruction of the eustachian tube. Pressure regulation occurs, but only after the nasopharynx-middle-ear pressure gradient reaches an opening pressure. It has
been suggested that these children should be considered at risk for middle-ear problems until more is learned about the normal and abnormal physiology of the eustachian tube. In normal adults, Alberti and Kristensen obtained resting middle-ear pressures of between 50 and $-50 \text{ mm H}_2\text{O}$. Again, a pressure outside this range does not necessarily mean the patient has ear disease.

Because infants have an inefficient active opening mechanism, they most likely compensate in some way to regulate pressure within the middle ear. One possible compensatory mechanism is crying, and high positive pressure is apparent when some infants with no middle-ear effusion cry during otoscopy and tympanometry. This mechanism could also explain why infants cry when they are descending in an airplane; they are most likely insufflating air into their middle ears (Figure 6).

The physiologic role of the mastoid air cell system in relation to the middle ear is not fully understood. However, the current thinking is that it acts as a surge tank of gas (air) available to the relatively smaller middle-ear cavity, that the mucosa lining the mastoid gas cells is the primary area for the transfer of gases between the middle ear and mastoid gas cells and the microcirculation, or that both functions coexist. During intervals of eustachian tube dysfunction, compliance of the tympanic membrane and ossicular chain (which affects hearing) would not be decreased owing to reduced middle-ear gas pressure because there is a reservoir of gas in the mastoid air cells. If this thinking is correct, a small mastoid air cell system could be detrimental to the middle ear if the eustachian tube is dysfunctional. Likewise, a small mastoid cell system would allow a less efficient gas exchange between the middle-ear cleft and the microcirculation of the mucosa. But, Doyle challenged the gas reserve function of the mastoid gas cells.

Posture appears to have an effect on eustachian tube function. The mean volume of air passing through the eustachian tube was found to be reduced by one-third when the body was elevated 20° to the horizontal and by two-thirds in the horizontal position. This reduced function with change in body position was found to be the result of venous engorgement of the eustachian tube.

A seasonal variation in eustachian tube function occurs in children. Children who had tympanostomy tubes inserted for recurrent or chronic otitis media with effusion and were evaluated by serial inflation-deflation studies had better eustachian tube function in the summer and fall than in the winter and spring.

**Protective Function**

The eustachian tube system's protective function helps maintain a healthy middle ear. The eustachian tube system helps protect the middle ear and mastoid gas cell system in 2 ways: (1) through its functional anatomy, and (2) through the immunologic and mucociliary defense of its mucous membrane lining. Protection of the middle ear from abnormal nasopharyngeal sound pressures and secretions depends on the normal structure and function of the eustachian
tube and the ability of the middle ear and mastoid gas cell system to maintain a “gas cushion.” In addition, the proximal end of the system (nasal cavities, palate, and pharynx) should have normal anatomy and physiologic gas pressures. The middle-ear–mastoid is also protected by the respiratory epithelium of the eustachian tube lumen through its local immunologic defense and its mucociliary defense (ie, clearance). An immunoreactive pulmonary surfactant protein that is thought to facilitate the clearance of microbial pathogens from the alveolus of the lung has been isolated from the middle ears of animals and humans and is hypothesized to have the same function in the ear.35–37

Studies using radiographic techniques have determined the protective function of the tube.38–41 In these studies, radiopaque material was instilled into the nose and nasopharynx of children who had otitis media, then a comparison was made with those who were otologically healthy. In the physiologic state, radiopaque material entered the nasopharyngeal end of the eustachian tube during swallowing activity but did not enter the middle ear. By contrast, the dye did reflux into the middle ear in some patients who had middle-ear disease, especially during closed-nose swallowing.

These radiographic studies in children revealed the following sequence of events. At rest, the normal eustachian tube is collapsed and the tubal lumen is closed. This prevents liquid—and abnormal nasopharyngeal sound pressures—from entering the nasopharyngeal end of the tube. During swallowing, when the proximal end (ie, the cartilaginous portion) opens, liquid can enter this part of the tube, but it does not go into the middle ear because of the tube’s narrow midportion (the isthmus).

**Flask Model of Protective Function**

To better understand this anatomic concept, think of the entire eustachian-tube–middle-ear system as a flask with a long, narrow neck. The mouth of the flask represents the nasopharyngeal end; the narrow neck, the isthmus; and the bulbous portion, the middle ear and mastoid gas cell system (Figure 7).39,42 Fluid flow through the neck depends on the pressure at either end, the radius and length of the neck, and the viscosity of the liquid. When a small amount of liquid is instilled into the mouth of the flask, the liquid’s flow stops somewhere in the narrow neck owing to capillarity within the neck and the relative positive air pressure that develops in the chamber of the flask. This basic geometric design is considered critical for the protective function of the eustachian-tube–middle-ear system.

**Clearance Function**

Clearance (drainage) of secretions from the middle ear into the nasopharynx is provided by two physiologic methods: mucociliary clearance and muscular clearance. The mucociliary system of the eustachian tube and some areas of the middle-ear mucous membrane clear secretions from the middle ear; the “pumping action” of the eustachian tube during closing provides the other method.

*Mucociliary clearance* has been studied by instillation of radiopaque material into the middle ear of children with non-intact tympanic membranes, when the material entered the middle ear (intact tympanic membrane) from

![Figure 7. Flask model of eustachian tube–middle-ear system: the eustachian tube, middle ear, and mastoid gas cell system is compared with a flask in which the mouth of the flask represents the nasopharyngeal end of the eustachian tube, the neck is the cartilaginous portion of the tube, and the bulbous portion is the middle ear and mastoid gas cells system.](image-url)
the nasopharynx, and after insertion of foreign material into the middle ear of animal models. Such material flows toward the middle-ear portion of the eustachian tube and out of the tube. This movement is related to ciliary activity in the eustachian tube and parts of the middle ear. Ciliated cells in the middle ear are increasingly more active as they become more distal to the opening of the tube.

The pumping action of the eustachian tube to drain middle-ear fluid was first reported by Honjo and colleagues. In experiments in both animal models and humans, the eustachian tube was shown during closing to pump radiographic contrast material that had been instilled into the middle ear out of the middle ear and into the nasopharynx. The passive closing process of the eustachian tube begins at the middle-ear end of the tube and progresses toward the nasopharyngeal end, thus pumping out secretions.

**Surface Tension Factors**

Other factors may be involved in maintaining normal eustachian tube function. One of these factors may be the surface tension within the lumen of the eustachian tube. Birkin and Brookler isolated surface-tension–lowering substances from the washings of eustachian tubes of dogs. They postulated that these substances could enhance eustachian tube functions, like surfactant in the lung. Rapport and colleagues described a similar substance and demonstrated the effect that washing out the eustachian tube had on the opening pressure in the experimental animal. Others have also demonstrated a surfactant-like phospholipid in the middle ear and eustachian tube of animals and humans. In a study in gerbils, Fornadley and Burns produced middle-ear effusions by injecting killed Streptococcus pneumoniae into the middle ear through the tympanic membrane to increase the opening pressure of the eustachian tube. When the investigators introduced exogenous surfactant, the opening pressure dropped.

**PATHOPHYSIOLOGY OF EUSTACHIAN TUBE WITHIN ITS SYSTEM**

Descriptors that can be used to characterize the dysfunctional eustachian tube are: too closed, will not open, too floppy, too open, too short, and too stiff. At either end of the eustachian tube, the system can be: too closed or too open, or there is too much or too little pressure at either end (Figure 8). More precisely, the pathophysiologic processes can be classified into (1) impairment of pressure regulation, (2) loss of protective function, and (3) impairment of clearance. Figure 9 depicts some of the types of eustachian tube dysfunction that are described in more detail in the following.

**Impairment of Pressure Regulation**

Impairment of pressure regulation within the middle ear (and mastoid) can be due to either (1) anatomic obstruction of the eustachian tube (the tube is too closed), or (2) failure of the opening mechanism of the eustachian tube (the tube will not open).

**Anatomic Obstruction**

Anatomic (ie, mechanical) obstruction of the eustachian tube can occur in the cartilaginous or osseous portion of the tube or at either end of the system, regardless of the status of the structure and function of the eustachian tube itself. When an anatomic obstruction involves the tube, it can...
be (1) intraluminal, (2) periluminal, or (3) peritubal (the eustachian tube is too closed). Obstruction of the lumen or within the periluminal tissues (ie, intrinsic obstruction) can be due to inflammation secondary to infection or allergy.\textsuperscript{55–58} Congenital or acquired stenosis of the eustachian tube has also been diagnosed in adults but is a rare finding in children.\textsuperscript{59} Peritubal obstruction of the cartilaginous portion of the tube (ie, extrinsic obstruction) could be the result of compression by a tumor or an adenoid mass (Figure 10).\textsuperscript{40,60–62}

Anatomic obstruction may be present at the middle-ear end of the tube (the system at the distal end of the eustachian tube is “too closed”). This type of obstruction is usually due to acute or chronic inflammation of the mucosal lining and may also be associated with polyps or a cholesteatoma due to middle-ear disease. Likewise, at the proximal end of the system—in the nasopharynx—the tubal orifice can be anatomically obstructed even when the eustachian tube itself is patent and functions normally. This is due to a variety of etiologic factors,
including adenoids, a foreign body (eg, packing), or a tumor (the nasopharynx is too closed).

**Failure of Opening Mechanism (Functional Obstruction)**

In one of the most common types of eustachian tube dysfunction, the lumen of the cartilaginous portion of the eustachian tube fails to open during swallowing activity (the eustachian tube *will not open*). This may be due to (1) persistent collapse of the eustachian tube because of increased tubal compliance (ie, lack of stiffness, or the tube is *too floppy*), (2) an inefficient active opening mechanism, or (3) both defects. This has also been termed *functional obstruction* of the eustachian tube—the tube is not anatomically (ie, mechanically) obstructed, but it is functionally obstructed and is considered to be one of the immature features of the infant tube (Figure 11). This deficiency was first described in infants with unrepaired palatal clefts who had had chronic otitis media with effusion. Failure of the opening mechanism of the eustachian tube is common in infants and younger children without cleft palate or history of middle-ear disease, but it is more common in children with middle-ear disease.\(^{22,39,63-66}\)

The eustachian tube’s failure to open can be due to persistent collapse of the tubal cartilage because there is less cartilage in infants than in older children and adults. Cartilage cell density also decreases with advancing age and can affect the stiffness of the tubal cartilage in the infant and young child.\(^{67,68}\) If the tubal cartilage lacks...
stiffness (the tube is too floppy), the lumen may not open when the tensor veli palatini muscle contracts. Also, the density of elastin in the cartilage is lower in the infant, and the Ostmann fat pad is lesser in volume in the infant than in the adult (see Chapter 2, “Anatomy”).

The failure of the eustachian tube’s opening mechanism may also be due to an inefficient tensor veli palatini muscle, which is related to the effect of age on the craniofacial base. The angle of a child’s tube is different from that of the adult’s. In the adult, the tube is approximately 45° relative to the horizontal plane. In infants, this inclination is only 10°. Some think this difference in the angle is related to possible clearance problems in children, but this hypothesis has not been confirmed. What is more likely is that this difference in angulation affects the function of the active opening mechanism (ie, tensor veli palatini muscle contraction). Swarts and Rood found that the angular relationship between the tensor veli palatini muscle and the cartilage varies in the infant but is relatively stable in the adult (see Chapter 2, “Anatomy”).

One way in which the eustachian tube becomes functionally obstructed is by development of sudden high negative pressure at either end of the eustachian tube system. This is graphically demonstrated by the flask model (see Figure 7). One of the major differences between a flask with a rigid neck and a biologic tube, such as the eustachian tube, is that the isthmus (neck) of the human tube is compliant. The effect of applied negative pressure in a flask with a compliant neck is shown in Figure 12. Flow of fluid—shown as a liquid for graphic purposes—through the neck does not occur until negative pressure is slowly applied to the bottom of the flask. However, if the negative pressure is applied suddenly, temporary locking of the compliant neck prevents the liquid from flowing. This is the locking phenomenon of the eustachian tube. Therefore, the speed with which the negative pressure is applied and the compliance in such a system are critical factors in whether the tube becomes functionally obstructed. Clinically, gas may be aspirated into the middle ear because negative middle-ear pressure develops slowly as gas is absorbed by the middle-ear mucous membrane. If negative middle-ear pressure is applied suddenly (during rapid alterations in atmospheric pressure, such as when an airplane descends; while diving in water, especially scuba diving; or during an attempt to test the ventilatory function of the eustachian tube), the tube can lock, preventing the flow of air (see Chapter 7, “Diagnosis”).

**Loss of Protective Function**

The eustachian tube system can lose its protective function because (1) the lumen of the tube is abnormally patent (the tube is too open), (2) the tube is relatively short (the tube is too short), (3) abnormal gas pressures develop at either end of the tubal system, or (4) there is a non-intact middle ear, for example, perforation (or tympanostomy tube) of the tympanic membrane resulting in a loss of the middle-ear gas cushion.
(the tube is too open at the middle-ear end of the eustachian tube system).

**Abnormal Patency**

The eustachian tube lumen may be abnormally open, and in the extreme, it is open even at rest. This is an abnormally patent, or *patulous*, eustachian tube; it is too open. Lesser degrees of abnormal patency result in a *semipatulous* tube that is closed at rest, but with a lumen that has low resistance to the flow of gas or liquids compared with the normal tube.\(^{73,74}\) Increased patency of the tube may be due to abnormal tube geometry or to a decrease in the peritubal pressure that can occur after weight loss or as a result of periluminal factors.\(^ {75}\)

The flask model is illustrative when the eustachian tube lumen is too open. Compared with a flask with a narrow neck, reflux of liquid into the body of the flask occurs if the neck is excessively wide. Increasing the radius of the flask neck increases fluid flow. This is analogous to an abnormally patent human eustachian tube in which there is free flow of air and nasopharyngeal secretions from the nasopharynx into the middle ear. The result is *reflux otitis media* (Figure 13).

The eustachian tube may be abnormally patent, even when the caliber of the lumen appears normal when collapsed at rest. It can also be functionally hyperpatent, making it less protective of the middle ear. Because the cartilaginous portion of the eustachian tube is *distensible* (compliant), fluid (gas or liquid) can be forced into the middle ear by abnormally high positive nasopharyngeal pressure, which can occur during nose blowing, with Valsalva’s maneuver, or during closed-nose swallowing (the Toynbee phenomenon; see “Abnormal Gas Pressures”). The ability to insufflate the middle ear during these activities depends on the amount of positive pressure developed in the nasopharynx and the degree of compliance (lack of stiffness) of the tube. Because the eustachian tube has been found to be highly compliant (the tube is too floppy) in infants and young children, this increase in distensibility of the tube may result in abnormal patency, especially when there is high nasopharyngeal pressure, possibly during crying (see Figure 6). A highly distensible tube can easily permit nasopharyngeal secretions to be insufflated into the middle ear as radiographic studies in infants with middle-ear disease have demonstrated.\(^ {38,39}\)

We can use the flask model to illustrate this phenomenon if the narrow portion of the flask’s neck is compliant, making it more consistent with the human eustachian tube. Applying positive pressure at the mouth of a flask with a compliant neck will distend the neck and enhance fluid flow—gas and liquid—into the vessel. Thus, less positive pressure is needed to insufflate liquid into the vessel. In humans, insufflation of nasopharyngeal secretions into the middle ear occurs more readily if the eustachian tube is abnormally distensible (has increased compliance).

In teenagers and adults, the patulous tube has been found to be *too stiff* compared with normal tubal compliance.\(^ {76}\) A patulous eustachian tube usually permits gas to flow readily from the nasopharynx into the middle ear, effectively regulating middle-ear pressure. However, unwanted secretions from the nasopharynx can more readily gain access (ie, reflux) into the middle ear when the tube is abnormally patent. Certain special populations have been found to have patulous or semipatulous eustachian tubes, including Native Americans and patients who have Down syndrome and middle-ear disease.\(^ {77,78}\) Chronic suppurative otitis media is a common disease in certain special populations...

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*Figure 13.* Loss of the protective function of the eustachian tube can occur if the tubal lumen is too open. Nasopharyngeal secretions can reflux into the middle ear. Reproduced with permission from Bluestone CD. Conquering otitis media. Hamilton (ON): BC Decker; 1999.
around the world, including the Australian Aborigines, North American Inuit, and Native Americans. Failure of the eustachian tube’s passive closing mechanism (the tube is too open) has been postulated to be related to “sniff-induced” middle-ear disease (see “Other Causes of Eustachian Tube Dysfunction”).

**Short Tube**

One of the most important structural differences of the eustachian tube between infants and young children and older children and adults is the length of the tube. The tube is shorter in children younger than 7 years (the tube is too short) (see Chapter 2, “Anatomy”). The tube is very short in the first year of life in humans, since we are “born too soon.” Certain special populations may also have shorter tubes. Infants and young children with cleft palate have eustachian tubes that are statistically shorter than those of age-matched control subjects before 6 years of age (Table 2). The tube is also shorter in children with Down syndrome. The shorter the tube, the more likely secretions can reflux into the middle ear. (An analogy can be made to the length of the urethra: females of all ages have more urinary tract infections than males do because the urethra is shorter in the female.) This may be one explanation for the frequent occurrence of troublesome otorrhea in infants and young children, especially in those with a cleft palate or Down syndrome or when the tympanic membrane is not intact (there is a perforation or a tympanostomy tube is in place). Cranial anatomy may also play a role in the length of the eustachian tube. Todd postulated from studies in cadavers that the longer the cranial base, the longer the eustachian tube, resulting in less middle-ear disease.

The effect of a short eustachian tube is shown in cartoon form in Figure 14. The flask model shows graphically the effect of a flask with a short neck (Figure 15). A flask with a short neck would not be as protective as a flask with a long neck. Accordingly, the tube that is too short is more likely to reflux secretions from the nasopharynx into the middle ear than is a tube that is longer. Because the eustachian tube of the infant is shorter than that of the adult, reflux is more likely in the baby. A tube that is too short can be included in the classification of being too open, because secretions from the nasopharynx can more easily enter the middle ear than when a tube is of normal length.

**Abnormal Gas Pressures**

A loss of the tube’s protective function can also occur when unphysiologic pressures develop at either end of the eustachian tube system. At the distal end of the system, high negative middle-ear pressure, secondary to obstruction of the eustachian tube that is anatomic (common during a viral upper respiratory tract infection) or due to a failure of the active opening, or both, may develop and result in aspiration of nasopharyngeal secretions into the middle ear. A chinchilla model of this process has been established.

A loss of the tube’s protective function can also occur when high positive nasopharyngeal pressures develop at the proximal end of the eustachian tube. This can occur due to certain special populations, such as infants and young children with cleft palate, or when the tympanic membrane is not intact (there is a perforation or a tympanostomy tube is in place). Cranial anatomy may also play a role in the length of the eustachian tube. Todd postulated from studies in cadavers that the longer the cranial base, the longer the eustachian tube, resulting in less middle-ear disease.

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### Table 2. ABNORMALITIES OF EUSTACHIAN TUBE ANATOMY IN EXTENDED TEMPORAL BONE SPECIMENS FROM INFANTS AND YOUNG CHILDREN WITH CLEFT PALATE

<table>
<thead>
<tr>
<th>Abnormality Compared with Specimens without Cleft Palate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of tube shorter</td>
<td>Sadler-Kimes et al²⁷; Siegel et al²⁶⁷</td>
</tr>
<tr>
<td>Angle between cartilage and TVP larger</td>
<td>Sadler-Kimes et al²⁷</td>
</tr>
<tr>
<td>Cartilage cell density greater</td>
<td>Shibahara and Sando¹⁰²</td>
</tr>
<tr>
<td>Ratio of lateral and medial laminae area of cartilage smaller</td>
<td>Matsune et al¹⁰⁰; Takasaki et al¹⁶⁸</td>
</tr>
<tr>
<td>Curvature of lumen less</td>
<td>Matsune et al¹⁰⁰</td>
</tr>
<tr>
<td>Elastin at hinge portion of cartilage less</td>
<td>Matsune et al⁷⁰</td>
</tr>
<tr>
<td>Insertion ratio of TVP to cartilage less</td>
<td>Matsune et al¹⁰¹</td>
</tr>
</tbody>
</table>

TVP = tensor veli palatini.
eustachian tube system. This abnormally high pressure, from blowing the nose, during crying in the infant, or when nasal or nasopharyngeal obstruction is present, can cause nasopharyngeal secretions to be insufflated into the middle ear. An animal model has been developed in which high positive nasopharyngeal pressure produced by the Politzer technique can insufflate nasopharyngeal liquids into the middle ear.

Swallowing when the nasal cavities, nasopharynx, or both are obstructed (because of inflammation or enlarged adenoids) results in an initial positive nasopharyngeal gas pressure followed by a negative pressure phase. These pressures are produced in the mesopharynx and hypopharynx during swallowing activity and are reflected in the nasopharynx during closed-nose swallowing. When the tube is pliant, positive nasopharyngeal pressure might insufflate infected secretions into the middle ear, especially when the middle ear has high negative pressure. With negative nasopharyngeal pressure, a pliant tube could be prevented from opening and could be further obstructed functionally. The effect of closed-nose swallowing has been termed the Toynbee phenomenon (Figure 16). Other investigators have reported this phenomenon in the human, and a ferret animal model of complete nasal obstruction resulted in persistent high positive middle-ear pressure, most likely secondary to insufflation of air into the middle ear during swallowing activity. Rapid alteration in ambient pressures, which can occur during swimming, diving (Figure 17), airplane flying (Figures 18 and 19), and hypobaric pressure treatments, can also result in aspiration or insufflation of nasopharyngeal secretions.

Figure 20 uses the flask model to show the effect of these unphysiologic pressures at either end of the eustachian tube system. When negative
pressure (too little pressure) is applied to the bottom of the flask, liquid is aspirated into the vessel. In the clinical situation, high negative middle-ear air pressure can cause nasopharyngeal secretions to be aspirated into the middle ear. When positive pressure (too much pressure) is applied to the mouth of the flask, liquid is insufflated into the vessel. Nose blowing, crying, closed-nose swallowing, ascent in an airplane, or scuba diving could create high positive nasopharyngeal pressure related to middle-ear pressure and result in a similar condition in the human system.

**Nonintact Middle Ear and Mastoid**

Nasopharyngeal secretions cannot enter the middle ear when the structure of the eustachian tube is normal and because of the cushion of gas within an intact middle ear and mastoid gas cell system. When there is a perforation of the tympanic membrane (or a tympanostomy tube is in place) or, in the extreme condition, when a radical mastoidectomy is present (the eardrum is absent, and the middle ear, mastoid, and ear canal communicate, forming a single cavity), the gas pocket (cushion) is lost allowing secretions from the nasopharynx to reflux into the middle ear (Figure 21). Thus, even though the anatomy and function of the tube itself are normal, the system at its distal end is defective.

---

**Figure 16.** When the nose or nasopharynx is obstructed, unphysiologic pressures can develop in the nasopharynx and adversely affect the eustachian tube and middle ear, which is termed the Toynbee phenomenon. Reproduced with permission from Bluestone CD. Conquering otitis media. Hamilton (ON): BC Decker; 1999.

**Figure 17.** Diving into a swimming pool can cause acute otitis media when an upper respiratory tract infection is present. Reproduced with permission from Bluestone CD. Conquering otitis media. Hamilton (ON): BC Decker; 1999.
(the tube is too open). This concept is important when the surgeon is considering repairing a perforation of the tympanic membrane or removing a retained tympanostomy tube (see Chapter 9, “Complications and Sequelae: Intratemporal”).

Using the flask model, Figure 20 illustrates how liquid can reflux into the vessel if there is a hole in the bulbous portion of the flask. This prevents the creation of the slight positive pressure in the bottom of the flask that deters reflux, and thus the middle ear and mastoid physiologic gas cushion is lost. This hole is analogous to a perforation of the tympanic membrane or the presence of a tympanostomy tube, both of which can allow reflux of naso-

---

Figure 18. Explanation of how the normal eustachian tube and middle ear respond during airplane flying. Reproduced with permission from Bluestone CD. Conquering otitis media. Hamilton (ON): BC Decker; 1999.

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Figure 19. Explanation of how abnormal eustachian tube and middle ear respond during airplane flying, especially when an upper respiratory tract infection (or nasal allergy) is present. Reproduced with permission from Bluestone CD. Conquering otitis media. Hamilton (ON): BC Decker; 1999.
pharyngeal secretions because the middle ear and mastoid air cushion is lost. Similarly, after a radical mastoidectomy, a patent eustachian tube could cause troublesome otorrhea. 64

**Impairment of Clearance Function**

Clearance (drainage) of secretions from the middle ear and eustachian tube can be adversely affected in several ways. Ohashi and colleagues conducted studies in guinea pigs and demonstrated that bacteria, their toxins, and irradiation can impair ciliary function. 86 Park and associates demonstrated that influenza A virus alters the ciliary activity and dye transport function in the eustachian tube of the chinchilla. 87 Rhee and associates reported that platelet-activating factor, an inflammatory mediator induced by infection, impairs ciliary clearance in the eustachian tube. 88 Allergic response probably does not impair ciliary motility but may alter the mucus blanket in the eustachian tube. 89 Most investigators consider an impaired clearance function to be related to failure to resolve middle-ear effusions and not the primary cause of the disease. 90 However, patients with ciliary dysmotility in their upper respiratory tract mucous membrane have been observed to have chronic middle-ear effusions. 91 Also, the tube’s pumping action is most likely ineffective when its opening mechanism is inadequate, and this function has been demonstrated to be impaired when negative pressure is in the middle ear. 92, 93

If the physiologic clearance system—mucociliary and pumping action—is impaired, retained liquid is not likely to come out owing to the negative pressure that develops within the

---

**Figure 20.** The flask model of the middle-ear system for fluid flow. A, Model of normal function. B, Effect of perforation. C, Effect of negative pressure on the bottom of the flask. D, Effect of positive pressure on the mouth of the flask.
middle ear and mastoid gas cell system. This is because the liquid moves even by gravity toward the eustachian tube and into the nasopharynx. This can be graphically shown with the flask model. Figure 3-21 shows certain aspects of fluid flow from the middle ear and eustachian tube into the nasopharynx by inverting the flask of the model. In this case, the liquid trapped in the bulbous portion of the flask does not flow out of the vessel because of the relative negative pressure that develops inside the chamber. However, if a hole is made in the vessel, the liquid drains out of the flask because the suction is broken. Clinically, these conditions occur in cases of middle-ear effusion (ie, pressure is relieved when the tympanic membrane ruptures spontaneously or by myringotomy). Inflating air into the flask could also relieve the pressure, possibly explaining the frequent success of Politzer’s method or Valsalva’s maneuver in clearing a middle-ear effusion (see Chapter 8, “Management”).

Even though there are several known mechanisms of impairment of the clearance function, in general, this dysfunction can be included in the simplified classification as being related to the tube being too closed.

**Dysfunction Related to Cleft Palate**

Otitis media is universally present in infants with an unrepaired cleft palate. Palate repair appears to improve middle-ear status, but middle-ear disease nonetheless often continues or recurs even afterward. Studies suggest failure of the tube’s opening mechanism in infants with an unrepaired cleft palate as the primary cause of dysfunction. Histopathologic temporal bone studies have confirmed that the eustachian tube of cleft palate patients is not anatomically obstructed, giving credence to a failure of the opening mechanism as the underlying defect (that is, functional as opposed to anatomic obstruction). Other anatomic findings, such as the abnormal cartilage and lumen, insertion ratio of the tensor veli palatini muscle into the cartilage, deficient attachment of the tensor veli palatini muscle into the lateral lamina of the cartilage, and deficient elastin at the hinge portion of the cartilage, most likely explain the functional obstruction identified by radiographic and manometric eustachian tube function tests (see Table 2). Animals whose palates had been surgically split also developed middle-ear effusion.

From these studies in humans and animals, it appears that the high incidence of otitis media in children with cleft palate is related to a failure of the tube’s opening mechanism and that the tube is functionally obstructed (the tube will not open). It may also be related to the deficient length of the eustachian tube, because a short tube may permit nasopharyngeal secretions to enter the middle ear, causing troublesome otorrhea. If infants with an intact palate are able to inflate their middle ears during crying as a physiologic compensatory mechanism for their ineffective active tubal opening, then infants with an unrepaired cleft palate have an additional

![Figure 21. The flask model of the middle-ear system for fluid flow from an inverted flask.](image-url)
handicap (the proximal end of the eustachian tube system is too open).

Children with cleft palate have middle-ear disease characterized by either persistent or recurrent high negative middle-ear pressure, effusion, or both. Cholesteatoma is a frequent sequela. However, this is not the case in Native Americans, in whom the eustachian tube has been shown to be hyperpatent (ie, to have low tubal resistance).

Patients with a submucous cleft of the palate appear to have the same risk for development of middle-ear disease as do those with an overt cleft. In addition, a bifid uvula has been associated with a high incidence of otitis media. Both conditions are probably associated with the same pathogenic mechanism for otitis media that is found in patients with overt cleft palates (ie, functional obstruction of the eustachian tube).

**Dysfunction Related to Allergy**

Allergy is thought to be one of the etiologic factors in otitis media because otitis media occurs frequently in allergic individuals. The mechanism by which allergy might cause otitis media is hypothetical and controversial. Figure 22 illustrates allergy’s role in the etiology and pathogenesis of otitis media by one or more of the following mechanisms: (1) functioning of the middle-ear mucosa as a “shock (target) organ”, (2) inflammatory swelling of the eustachian tube mucosa, (3) inflammatory obstruction of the nose, or (4) aspiration of bacteria-laden allergic nasopharyngeal secretions into the middle-ear cavity. Doyle proposed another mechanism. This hypothesis is based on the possible increase in circulating inflammatory mediators from local allergic reactions in the mucosa of the nose or stomach, which in turn could alter the middle-ear mucosal permeability and result in altered gas exchange. Ohashi and colleagues found that allergic responses did not impair mucociliary activity but could adversely affect the structure of the eustachian tube’s mucus blanket.

Bernstein and coworkers provided evidence that the eustachian tube may be adversely affected by allergy, as opposed to the middle ear as a target organ. They investigated the role of immunoglobulin E (IgE)–mediated hypersensitivity in 100 children with recurrent otitis media. The children were divided into nonallergic and allergic on the basis of their history and physical examination findings, prick-testing results for selected antigens, total IgE levels, and specific IgE radioallergosorbent test responses. After aspiration of their middle ears and testing for IgE, the investigators concluded that 35% of the 100 children may have had IgE-mediated allergy as a cause of their effusion, and in 8% of the children, the middle ear was a possible target organ. In the other 27%, they postulated that the eustachian tube might have been the target organ (Table 3).

Studies at the Children’s Hospital of Pittsburgh involving adult volunteers demonstrated a relationship between intranasal antigen challenge, allergic rhinitis, and eustachian tube obstruction. Table 4 summarizes studies that demonstrated a relationship between intranasal challenge with allergens, viruses, and mediators in volunteers who did and did not have allergic rhinitis and the effect on their nasal...
and eustachian tube function. None of these studies produced otitis media in the volunteers, and none had preexisting eustachian tube dysfunction.

Passali and colleagues conducted studies on the possible relationship between nasal allergy and otitis media with effusion in 112 children and concluded that there is a correlation between middle-ear disease and perennial allergic rhinitis, but not when the allergy was seasonal.118 It is possible that repeated challenge with antigen during a prolonged period would cause individuals who are hypersensitive to the specific antigen and who also have poor eustachian tube function to develop middle-ear effusion. It seems reasonable that children with signs and symptoms of upper respiratory allergy may have otitis media as a result of the allergic condition.

**Other Causes of Eustachian Tube Dysfunction**

Eustachian tube dysfunction has also been associated with deviation of the nasal septum (the tube is too closed at the proximal end of the system); trauma induced by nasogastric and nasal endotracheal tubes (the tube is too closed); trauma to the palate, pterygoid bone, or tensor veli palatini muscle (the tube will not open); injury to the mandibular branch of the trigeminal nerve (the tube will not open); and trauma associated with surgical procedures, such as palatal or maxillary resection for tumor (the tube will not open or is too open at the proximal end of the system).119–124 Benign or malignant neoplastic disease that invades the palate, pterygoid bone, or tensor veli palatini muscle can also cause the opening mechanism of the tube to fail (the tube will not open), causing otitis media.121,125–127

Because a cleft of the palate can functionally obstruct the eustachian tube, any child with a craniofacial malformation that has an associated cleft of the palate will have recurrent and persistent otitis media. A common example is Pierre Robin syndrome. However, children with craniofacial anomalies that do not include an overt cleft of the palate also have an increased incidence of middle-ear disease. Eustachian tube dysfunction has been described in children with Down syndrome and otitis media.78 Even though there have been no reports of formal eustachian tube function studies in individuals with other disorders, such as Turner syndrome, Apert’s syndrome, or Crouzon’s disease, eustachian tube dysfunction is the most likely cause of ear disease in these patients.128 A defect related to the abnormal craniofacial complex, most often at the base of the skull, also presumably influences

---

**Table 3. SUMMARY OF 100 ALLERGIC AND NONALLERGIC BUFFALO CHILDREN WITH RECURRENT OTITIS MEDIA**

<table>
<thead>
<tr>
<th>Possible Target Organ</th>
<th>Middle Ear</th>
<th>Eustachian Tube</th>
<th>Probably Not Target Organs</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic</td>
<td>8</td>
<td>27</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>Nonallergic</td>
<td>0</td>
<td>0</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Bernstein JM, et al.110

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**Table 4. STUDIES AT CHILDREN’S HOSPITAL OF PITTSBURGH THAT EVALUATED THE EFFECT OF NASAL CHALLENGE ON NASAL AND EUSTACHIAN TUBE FUNCTION**

<table>
<thead>
<tr>
<th>Nasal Provocation</th>
<th>Normal</th>
<th>Allergic</th>
<th>Eustachian Tube Function</th>
<th>Normal</th>
<th>Allergic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergens (pollens, mite)</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Virus</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Mediators</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histamine</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Prostaglandin</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Methacholine</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

+ = adverse effect; 0 = little effect.
the relationship between the eustachian tube and the tensor veli palatini muscle.\textsuperscript{129}

Patients with dentofacial abnormalities often have otitis media or develop middle-ear disease as a result of these abnormalities.\textsuperscript{129a} Correction of the defect to relieve the eustachian tube dysfunction may be indicated, but this remains to be definitively proven.

Some individuals, but rarely children, are habitual sniffers and actually create underpressure within the middle ear by this act.\textsuperscript{24} In a study from Japan, Sakakihara and coworkers evaluated 17 subjects (mean age, 16 years) who had “sniff-induced otitis media” and found that their eustachian tubes were excessively patent (the tube is too open) with poor active opening mechanisms (the tube will not open).\textsuperscript{76}

### Evidence-Based, Simplified Classification of Eustachian Tube Dysfunction

As described, we now have enough evidence from assessments of human temporal bones, experiments in animals, and clinical studies to simplify the classification of the pathophysiology of the eustachian tube system. This classification can be helpful in describing these abnormalities to patients and parents. Simply stated, dysfunction of the eustachian tube within its system can be summarized as follows: *the tubal system is either too closed or too open, or too much or too little pressure is present at either end* (see Figure 8).

### Role of Eustachian Tube in Pathogenesis of Otitis Media

Experiments on animal models and clinical studies involving adult volunteers have proven that eustachian tube dysfunction is involved in the pathogenesis of certain types of middle-ear disease. Several clinical studies in which adult volunteers had an intranasal virus challenge have convincingly demonstrated the sequence of events from a viral upper respiratory tract infection, to eustachian tube obstruction, to negative middle-ear pressure, to otitis media.\textsuperscript{7} The following details these animal and clinical studies.

#### Experiments in Animals

Both underpressures and middle-ear effusion have been successfully produced in animal models by several methods. These studies are summarized in Table 5.

When the tensor veli palatini muscle is experimentally impaired (altered or inactivated) in animal models, the active opening of the

### Table 5. Animal Models of High Negative Middle-Ear Pressure and Middle-Ear Effusion

<table>
<thead>
<tr>
<th>Experiment Number</th>
<th>Year (Reference)</th>
<th>Animal</th>
<th>Diagnostic</th>
<th>Method</th>
<th>HNP</th>
<th>MEE</th>
<th>Resolved Long-Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1977 (Cantekin et al)</td>
<td>Monkey</td>
<td>Otomicroscopy and tympanometry</td>
<td>TVP excised</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>1980 (Cantekin et al)</td>
<td>Monkey</td>
<td>Otomicroscopy and tympanometry</td>
<td>TVP 1) excised</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2) transected</td>
<td>Yes</td>
<td>Yes</td>
<td>No/Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3) transposed</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>1988 (Casselbrant et al)</td>
<td>Monkey</td>
<td>Otomicroscopy and tympanometry</td>
<td>Botulinum into TVP</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>1995 (Buchman et al)</td>
<td>Ferret</td>
<td>Otomicroscopy and tympanometry</td>
<td>Influenza A nasal inoculation</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>1995 (Swarts et al)</td>
<td>Monkey</td>
<td>MRI</td>
<td>CO₂ insufflation into ME</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>1997 (Alper et al)</td>
<td>Monkey</td>
<td>MRI</td>
<td>Botulinum into TVP</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

HNP = high negative middle-ear pressure; ME = middle ear; MEE = middle-ear effusion; MRI = magnetic resonance imaging; NA = not applicable (acute experiment); TVP = tensor veli palatini muscle.
The eustachian tube is impaired. This results in negative middle-ear pressure followed by middle-ear effusion. In one experiment, excision of a portion of the tensor veli palatini muscle at the pterygoid hamulus in the palate resulted in negative pressure in the middle ear followed by an effusion. A similar experiment in which the muscle was completely excised or the superficial muscle bundle was transected, or the tendon medial to the hamular process was transposed, had comparable outcomes. Complete excision resulted in middle-ear underpressures followed by persistent effusion. Transection of the muscle resulted in negative middle-ear pressure, effusion, or both (and in some animals, the middle ear returned to normal after the muscle healed). When the tendon was transposed, outcomes were similar to surgical alteration, but the middle ear rapidly returned to normal. Using a non-invasive method, Casselbrant and associates injected botulinum toxin into the tensor muscle, which resulted in negative pressure and then effusion. When the effect of the botulinum toxin resolved, the middle-ear status returned to normal.

In these earlier studies, middle-ear status was diagnosed with otomicroscopy and tympanometry. More recently, Alper and colleagues used magnetic resonance imaging (MRI) and tympanometry to identify middle-ear and mastoid effusion. These investigators also injected botulinum toxin into the tensor muscle of monkeys, which resulted in negative pressure and then effusion. When the effect of the botulinum toxin resolved, the middle-ear status returned to normal.

Buchman and associates, using a ferret, evaluated the effect of influenza A virus nasal challenge on the function of the eustachian tube. Results were assessed by forced-response and inflation-deflation tests, and middle-ear status was evaluated by otomicroscopy and tympanometry. All 10 animals in the experiment became infected, and all had eustachian tube dysfunction associated with middle-ear underpressures, although no middle-ear effusion developed in any of the ferrets. The investigation also showed that, even though the eustachian tube did not become totally obstructed, abnormally high negative pressures developed in the middle ear.

Using a different approach, Swarts and coworkers were also able to produce unilateral middle-ear effusion in the monkey shortly after inducing middle-ear negative pressure by inflating the middle ear with carbon dioxide. Increased vascular permeability was identified on MRI with use of a contrast agent. None of these changes were found in the contralateral, control ear. When the middle-ear cleft was flushed with oxygen, lesser middle-ear underpressures developed, but no middle-ear effusion or other changes on the MRI scan developed. Even though the eustachian tube was not altered in this experiment, the study showed the effect of middle-ear negative pressure in the development of middle-ear effusion.

These six experiments show that the eustachian tube has an important role in the development of otitis media in animal models. There is now equally convincing evidence from studies in adult volunteers that the eustachian tube is involved in the pathogenesis of otitis media. This is described next.

**Studies in Humans**

Several studies of adult volunteers assessed nasal function, eustachian tube function, and status of the middle ear after intranasal challenge of viruses. These studies demonstrate the role the eustachian tube plays in the pathogenesis of middle-ear underpressures, otitis media with effusion, and AOM and are summarized in Table 6.
Doyle and coworkers determined the effect of an upper respiratory tract infection (ie, a cold) on eustachian tube function and the status of the middle ear after intranasal challenge of rhinovirus in a group of 40 adult volunteers. After rhinovirus was inoculated into the nose, all subjects were found to be infected, but only 80% developed the signs and symptoms of a clinical illness. Before (and periodically, after) this nasal challenge, assessments were made of eustachian tube function (using sonotubometry and the nine-step test), middle-ear pressure (using tympanometry), and nasal patency (using active posterior rhinomanometry). All subjects with a cold had decreased nasal patency, 50% had eustachian tube obstruction, and 30% had abnormal negative middle-ear pressure for approximately 1 week after the inoculation. All outcomes completely resolved within 16 days, and none of the volunteers developed a middle-ear effusion.

In another study, Buchman and colleagues evaluated 60 adult volunteers using a design similar to that of the preceding two studies. After nasal inoculation with rhinovirus, 95% became infected and 60% had a clinical cold. Before the nasal challenge, three volunteers (5%) had abnormal middle-ear pressure, and a middle-ear effusion developed in two of these subjects. Of the 60 subjects, 22 (39%) had high negative middle-ear pressure. None of the subjects who had normal middle-ear pressure before the challenge developed an effusion, indicating that a rhinovirus infection may result in a middle-ear effusion if the patient has a preexisting dysfunction of the eustachian tube. Doyle and colleagues also reported that intranasal challenge with influenza A virus in 33 healthy adult volunteers resulted in 80% demonstrating eustachian tube obstruction and 80% having negative middle-ear pressure. However, with this virus, 5 of 21 infected subjects (23%) also developed a middle-ear effusion. Most likely, influenza A virus is more virulent than rhinovirus in the pathogenesis of eustachian tube and middle-ear abnormalities.

Using methods and design similar to those described in the study of Doyle and coworkers, McBride and associates recruited 32 adult volunteers. After the challenge with rhinovirus, abnormal findings were limited to the 24 subjects (75%) who developed clinical signs and symptoms of infection. After 2 days, 80% had eustachian tube obstruction, 50% had high negative middle-ear pressure, and 46% had decreased nasal patency. Again, none of the subjects developed a middle-ear effusion. These abnormal findings resolved 6 to 10 days after the challenge.

In an important study, Buchman and coinvestigators demonstrated the events leading to the development of AOM in the human. Using a design similar to that of the preceding studies, they recruited 27 adult volunteers, in whom influenza A virus was inoculated into the nose.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Year (Reference)</th>
<th>Number Of Subjects</th>
<th>Virus</th>
<th>ET OBS</th>
<th>HNP</th>
<th>MEE</th>
<th>AOM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1988 (Doyle et al)</td>
<td>40</td>
<td>Rhinovirus</td>
<td>50</td>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1989 (McBride et al)</td>
<td>32</td>
<td>Rhinovirus</td>
<td>80</td>
<td>50</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1994 (Buchman et al)</td>
<td>60</td>
<td>Rhinovirus</td>
<td>NT</td>
<td>39</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1994 (Doyle et al)</td>
<td>33</td>
<td>Influenza A</td>
<td>80</td>
<td>80</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>1995 (Buchman et al)</td>
<td>27</td>
<td>Influenza A</td>
<td>NT</td>
<td>59</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>2000 (Doyle et al)</td>
<td>18</td>
<td>Influenza A</td>
<td>Yes/No*</td>
<td>Yes/No*</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>2002 (Buchman et al)</td>
<td>32</td>
<td>RSV</td>
<td>NT</td>
<td>54</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Reproduced with permission from Bluestone C. Eustachian tube dysfunction and abnormal middle-ear pressures in individuals are more prevalent when the tube is found to have poor function prior to the challenge.

AOM = acute otitis media; ET OBS = eustachian tube obstruction; HNP = high negative pressure; MEE = middle-ear effusion; NT = not tested; RSV = respiratory syncytial virus.
All subjects developed a nasal infection, and 16 (59%) subsequently developed high negative middle-ear pressure. In one subject, AOM was present. With use of polymerase chain reaction, a middle-ear aspirate revealed the virus and S. pneumoniae; traditional viral and bacterial culture methods failed to grow these organisms from the middle-ear effusion. It is possible that these microorganisms were aspirated from the nasopharynx into the middle-ear cavity as a result of the high negative middle-ear pressure.

Two later clinical studies employing viral (influenza A, respiratory syncytial) challenge resulted in high negative middle-ear pressures, primarily in those subjects who had poor eustachian tube function prior to the challenges.135,136

An informative clinical investigation by Moody and colleagues also demonstrated this sequence of events in children.5 In this study, the parents of 20 children between the ages of 2 and 6 years monitored the middle-ear status of their children every day with a tympanometer. They reported that, when an upper respiratory tract infection developed in the children, many soon also developed middle-ear underpressures, and some then developed a middle-ear effusion.

These studies in both humans and animal models support the causal relationship between a viral upper respiratory tract infection, partial eustachian tube obstruction, abnormal middle-ear underpressures, and otitis media.

PATHOGENESIS OF OTITIS MEDIA AND RELATED CONDITIONS

AOM, otitis media with effusion, eustachian tube dysfunction, and chronic suppurative otitis media are the most frequent middle-ear diseases clinicians encounter. After the onset of either AOM or otitis media with effusion, persistent middle-ear effusion may develop (see Chapter 8, “Management” and Chapter 9, “Complications and Sequelae: Intratemporal”).

Acute Otitis Media

The pathogenesis of AOM in most children usually follows this pattern: the patient has an antecedent event (usually an upper respiratory viral infection) that results in congestion of the mucosa of the upper respiratory tract, including the nasopharynx and eustachian tube. Congestion of the mucosa in the eustachian tube obstructs the eustachian tube, and negative middle-ear pressure develops; if prolonged, potential pathogens (viruses and bacteria) are aspirated from the nasopharynx into the middle ear. Because the eustachian tube is obstructed, the middle-ear effusion, due to the infection, accumulates in the middle ear. Microbial pathogens proliferate in the secretions, resulting in a suppurative and symptomatic otitis media.137

For children with recurrent AOM, an anatomic or physiologic abnormality of the eustachian tube appears to be an important factor, if not the most important factor. In Sweden, Stenstrom and coworkers studied the pathogenesis of recurrent AOM in 50 otitis-prone children (more than 11 episodes of acute otitis media).56 Using the pressure chamber to test eustachian tube function, they found the otitis-prone children had significantly poorer active tubal function than 49 normal (control) children who had no history of AOM. This finding indicates that recurrent AOM is the result of functional obstruction of the eustachian tube, as opposed to mechanical obstruction. Also, cytokine gene polymorphism may play a role in recurrence, especially in children who have allergic disorders.138 However, it is likely that infants and young children with their short, floppy eustachian tubes can reflux or insufflate nasopharyngeal secretions into the middle ear during a viral upper respiratory tract infection. Another possible mechanism is an infection that progressively ascends from the nasopharynx into the mucosa of the eustachian tube. This most likely occurs when an indwelling obstructing foreign object is in the nasopharynx, such as a nasogastric or nasotracheal tube (see Chapter 8, “Management”).
Otitis Media with Effusion

The acute onset of otitis media with effusion is relatively asymptomatic in children but usually has a sequence of events similar to those described for AOM. Bacteria can be isolated from middle-ear effusions of patients with otitis media with effusion, but prolonged negative pressure within the middle ear can cause a sterile middle-ear effusion. As described before, otitis media with effusion has been produced in the monkey animal model after excision of and injection of botulinum toxin into the tensor veli palatini muscle, which resulted in the eustachian tube’s failing to open, middle-ear underpressures, and effusion. These experiments confirm the hydrops ex vacuo theory of the pathogenesis of middle-ear effusion. This theory postulates that, when the eustachian tube does not open, the gas exchange from the middle ear into the microcirculation of the mucous membrane causes a middle-ear underpressure, followed by transudation of effusion. Swarts and associates were also able to produce middle-ear effusion in the monkey by flushing the middle ear with carbon dioxide shortly after inducing middle-ear negative pressure. In the studies cited earlier by McBride and colleagues and by Buchman and coworkers that involved adult volunteers, nasal challenge with rhinovirus resulted in eustachian tube obstruction, negative middle-ear pressure, and, in two subjects, middle-ear effusion. Doyle and colleagues also demonstrated that intranasal challenge of influenza A virus in adult volunteers resulted in eustachian tube obstruction, negative middle-ear pressure, and, in infected subjects, middle-ear effusion. Doyle and colleagues also demonstrated that intranasal challenge of influenza A virus in adult volunteers resulted in eustachian tube obstruction, negative middle-ear pressure, and, in infected subjects, middle-ear effusion. Most likely, influenza A virus is more virulent than rhinovirus.

Periods of upper respiratory tract infection can then result in atelectasis of the tympanic membrane-middle ear (ie, high negative middle-ear pressure), sterile otitis media with effusion, or acute bacterial otitis media. Because the tube can open in a middle ear with an effusion, nasopharyngeal secretions can be aspirated, creating the clinical condition in which otitis media with effusion and recurrent acute bacterial otitis media occur together. The most dramatic example of the ex vacuo cause of acute middle-ear effusion is barotrauma (eg, descent during scuba diving or airplane flying). In a study of eustachian tube function in 163 ears of Japanese children and adults who had otitis media with effusion and chronic otitis media, Iwano and colleagues found an impaired active opening function of the tube in children and adults. They concluded that the tube was functionally obstructed. “Organic” (ie, mechanical or anatomic) obstruction was also considered to be involved in the pathogenesis in adults (see Chapter 8, “Management”). More recently, van Heerbeek and co-workers further confirmed that children who have persistent middle-ear effusion have poor eustachian tube function, as described initially some 30 years ago. As reported by Swartz and Bluestone, older children, adolescents and adults who had chronic otitis media effusion had paradoxical constriction of the eustachian tube during swallowing, as opposed to dilation. This defective tubal opening would be detrimental in clearing middle-ear secretions, as well as in the initial pathogenesis of the disease.

There is some evidence that the presence of biofilm formation on the middle-ear mucosa may be involved in the prolonging of middle-ear effusion into the chronic stage. Mucous is also a common finding in the middle ears of children with otitis media with effusion, which may be the result of an antecedent acute otitis media. There have been reports that gastroesophageal reflux may be involved in the pathogenesis of otitis media, but more recently reported studies failed to implicate reflux as a cause. It is possible that secretions from the stomach in individuals who have proven reflux could be interfering with tubal function. It would appear to be prudent to treat reflux, if symptomatic, in patients who have recurrent and chronic otitis media, even though the role of reflux remains unclear. If the patient has symptomatic reflux, management is indicated irrespective of the presence or absence of middle-ear disease.
Persistent Middle-Ear Effusion

There are probably similarities in the pathogenesis of persistent middle-ear effusion after the initial stage of a viral or bacterial infection in the middle ear or after transudation of effusion when high negative pressure is in the middle ear. Cytokines are stimulated, such as interleukins 1, 2, and 6; tumor necrosis factor; interferon-γ from inflammatory cells of the middle-ear mucous membrane; and growth factors. This is followed by two pathways of inflammation: (1) up-regulation of submucosal receptors, primarily selectins and integrins that trap lymphocytes into the mucosa, which also produce cytokines and inflammatory mediators; and (2) stimulation of inflammatory mediators, such as leukotrienes, prostaglandins, thromboxane, prostacyclin, and platelet-activating factor, which in turn can promote fluid leakage from the mucous membrane.

Nitric oxide and free radicals have also been implicated in the pathogenesis of persistent middle-ear effusion. At this stage, there is probably an increase in blood flow within the mucous membrane due to engorgement of blood vessels and angioneogenesis. This results in further negative pressure within the middle ear because of an increase of nitrogen into the microcirculation of the mucosa.

There is some evidence that infection caused by Haemophilus influenzae predisposes the middle-ear cleft to persistent effusion due to changes in mucosal goblet cell density. In addition, the effusion that is produced is trapped in the middle ear because of the anatomy of the system (ie, a closed space with a narrow outlet, the eustachian tube). The mucociliary system and the pumping action of the tube are also most likely impaired, causing persistent middle-ear effusion (see Chapter 8, “Management”).

Eustachian Tube Dysfunction

Eustachian tube dysfunction can be due to either an obstruction of the tube or a patulous tube. These cause signs and symptoms referable to the ear, despite the lack of a middle-ear effusion.

Obstruction of the tube can cause middle-ear negative pressure, retraction of the tympanic membrane, hearing loss, and, in its severe form, atelectasis of the middle ear (ie, loss of the middle-ear space). Obstruction can be due to inflammation or failure of the opening mechanism. Obstruction can be acute or chronic, but infrequent periodic tubal opening probably occurs to prevent the accumulation of an effusion. A patulous tube can cause patients to complain of autophony and hearing their own breathing. Both conditions have been documented during the last trimester of pregnancy. Eustachian tube obstruction is common in girls during puberty and may be related to hormonal changes, but we do not know the underlying cause of this problem (see Chapter 8, “Management”).

Chronic Suppurative Otitis Media

Chronic suppurative otitis media (without cholesteatoma) is the chronic stage that follows an attack of AOM in which there is perforation of the tympanic membrane (or a tympanostomy tube is present) and continuous discharge. From our studies of the pathogenesis of chronic suppurative otitis media, it appears that the sequence of events may be in 1 of 2 ways. In one way, the tympanic membrane is not intact, and bacteria from the nasopharynx gain access to the middle ear by reflux of nasopharyngeal secretions. This is especially true when there is inflammation (secondary to infection or possibly allergy) of the nose, nasopharynx, or paranasal sinuses and reflux occurs through the eustachian tube, because the middle-ear gas cushion is lost. In most instances, these bacteria are initially the same as those isolated when AOM occurs behind an intact tympanic membrane, such as S. pneumoniae and H. influenzae, and when acute otorrhea develops when tympanostomy tubes are in place. After the acute otorrhea, Pseudomonas aeruginosa, Staphylococcus aureus, and other organisms from the external ear canal enter the middle ear through the non-intact tympanic membrane, resulting in
the chronic infection. In the second common way in which chronic suppurative otitis media occurs, organisms (eg, P. aeruginosa) present in water enter through the non-intact eardrum during bathing and swimming and contaminate the middle-ear cleft (see Chapter 9, “Complications and Sequelae: Intratemporal”).

CONCLUSIONS AND TREATMENT IMPLICATIONS

The etiology and pathogenesis of otitis media are multifactorial, but abnormalities of the structure and function of the eustachian tube appear to be the most important. Eustachian tube dysfunction can cause otitis media and related conditions because of (1) impairment of pressure regulation as the result of anatomic obstruction of the tube (the tube is too closed) or failure of the tubal opening mechanism (the tube will not open)—that is, functional obstruction; (2) loss of protective function due to abnormal patency of the tube (the tube is too open), a tube that is too short, abnormal gas pressures within the middle ear or nasopharynx, or a non-intact middle ear and mastoid; or (3) impairment of clearance function. These abnormalities can be simply described: the eustachian tube system is either too closed or too open, or either end of the system is too open or too closed, or too much or too little pressure is present.

With this better understanding of the physiology and pathophysiology of eustachian tube function and studies that have demonstrated the effect of intranasal challenge with virus, allergens, and mediators in adult volunteers on nasal and eustachian tube function, our knowledge of the pathogenesis of otitis media has greatly increased. This should lead to improved management methods.

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