Eur J Pediatr (2001) 160: 407–413

REVIEW

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The microbiologic and immunologic basis for recurrent otitis media in children

Received: 18 September 2000 and in revised form: 25 January 2001 / Accepted: 30 January 2001

Abstract Otitis media is very common in children. A subpopulation of children, representing 5–10% of the general population, are otitis prone and they experience 4 or more episodes of acute otitis media (AOM) in the first year of life. Nasopharyngeal colonization with the three major middle ear pathogens, *S. pneumoniae*, nontypeable *H. influenzae* and *M. catarrhalis* is frequent in otitis prone children and is directly related to the frequency of AOM. Colonization stimulates the production of mucosal as well as serum antibodies to the pathogens. Specific IgA mucosal antibody limits the duration and frequency of colonization. Serum IgG antibody protects children against the development of otitis media but does not affect colonization. Antibody detected in the middle ear often reflects passive transfer from serum rather than local production. Antibody responses to the three pathogens following AOM are generally reduced in the first 2 years of life and rise rapidly thereafter. There are many different strains of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. Among the different strains, there are heterologous surface antigens and some conserved antigens. Conserved antigens induce broadly protective antibodies while strain specific antigens induce limited protection. Although otitis prone children may display strain specific immunity, they often fail to develop a broadly protective antibody response. This subtle immunologic defect makes them susceptible to recurrent and persistent otitis media.

Conclusions Otitis media is common. Otitis prone children appear to display a subtle immunologic abnormality that predisposes them to recurrent infections. Recent advances in vaccine development may reduce the frequency of otitis media in the general population but the impact on otitis prone children remains unknown.

Key words Otitis media · Mucosal immunity · Nasopharyngeal colonization · Otitis prone children

Abbreviations *AOM* Acute otitis media · *OME* Otitis media with effusion · *DNA* Deoxyribonucleic acid · *PspA* Pneumococcal surface protein A · *UspA* Ubiquitous surface protein A · *COME* Chronic otitis media with effusion · *CSOM* Chronic suppurative otitis media

The term otitis media is broad and includes myringitis, acute otitis media, otitis media with effusion, chronic otitis media with effusion and chronic suppurative otitis media (Table 1). This review will focus on acute otitis media (AOM). However, AOM is often confused with otitis media with effusion (OME). These two clinical entities can be distinguished by signs/symptoms and examination of the tympanic membrane (Table 2) [9]. Acute otitis media is a symptomatic illness associated with upper respiratory symptoms in 95%, pain in 75%,

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fever in 25% and otorrhea in < 5% [9]. In contrast, OME is less symptomatic and associated with upper respiratory symptoms in 75%, pain in 0%, fever in 0%, and otorrhea in 0% [9]. Whereas, the tympanic membrane in AOM is often discolored, bulging, and thickened, it is relatively normal in OME, although air fluid levels may be seen behind the membrane. The fluid is most often purulent in AOM and serous in OME. The disease is bilateral in about half the cases in either disorder. The tympanic membrane exhibits reduced mobility in both disorders. Finally, antibiotics are indicated for AOM but not for OME.

Acute otitis media is fairly common and by 1 year of age nearly half of infants will have experienced ≥1 episodes (Fig. 1) [9]. Children experience an average of 1.5 episodes in the first year and spend approximately 2.5 months with middle ear effusions related to AOM. The effusions disappear at a predictable rate so that by 1 month after diagnosis, effusions have resolved in 60%, by 2 months in 80% and by 3 months in 90% [9]. The duration of an effusion depends somewhat on the number of episodes experienced. For example, in the first year of life, first episodes last an average of 1.5 months, second episodes 1.8 months and third episodes 2.1 months [9]. This pattern appears to characterize the otitis prone child who represents 5–10% of the general population, resolves the infection slowly and who, by definition, experiences ≥4 episodes of AOM and spends ≥7 months with middle ear effusions following acute otitis media in the first year of life alone.

Microbiology of acute otitis media

Three pathogens account for the majority of AOM. *Streptococcus pneumoniae* is the predominant pathogen, causing 35% of the episodes [6]. Over the past 100 years, *S. pneumoniae* has consistently caused the same proportion of cases (Table 3) [6]. Nontypeable *Haemophilus influenzae* is the second most important pathogen, causing 20% of the episodes [6]. *Moraxella catarrhalis* is the third most important pathogen, causing 15% of the episodes [6]. Group A streptococcus was the leading pathogen of AOM 100 years ago but today it is responsible for less than 5% of the episodes [6]. About 25% of the episodes remain etiologically obscure.

The three major pathogens are common causes of AOM because they frequently colonize the upper airway near the eustachian tube opening. For example, at 6 months of age 26% of infants are colonized with *M. catarrhalis*, 24% with *S. pneumoniae*, and 9% with *H. influenzae*. By one year of age 72% of all infants will have been colonized with *M. catarrhalis* at least once, 54% with *S. pneumoniae*, and 33% with *H. influenzae* [10]. Early colonization is associated with early first episodes of AOM [10]. There is also a direct relationship between the frequency of colonization and the frequency of AOM [18]. In fact, otitis prone children are more often colonized with these pathogens when they are healthy and when they are ill with upper respiratory tract infections when compared to normal children (Fig. 2) [15]. The mere fact that a child becomes colonized with either *S. pneumoniae* or *H. influenzae* in the first year of life increases their risk of becoming otitis prone 4 fold when compared to children who escape colonization [10]. The same trend is seen with *M. catarrhalis* but the risk is lower [12].

Table 1 Categories of otitis media

Myringitis
Acute Otitis Media (AOM)
Otitis Media with Effusion (OME)
Chronic Otitis Media with Effusion (COME)
Chronic Suppurative Otitis Media (CSOM)

Table 2 Differences between acute otitis media and otitis media with effusion [9]

Characteristics	AOM (%)	OME (%)
Respiratory symptoms	95	75
Pain	75	0
Fever	25	0
Otorrhea	< 5	0
Tympanic Membrane		
Discolored, bulging, thickened	100	0
Immobile	100	100
Bilateral	50	50
Fluid	Pus	Serous

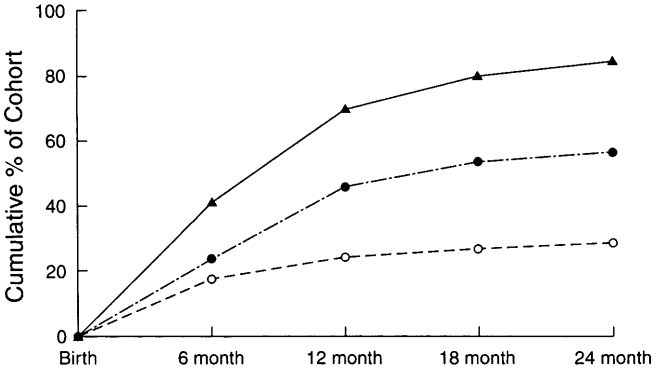

Fig. 1 Cumulative frequency of first episodes of otitis media. ▲-▲ all cases; ●-● AOM; ○-○ OME [9]

Table 3 Shifts in the bacterial causes of acute otitis media, 1900–2000 [6]

Pathogens	1900	1950	2000
S. pneumoniae	30	40	35
H. influenzae	0	20	15
M. catarrhalis	0	0	15
Group A streptococcus	50	20	< 5
No pathogen	5	25	25

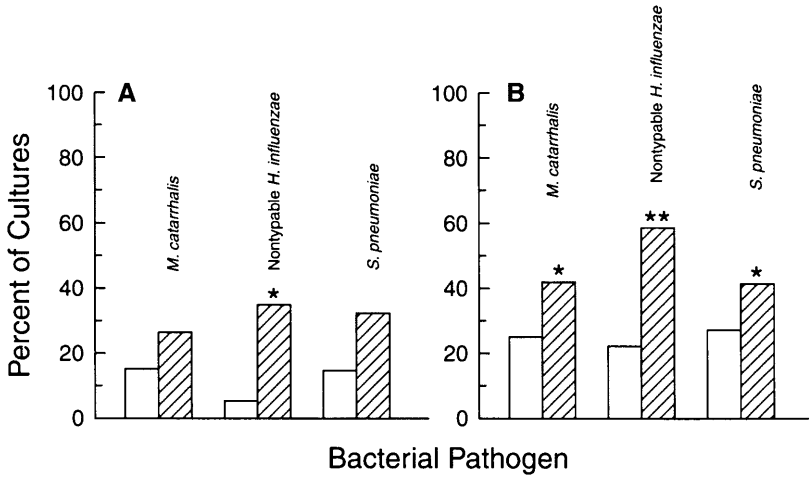

Fig. 2 Comparison of nasopharyngeal carriage of *S. pneumoniae*, nontypeable *H. influenzae* and *M. catarrhalis* in normal □ and otitis prone ▨ children during health **(A)** and during upper respiratory tract illness **(B)** $*P < 0.05$; $**P < 0.001$ [15]

In order to understand the immunologic aspects of AOM, it is important to understand that there are many different strains of each pathogen. For instance, there are more than 90 types of *S. pneumoniae* based on their capsular polysaccharides. Some children are never colonized with *S. pneumoniae* while others became colonized with one type to as many as 4 different types during the first year of life [24]. As for *H. influenzae*, strains may distinguished by the proteins displayed in the outer membrane. Fifty percent of children who become colonized in the first year become colonized with only 1 strain while others become colonized sequentially with as many as 7 different strains [11]. Recolonization with the same strain is unusual. Additionally, the duration of colonization with a single strain varies from less than 1 month to as long as 10 months [11]. A similar pattern is observed with *M. catarrhalis*; however, since outer membrane protein patterns appear very similar between strains in SDS polyacrilamide gel electrophoresis preparations, the strains are best distinguished by DNA finger printing techniques [12].

The differences in patterns of colonization with the various pathogens among individuals suggest that the local immune response plays an important regulatory role in the trafficking of pathogens in the upper airway. One might infer that a brisk local immune response to an organism would limit the duration of colonization while a poor immune response would result in prolonged carriage. Furthermore, an immune response to a highly conserved antigen might protect against colonization with different strains while an immune response to an heterologous antigen might only protect against recolonization with the same strain.

Antigens of Immunologic Importance among Middle Ear Pathogens (Table 4)

As described previously, there are more than 90 types of *S. pneumoniae* based on the capsular polysaccharide antigens [5]. Antibody to the capsule is highly specific with very little cross reactivity. The antibody functions as an opsonin and is protective. A second antigen, pneumococcal surface protein A (PspA) is found on all clinically important strains of *S. pneumoniae* [17]. Antibody to PspA appears to be protective [5, 26]. Antibody to PspA from different strains displays cross-reactivity [5, 26].

H. influenzae exhibits more than 20 proteins in the outer membrane with at least 7 major ones [16]. Two of the proteins, P4 and P6, are highly conserved while others, such as P2, are heterologous and strain specific. Many of these major proteins are targets for bactericidal antibody.

Less is known about the outer membrane proteins of *M. catarrhalis* except that there are at least nine of them and none are highly conserved [1]. At this point, it is difficult to determine which of the proteins is important for protection. One protein, UspA, is found on all *M. catarrhalis* strains, contains a highly conserved epitope on the surface of the organism, and is the target for protective antibody [19].

Immune response to middle ear pathogens

S. pneumoniae

Because children do not generate a good serum immune response to polysaccharide antigens prior to the age of 2

Table 4 Characterization of strains of *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* according to important antigens

Pathogen	Method of characterization	Serotypes
S. pneumoniae	Capsular polysaccharides	>90 [5]
	Surface protein A	2
H. influenzae	Major outer membrane proteins	7[a] [16]
M. catarrhalis	Major outer membrane proteins	9[b] [1]

[a] 2 highly conserved, [b] none highly conserved

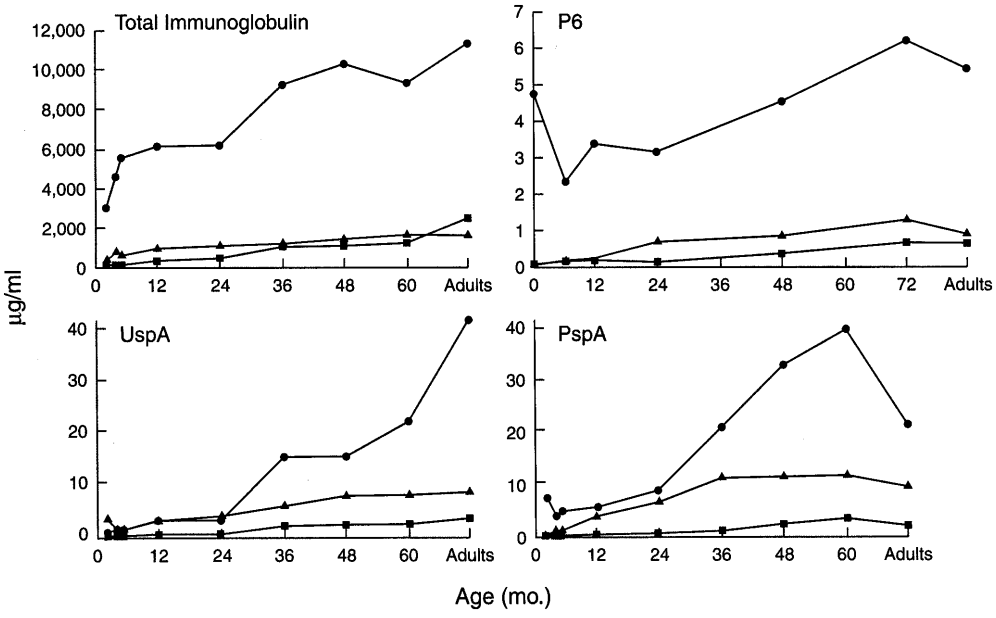

Fig. 3 Seroprevalence of antibody to *S. pneumoniae* (PspA), nontypeable *H. influenzae* (P6) and *M. catarrhalis* (UspA) according to age. ●-● IgG; ▲-▲ IgM; ■-■ IgA [22]

years, the antibody response to PspA has been surveyed in the general population. The serum antibody pattern is similar to that seen with *H. influenzae* (Fig. 3). Immunoglobulin G PspA antibody is the dominant isotype of immunoglobulin. It remains at relatively low levels in the serum until the age of 2 years when it rises rapidly [22]. Adult levels surprisingly drop to levels observed in 3 year olds. Perhaps, this explains, in part, the heightened susceptibility of certain adults to pneumococcal infection. Immunoglobulin A to PspA in the respiratory tract after colonization is detected in about one third of children with measurable amounts of IgA in secretions, suggesting that PspA is an immunogen in the respiratory tract, albeit a poor one in the very young.

The antibody response to *S. pneumoniae* has been studied in children with AOM. The response to capsular polysaccharide is poor in young children as one might expect. Although IgG specific *S. pneumoniae* antibody may be detected in all acute and convalescent sera, the levels are less than 1/5 of adult values and few children mount an immune response during convalescence. The highest concentration of antibody is detected in older children. Middle ear fluid levels of antibody are undetectable except for the children with the highest serum levels of antibody. In contrast, antibody responses to pneumococcal surface protein A are detected regardless of age. Although convalescent serum contains higher levels of IgG and IgM PspA specific antibody, the increases are minimal (IgG acute 4.9 µg/ml vs convalescent 5.8 µg/ml, $P = 0.04$; IgM acute 1.1 µg/ml vs convalescent 3.6 µl/ml, $P = 0.02$) [23]. Children may experience 2 episodes of AOM due to different capsular types despite a good immune response to PspA following the first infection, suggesting that an immune response to PspA may not be fully protective.

H. influenzae

Immunoglogulin G antibody to *H. influenzae* is detected in cord blood at adult levels in most newborns [13, 27]. The level of antibody declines to the lowest point over the next 6 months and remains relatively low until 2 years of age when it rises rapidly, almost achieving adult levels by 4 or 5 years of age (Fig. 3). Immunologlobulin M and A specific *H. influenzae* antibodies are not present at birth but rapidly appear over the next 3 years. Immunoglobulin G antibody is the dominant serum *H. influenzae* antibody followed by IgM.

The passively acquired serum antibody of the newborn plays a role in protecting the child against otitis media but it does not appear to prevent nasopharyngeal colonization. In fact, 50% of infants demonstrate strain specific serum bactericidal antibody at the time they acquire their first nasopharyngeal strains of *H. influenzae* [3, 18]. During colonization and thereafter the proportion of children exhibiting strain specific bactericidal antibody progressively rises to 100% [3]. At the same time, 0% of children possess mucosal antibody to *H. influenzae* prior to colonization and 100% do after colonization [3, 18]. The mucosal antibody response, unlike that seen in the serum, is predominantly IgA [18, 28]. The magnitude of the mucosal antibody response affects the colonization pattern. A brisk response shortens the course of colonization while a poor or delayed response results in prolonged colonization with the same strain and/or recurrent colonization with a number of different strains (Fig. 4) [11].

Children also develop an immune response to *H. influenzae* during otitis media. At the start of the infection, the majority of children lack bactericidal antibody to the infecting strain; however, within 1 month, 100% acquire antibody [7]. The antibody persists for a

prolonged period. It can be detected as long as six years after an episode of AOM. Homologous antibody can also be detected in the middle ear. As with serum, immunoglobulin G specific antibody predominates in the middle ear [8]. The level of antibody in middle ear fluid is directly proportional to the serum level, suggesting that antibody enters the middle ear from the serum during the inflammatory stage of the infection, $r = 0.89$, [28]. The level of antibody in the middle ear is also inversely proportional to the number of viable bacteria present, indicating a direct bactericidal effect of the antibody on the organism [7, 28].

M. catarrhalis

The serum immune response to surface protein UspA in children of various age groups has been surveyed in the general population. During the first 2 years of life antibody levels remain relatively low (Figure 3) [22]. However, unlike *H. influenzae* and *S. pneumoniae*, IgM UspA specific antibody concentrations are comparable to IgG specific antibody concentrations for the first 2 years; thereafter, IgG UspA specific antibody levels rise gradually, reaching a peak in adulthood. IgA UspA specific antibody is not detected in the respiratory tracts of children colonized in the first 6 months of life [22].

The immune response to *M. catarrhalis* in children with acute otitis media has been investigated. There is no significant serum antibody response to the whole outer membrane for IgG, M, or A isotypes [14]. In contrast to *H. influenzae*, the middle ear fluid demonstrate a significant IgA response suggesting local production of antibody. More recently, the antibody response to UspA in acute and convalescent sera in children with *M. catarrhalis* AOM has been investigated. An antibody response is detected in certain individuals but overall the response is meager [23]. The only significant rise in specific antibody occurs in the IgA class of immunoglobulins (IgA acute 0.1 μg/ml vs convalescent 0.2 μg/ml, $P = 0.01$) [23].

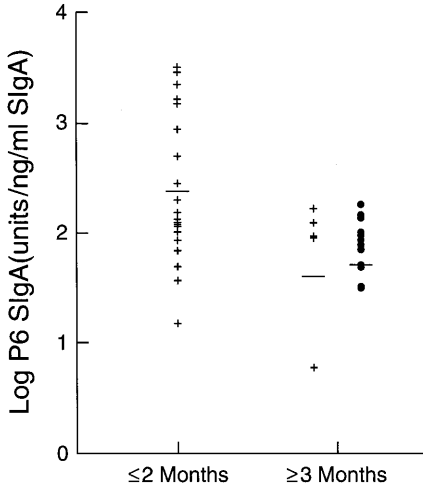

Fig. 4 Comparison of nasopharyngeal antibody response to P6 protein of *H.influenzae* according to duration of colonization and number of different strains carried. + single strain; • multiple strains [11]

The immune response in children with recurrent otitis media

Haemophilus influenzae represents a major cause of recurrent or persistent middle ear disease in children. A number of otitis prone children experience multiple episodes of AOM with different strains of *H. influenzae*. A child may develope strain specific antibody after each episode. At the time of the acute stage of a second or third episode, the child still possesses bactericidal antibody to the previous strain or strains as the case might be (Fig. 5) [7] . This suggests that the antibody is truly strain specific and does not cross react with other strains [7]. We hypothesize that the bactericidal antibody recognizes an important heterologous surface protein, such as P2, rather than an important highly conserved surface protein, such as P6.

Otitis prone children also fail to demonstrate an age-related rise in P6 antibody, most evident after the age of 2 years (Fig. 6) [27]. In addition, otitis prone children do not exhibit anamnestic antibody responses during recurrent episodes of *H. influenzae* otitis media [27]. Possible explanations for the recurrent episodes include: 1) Normal children recognize highly conserved antigens like P6, develop bactericidal antibody to all strains, and are protected against further disease. 2) Otitis prone children recognize strain specific antigens like P2, develop bactericidal antibody to a single strain, are protected against reinfection, and are susceptible to other strains. Severely involved children may not develop an adequate immune response to strain specific antigens either. 3) Normal children develop a T lymphocyte response to highly conserved antigens while otitis prone children do not; thus, antibody declines in otitis prone children and fails to exhibit an anamnestic response. Evidence for explanation number 3 comes from a study in our laboratory of adenoids from otitis

Date	Strain		
	955	3737	1080
1/86	0*	-	-
5/86	40	-	-
6/87	40	0*	-
12/87	80	20	-
9/88	10	20	0*
1/89	10	20	20

*Episode of AOM

Fig. 5 Reverse bactericidal antibody titers to 3 different strains of nontypeable *H. influenzae* in a single individual [2]

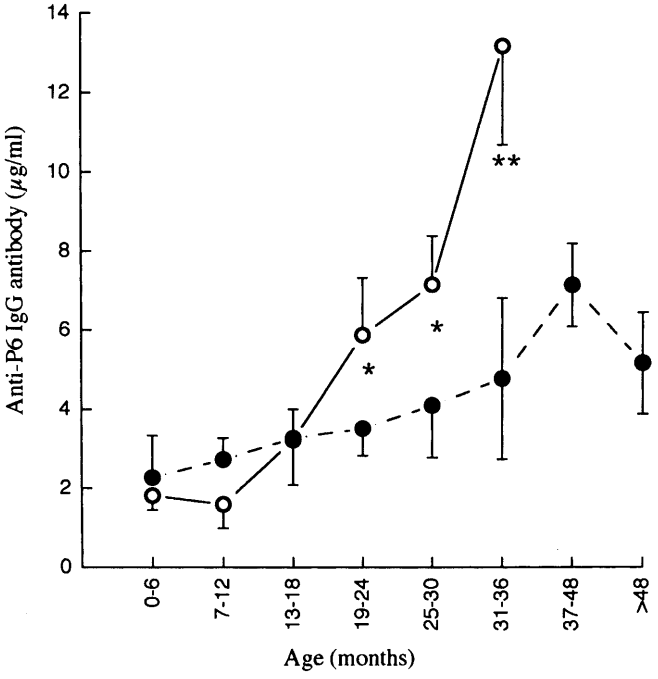

Fig. 6 Development of antibody to P6 of *H. influenzae* according to age in normal (○–○) and otitis prone children (●–●) $*P < 0.05$; $**P < 0.01$ [27]

prone children; adenoidal lymphocytes from otitis prone children demonstrate reduced proliferative responses to P6 when compared to normal children [20].

Current trends

At present there are two vaccines commonly available against *S. pneumoniae* and none against nontypeable *H. influenzae* or *M. catarrhalis*. The first pneumococcal vaccine is prepared with capsular polysaccharides from 23 types of *S. pneumoniae*. It is recommended for use in children older than two years of age. It is not recommended for prevention of otitis media, even through several earlier studies had demonstrated some type specific efficacy [21, 25]. The second and more recently manufactured vaccine is comprised of seven types of *S. pneumoniae*; however, it is a conjugated vaccine which enables it to be used in children as young as 2 months. This vaccine may be effective in reducing the number of pneumococcaal episodes of AOM [4]. Nine and eleven valent pneumococcal vaccines are currently undergoing field trials. Vaccines for nontypeable *H. influenzae* and *M. catarrhalis* are under development as well but are not as far along as the pneumococcal vaccines.

Conclusions

Young children are exposed to a number of different respiratory pathogens early in life. The normal child becomes colonized relatively infrequently and develops an immune response that will protect against repeated episodes of colonization as well as against otitis media; on the other hand, the otitis prone child becomes colonized frequently with potential middle ear pathogens and fails to develop a broadly based immune response. As a result, the otitis prone child experiences repeated episodes of colonization and infection. The basis for the abnormal immune response is not understood. Although, there may be a familial predisposition to otitis proneness, it is also possible that the immune abnormality could result from early or frequent exposure to middle ear pathogens. The success of vaccines in the otitis prone population is yet to be determined.

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