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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 50-675/S-014 **Submission Dates:** December 19,1997
Cefpodoxime Proxetil, Vantin ®

Reviewers: Jenny Zheng, Ph.D.
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Pharmacia & Upjohn Trading Corporation

Type of submission: Efficacy Supplement

D. HUMAN PHARMACOKINETIC AND BIOAVAILABILITY SUMMARY

1. INTRODUCTION

The pharmacokinetics of cefpodoxime in adults and in children are fully described in NDAs 50-674 and 50-675 and supplement NDA 50-675/S-008. Systemic bioavailability of cefpodoxime proxetil is approximately 50%. Peak plasma levels are reached about 2 to 3 hours after oral administration in healthy adult volunteers or pediatric patients. Cefpodoxime elimination half-life ranges from 1.3 to 2.2 hours in pediatric patients and from 1.9 to 2.8 hours in healthy adult volunteers.

A previous study in children with chronic otitis media demonstrated the ability of cefpodoxime to penetrate into chronic middle ear effusions (MEE). Drug levels in MEE were somewhat low, however, the range was from <0.04 to 0.42 µg/mL and <0.08 to 0.65 µg/mL in patients receiving single 5 mg/kg or 10 mg/kg doses, respectively. Overall, the ratio of MEE to plasma concentration ranged from 0 to 0.18. In AOM, penetration of antibiotics into respiratory secretions may proceed more quickly and result in higher drug concentrations than in chronic otitis media, due to capillary leakage in a hyperemic mucosa. The present study (Protocol M/1140/0116) was conducted to assess cefpodoxime penetration into MEE of pediatric patients with AOM after once or twice daily dosing with cefpodoxime proxetil oral suspension.

2. STUDY DESIGN:

Protocol M/1140/0116 was a randomized, open-label study in which the penetration of cefpodoxime into the middle ear of 50 pediatric patients (ages 6 months to 10 years) with acute otitis media was evaluated after administration of cefpodoxime proxetil oral suspension 5 mg/kg twice a day (BID) or 10 mg/kg once daily (QD). After at least one complete day of treatment, tympanocentesis was performed at either 2, 4, 6, or 8 hours after the morning dose; a blood sample was collected at the same time as the MEE. Drug concentrations in MEE and plasma were determined using an method with

Table D-1 displays information regarding where this study was conducted, the study design, treatment regimens, number of subjects treated, and demographics.

Table D-1. Clinical Pharmacokinetic Study Supporting Use of Cefpodoxime Proxetil Oral Suspension in Pediatric Patients with Acute Otitis Media

Protocol No./ Investigator/ Location	Study Design, Description, and -Population	Cefpodoxime Proxetil		No. Eval. Subj (M/F)	Sponsor's Conclusions
		Dose Regimen	No. Doses		
M/1140/0116 RH Schwartz Vienna, VA DP McCormick Galveston, TX	Randomized, open-label, parallel-group, multiple-dose study in pediatric patients with acute otitis media (AOM): Penetration into middle ear effusion (MEE).	5 mg/kg (200 mg max) twice a day (BID)	2-8	17 (10M/7F)	The MEE/plasma cefpodoxime concentration ratio for the 5 mg/kg BID and 10 mg/kg QD treatment groups ranged from 0.14 to 12 and 0.13 to 3.2, respectively. MEE cefpodoxime levels exceeded the MIC_{90} for the majority of isolates associated with AOM in greater than 90% of the patients.
		10 mg/kg (400 mg max) once a day (QD)	2-4	17 (12M/5F)	

3. RESULTS

Among the fifty subjects, 34 subjects (22 males, 12 females), ranged in age from 6 months to 10 years old and in body weight from 7.9 to 41 kg, were evaluable. Median (range) cefpodoxime concentrations in plasma and MEE are shown in Table D-2 and D-3 for the 34 evaluable patients:

Table D-2. Median (Range) Cefpodoxime Concentrations in Plasma after Administration of Cefpodoxime Proxetil Oral Suspension

Target Collection Time (h)	5 mg/kg BID (n=17)		10 mg/kg QD (n=17)	
	No. of Samples	Concentration (µg/mL)	No. of Samples	Concentration (µg/mL)
2	4	3.40 (2.67-3.67)	5	5.30 (2.38-7.16)
4	5	1.75 (0.09-2.48)	5	4.25 (3.81-5.63)
6	4	0.73 (0.42-1.95)	3	1.64 (1.55-2.35)
8	4	0.66 (0.45-0.89)	4	1.23 (0.63-4.72)

Table D-3. Median (Range) Cefpodoxime Concentrations in Middle Ear Effusion of Pediatric Patients with Otitis Media

Target Collection Time (h)	5 mg/kg BID (n=17)		10 mg/kg QD (n=17)	
	No. of Samples	Concentration (μg/mL)	No. of Samples	Concentration (μg/mL)
2	5	2.28 (0.90–3.27)	5	1.72 (0.65–1.92)
4	6	0.98 (0.36–1.55)	6	3.24 (2.11–12.2)
6	6	0.88 (0.33–1.41)	3	0.55 (0.20–3.12)
8	5	0.97 (0.53–1.28)	5	1.55 (0.92–4.03)

The plasma and MEE cefpodoxime concentrations at 5 mg/kg bid and 10 mg/kg qd as well as MEE/plasma cefpodoxime concentration ratios are plotted in Figures 1-3. Cefpodoxime levels ≥0.50 μg/mL were attained in the MEE of approximately 91% of the patients in the study. These levels exceed the minimum inhibitory concentration for the majority of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* isolates, the most common etiologic agents of acute otitis media. Approximately 73% of the MEE samples collected in this study had concentrations in excess of the MIC_{90} for penicillin-susceptible *Streptococcus pneumoniae* (0.05 μg/mL), *Haemophilus influenzae* (0.24 μg/mL), and *Moraxella catarrhalis* (0.63 μg/mL). The MEE/plasma cefpodoxime concentration ratio ranged from 0.14 to 12 and from 0.13 to 3.2 in the 5 mg/kg BID and 10 mg/kg QD groups, respectively. There were no differences in the MEE/plasma cefpodoxime concentration ratios between dose groups (p>.14), suggesting a similar extent of penetration for the two regimens.

Medical Officer's Note: An effective dosing regimen for otitis media would require drug concentrations in middle ear mucosa and fluids to exceed the MIC of the causative pathogen for at least 40-50% of the dosing interval (WA Craig: Pharmacokinetics and pharmacodynamics of antibiotics in otitis media, Pediatr Infect Dis J 1996;15:255-9).

Pharmacokinetic reviewer's Note: Limited plasma samples were collected from the subjects at either 2,4,6, and 8 hours. Theoretically, using the nonlinear mix effect model, population pharmacokinetic parameters such as clearance (CL) and volume distribution (V) and the intersubject and intrasubject variability can be estimated although only limited data is available(only two or three samples per individual). Using the Bayesian approach, the individual pharmacokinetic parameters can be extrapolated, therefore, the concentration vs time profile for each individual can be simulated and the information of time above MIC can be available..

In order to extrapolate the time above MIC information from the limited plasma concentration data, attemptshave been made to perform a population pharmacokinetic analysis. The plasma concentrations for each individual who received both 5 mg/kg or 10 mg/kg were plotted (Figure 4). The profile indicates that plasma concentrations are decreased with time but with very high

variability. The attempt of population pharmacokinetic analysis was not successful due to the following reasons:

1. *Only one plasma sample was collected for each individual. The intrasubject variability could not be identified although a population pharmacokinetic approach was applied;*
2. *The plasma samples were collected after 2 hours. It is known that the T_{max} after oral administration of cefpodoxime was about 2.5 hours. No absorption information was available;*
3. *From previous data (NDA50-674 and NDA 50-675), absorption rate constant (ka) and elimination rate constant are about 0.6 hr^{-1} and 0.2 hr^{-1}, respectively. Since the lack of absorption information, ka were fixed at 0.6,0.4,0.2 and 0.1 hr^{-1} and the goodness of fit was evaluated and compared. The results indicated when ka was fixed to 0.2 hr, the data could be best fitted. However, the estimated parameters (CL and V) were not reliable compared with the parameter obtained previously. The reason was that because the value of ka and ke were very similar, although ka was fixed, the estimation of elimination parameter was still very unstable since the confusion between ka and ke estimation (flip-flop phenomena).*

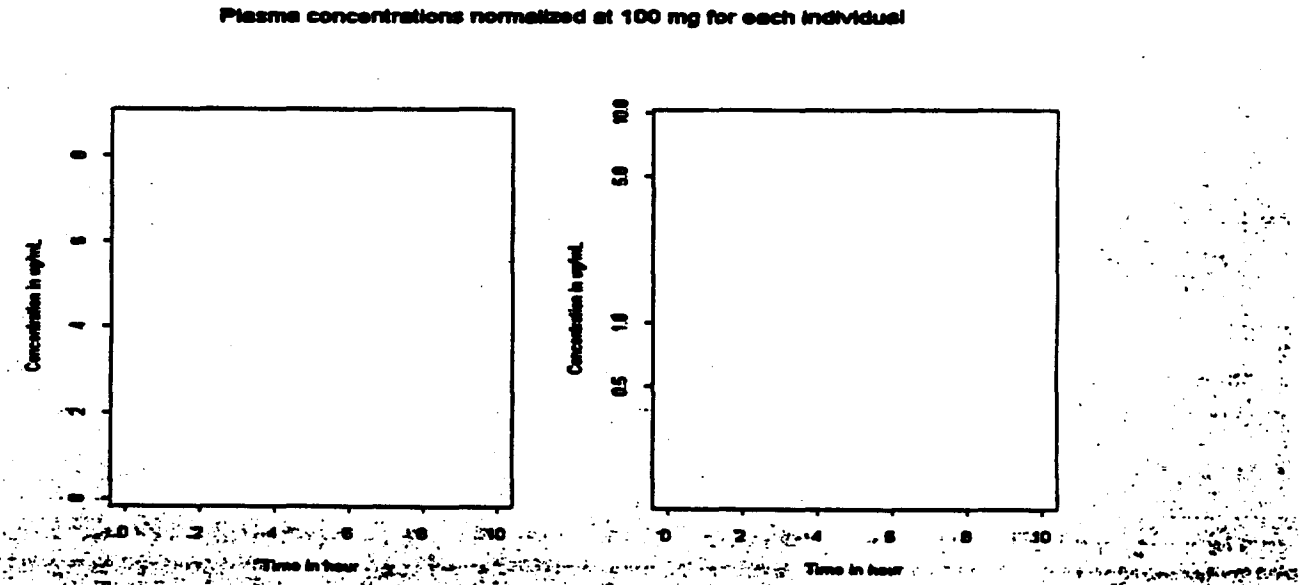

Figure 4

In the reference mentioned above (WA Craig: Pharmacokinetics and pharmacodynamics of antibiotics in otitis media, Pediatr Infect Dis J 1996,15:255-9), except the parameter of time above MIC, which is believed to be able to predict the efficacy for treatment of acute otitis media, another parameter, peak MEE/MIC ratio, is highly correlated with time above MIC. From nonlinear regression analysis it appears that an MEE/MIC ratio of between 3.2 and 6.3 correlates with 80% to 85% bacterial eradication. In this study, the MEE samples were collected at about 2, 4, 6, and 8 hours. From the MEE concentration vs time profile, it was observed that the peak concentration occurred at about 2 and 4 hours when 5 and 10 mg/kg was given to patients, respectively. Only five and six peak concentration samples were collected at doses of 5 and 10 mg/kg, respectively. The concentrations are listed in the following tables.

The MEE peak concentrations and the MEE/MIC ratio at dose of 5 mg/kg

MEE peak concentration at about 2 hours	*MEE/MIC*		
(μg/mL)	*S. pneumoniae*[1]	*H. influenzae*[2]	*M. catarrhalis*[3]
1.96	39.2	8.2	3.1
2.70	54.0	11.3	4.3
0.89	17.8	3.7	1.4
3.27	65.4	13.6	5.2
2.28	45.6	9.5	3.6

The MEE peak concentrations and the MEE/MIC ratio at dose of 10 mg/kg

MEE peak concentration at about 4 hours	*MEE/MIC*		
(μg/mL)	*S. pneumoniae*[a]	*H. influenzae*[b]	*M. catarrhalis*[c]
2.20	44.0	9.2	3.5
12.22	244.4	50.9	19.4
2.11	42.2	8.8	3.3
4.07	81.4	17.0	6.5
2.40	48.0	10.0	3.8
6.04	120.8	25.2	9.6

a. MIC_{90} for penicillin-susceptible *Streptococcus pneumoniae* is 0.05 μg/mL;
b. MIC_{90} for *Haemophilus influenzae* is 0.24 μg/mL;
c. MIC_{90} for *Moraxella catarrhalis* is 0.63 μg/mL.

The results of MEE/MIC indicated that both regimens could be good for acute otitis media caused by S. pneumoniae and H. influenzae but some patients may not response to the treatment of Vantin® at 5 mg/kg due to the low penetration of Vantin® into middle ear effusion. However, due to the limited sample size, the statistical analysis may not be reliable.

4. DISCUSSION

Plasma cefpodoxime concentrations in pediatric patients with acute otitis media were similar to those previously reported in noninfected pediatric patients and in patients with chronic otitis media after a single oral dose. However, patients with acute otitis media had higher MEE drug concentrations than patients with chronic otitis media who received a single 5 mg/kg or 10 mg/kg dose[i,ii], suggesting better drug penetration during the infectious than noninfectious period.

5. CONCLUSIONS

Cefpodoxime reaches clinically relevant levels in MEE following dosing with either 5 or 10 mg/kg in pediatric patients with acute otitis media. These findings support the clinical use of cefpodoxime in treating acute otitis media.

6. ASSAY VALIDATION:

7. RECOMMENDATION:

The study is acceptable from pharmacokinetic point of view. Cefpodoxime reaches clinically relevant levels in MEE following dosing with either 5 or 10 mg/kg in pediatric patients with acute otitis media.

/S/ 7-9-98

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RD/FT initiated by F. PELSOR, Pharm.D., Team Leader /S/ 7/13/98

cc:
Division File: NDA 50-675
HFD-520 (R. Viraraghavan, MO)
HFD-520 (C. DeBellas, CSO)

HFD-880 (Division File)
HFD-880 (F. Pelsor, TL)
HFD-880 (J. Zheng, Reviewer)
CDR (attn: B. Murphy)

[i] Kearns GL, Darville T, Wells TG, Jacobs RF, Hughes GS, Borin MT. Single dose pharmacokinetics of cefpodoxime proxetil in infants and children. Drug Invest 1994;7:221-33

[ii] Borin MT, Ryan KK, Hughes GS. Cefpodoxime concentrations in plasma and non-acute middle ear effusions after single-dose administration of cefpodoxime proxetil (P/1140/0035). Pharmacia & Upjohn Technical Report 7215-94-035, 23 November 1994

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Figure 1. Plasma and MEE Cefpodoxime Concentrations: 5 mg/kg bid

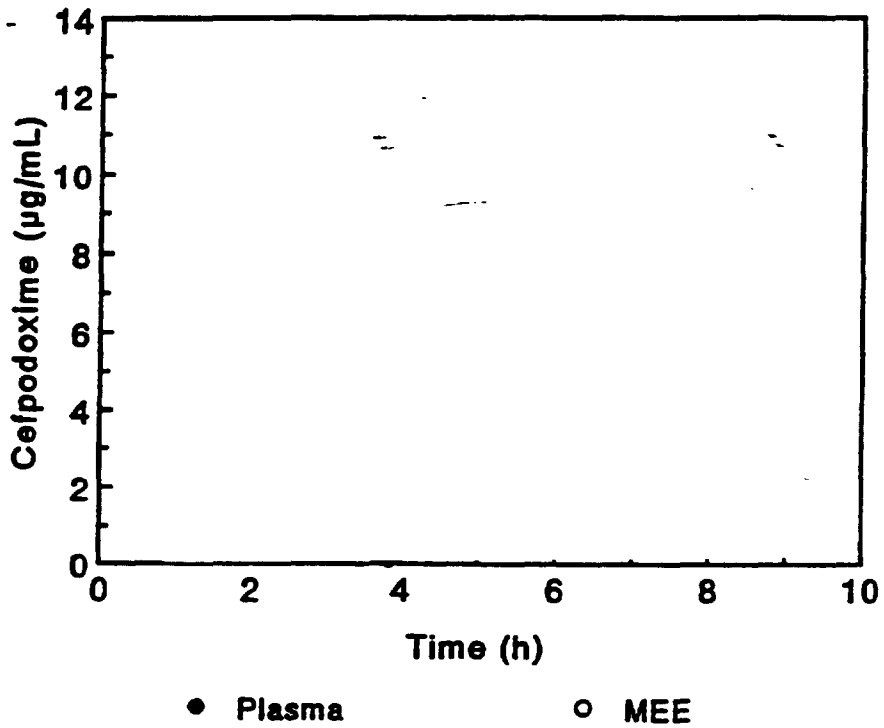


Figure 2. Plasma and MEE Cefpodoxime Concentrations: 10 mg/kg qd

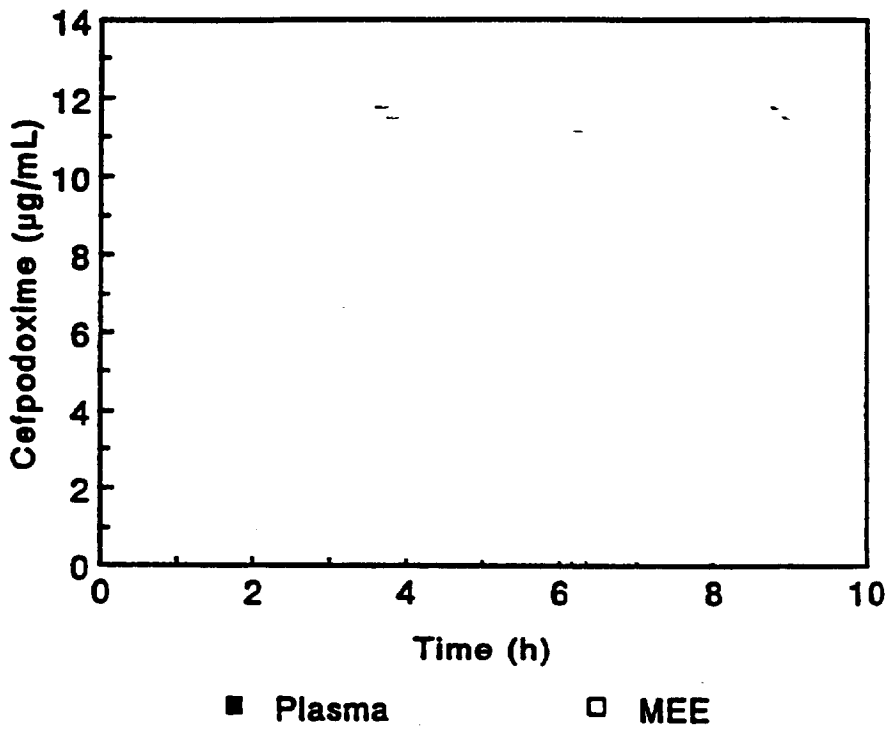
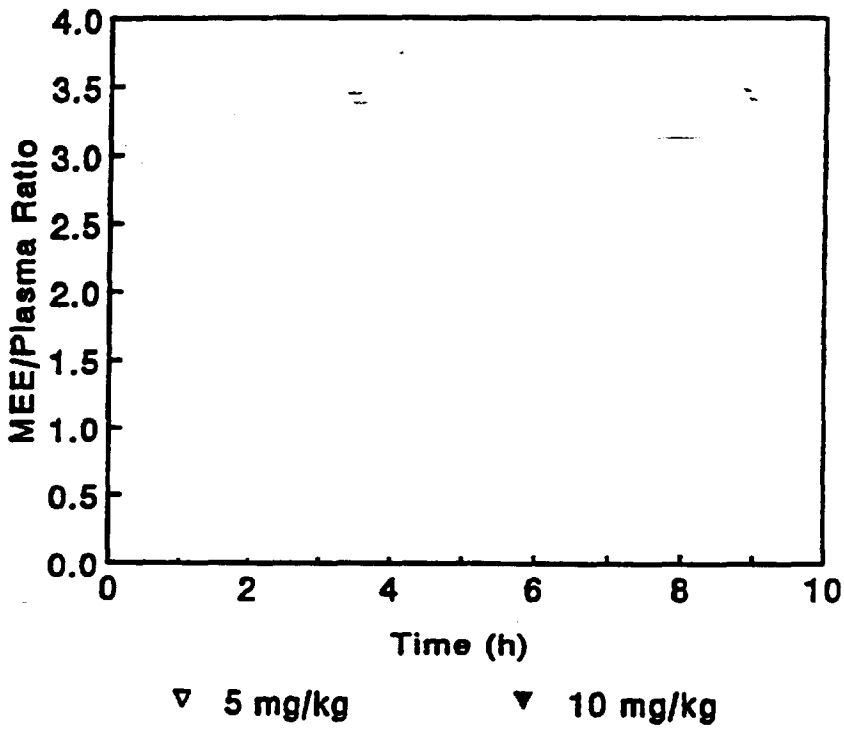


Figure 8. MEE/Plasma Cefpodoxime Concentration Ratios



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M/1140/0116: VANTIN MRE STUDY IN PEDIATRIC PATIENTS WITH AOM
DATA LISTING: AGE=YEAR, DOSE=MG, WEIGHT=KG, TIME=HOUR, CONC=MCG/ML
RESULTS FOR EVALUABLE PATIENTS

TREATMENT=A

OBS	GROUP	SUBJECT	AGE	WEIGHT	DOSE	TIME	CONC	TIME	CONC	CONCURRAT	TIME	CONC	CONCURRAT
1	1	102	6.4	21.1	104	2.26	3.17	.	.		2.17	1.96	
2	1	110	0.9	8.4	42	2.25	3.67	2.26	2.70		.	.	
3	1	110	2.4	13.2	66	2.17	2.57	.	.		2.25	0.09	
4	1	226	9.6	18.6	94	2.27	3.64	1.93	3.27		2.02	2.26	
5	2	103	1.1	10.3	52	4.42	2.48	4.25	0.35		.	.	
6	2	116	1.1	9.8	44	4.08	2.44	4.08	1.13		4.17	0.07	
7	2	205	2.4	13.6	66	4.27	1.75	.	.		4.17	0.43	
8	2	217	0.5	8.0	40	4.97	1.49	4.72	1.55		.	.	
9	2	237	2.7	11.8	59	3.85	0.89	4.92	1.10		.	.	
10	3	104	3.8	16.8	84	5.03	1.95	.	.		6.00	1.01	
11	3	206	2.6	12.9	64	6.13	0.67	5.97	0.79		6.08	0.97	
12	3	212	0.6	8.6	42	6.72	0.79	6.67	1.14		6.68	0.33	
13	3	218	1.7	12.6	64	5.53	0.42	.	.		5.68	0.50	
14	4	106	6.4	27.9	140	8.25	0.42	.	.		8.08	1.16	
15	4	111	10.2	40.8	200	7.75	0.72	8.25	0.53		.	.	
16	4	115	1.4	11.5	58	8.00	0.69	.	.		8.17	1.28	
17	4	1204	0.6	12.2	60	8.25	0.29	8.17	0.61		8.00	0.97	

TREATMENT=B

OBS	GROUP	SUBJECT	AGE	WEIGHT	DOSE	TIME	CONC	TIME	CONC	CONCURRAT	TIME	CONC	CONCURRAT
18	1	101	4.4	17.7	176	2.50	5.30	.	.		2.50	1.92	
19	1	112	1.4	10.6	106	2.92	2.36	.	.		2.50	1.79	
20	1	114	2.4	11.8	118	2.00	5.00	2.17	0.65		.	.	
21	1	115	1.9	10.0	100	2.17	7.04	.	.		2.33	1.72	
22	1	220	3.0	16.1	160	2.08	7.16	.	.		2.30	1.49	
23	2	108	0.9	9.0	100	4.17	4.25	.	.		4.25	2.20	
24	2	208	1.9	10.0	100	4.70	3.01	4.80	12.22		.	.	
25	2	224	3.5	23.7	238	4.00	5.20	4.03	2.11		.	.	
26	2	225	1.3	11.5	116	4.20	3.97	4.28	4.07		4.40	2.40	
27	2	227	4.2	19.2	192	4.17	5.63	.	.		4.25	6.04	
28	3	105	0.6	8.8	88	6.50	1.55	.	.		6.25	0.20	
29	3	109	1.6	21.0	126	6.05	2.35	.	.		6.25	3.12	
30	3	209	0.7	9.8	98	6.33	1.64	6.08	0.55		.	.	
31	4	117	0.7	10.5	102	8.08	1.21	8.17	1.55		.	.	
32	4	207	0.9	7.9	78	8.50	0.62	8.43	0.92		8.20	1.30	

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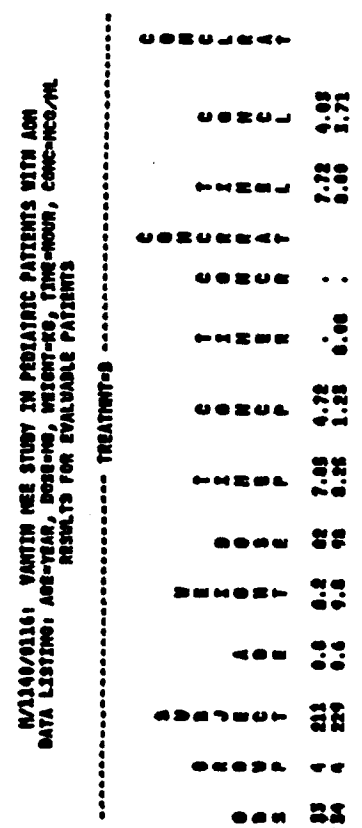

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TEXTBOOK OF PEDIATRIC INFECTIOUS DISEASES

THIRD EDITION VOLUME I

W. B. SAUNDERS COMPANY
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Philadelphia London Toronto Montreal Sydney Tokyo

with an appropriate aminoglycoside should be considered when otitis is caused by *P. aeruginosa*. For the duration of ... v, the patient should be advised to avoid showers ... cessive exercise. Severely infected external auditory ... may require drainage of abscesses that may be present. This should be done only after 24 hours of antibiotic coverage.

Fungal disease is best managed by careful cleansing and treatment of the canal by the physician once a day for 3 days with *m*-cresyl acetate.[14] Other treatment regimens include sulfanilamide powder insufflated into the canal to form a thin layer. Usually one treatment is sufficient.[7] Gentian violet, Burow solution, 3 per cent iodochlorhydroxyquin (Vioform), clotrimazole (Lotrimin) drops, and Tolnaftate may also be effective.[4, 10]

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15

OTITIS MEDIA

Ralph D. Feigin, Mark W. Kline, Susan R. Hyatt, and Kenneth L. Ford III

The term *otitis media* denotes inflammation of the mucoperiosteal lining of the middle ear. Otitis media may be acute, with suppurative middle ear infection of relatively sudden clinical onset, or chronic. The term *chronic otitis media* encompasses several suppurative or nonsuppurative conditions of insidious clinical onset, including otitis media with effusion (secretory otitis media). Complications of otitis media occur when there is extension of inflammation and infection beyond the mucoperiosteal lining of the middle ear (e.g., mastoiditis or epidural abscess).

INCIDENCE AND EPIDEMIOLOGY OF ACUTE OTITIS MEDIA

Acute otitis media is one of the most common infectious ...ses of childhood. In Boston, Teele and associates[143] ... that approximately 33 per cent of pediatric office visits ...ness of any kind were attributable to acute otitis media ... otitis media with effusion. The same group of investigators reported that, by 1 year of age, 62 per cent of children had at least one episode of acute otitis media, and 17 per cent had three or more episodes.[143] By 3 years of age, greater than 80 per cent of children had at least one episode of acute otitis media, and 46 per cent had three or more episodes. The peak incidence rate of disease occurred during the latter half of the first year of life. A similar preponderance of cases of acute otitis media during the first or second year of life with a decline in incidence rate thereafter has been reported by investigators from locations as diverse geographically as Finland,[124, 149] Sweden,[46] Cleveland,[98] Huntsville,[44] and Galveston.[14]

The frequent occurrence of otitis media in otherwise healthy infants is in part a reflection of the fact that the eustachian tube of the young child is shorter, wider, straighter, and more horizontal than that of the older child. Thus, organisms from the nasopharynx reach the middle ear more readily than they do in older individuals. The mucosa of the eustachian tube becomes hyperemic and edematous, resulting in its obstruction.

Acute otitis media, like most bacterial infections of infancy, appears to occur more commonly in boys than in girls.[149] In addition, there may be a genetic predisposition to acute otitis media in some cases. Particularly high rates of the disease have been observed among Eskimos,[72, 124, 125] American Indians,[153] and in cases where there is a sibling history

of otitis media.[47, 148] Otitis media is almost universal among children with cleft palate.[116, 118]

Studies in both the United Kingdom and the United States demonstrate seasonal variation in the occurrence of acute otitis media. The pattern within a period of a year is sinusoidal, with the peak incidence in December through March and lowest incidence in July through September.[88, 104, 138] These findings do not correlate with general climatic conditions, since the United States studies were performed in Texas and Washington, D.C. and the United Kingdom study in northern England. The incidence, however, coincides with the peak incidence of respiratory infections in both countries.

Other implicated factors in a predisposition to acute otitis media include lower socioeconomic group status,[102] bottle feeding in the horizontal position,[10] bottle feeding *versus* breast feeding,[4, 33, 138, 145] day care center attendance,[89, 125, 157, 172] and atopy.[159] Children who are "otitis-prone" (six or more episodes of acute otitis media) usually have two characteristics in common[64, 148]: (1) an initial episode of otitis media during the first 6 months of life, and (2) initial infection with *Streptococcus pneumoniae*.

ETIOLOGIC AGENTS

Numerous investigators have studied the etiologic agents of otitis media in children. Most studies have concentrated on bacterial pathogens in children between 1 month and 6 years of age. The etiologic role of viruses, *Mycoplasma*, and *Chlamydia* has only recently been defined.

Bacteria may be isolated from middle ear fluid in about two-thirds of patients with acute otitis media. The isolates obtained by needle tympanocentesis in nine separate studies of acute otitis media in children are shown in Table 15–1.[23, 40, 41, 47, 61–63, 71, 108, 109, 147] The most common bacterial pathogen recovered from the middle ear of patients in each study was *Streptococcus pneumoniae*, which was found in 26 to 50 per cent of cases. *Haemophilus influenzae* was also isolated with great frequency, varying from 12 to 27 per cent of cases. *Moraxella catarrhalis* (previously *Branhamella catarrhalis*) accounted for about 7 per cent of cases of acute otitis media in the studies cited. However, several recent reports suggest an increasing rate of isolation of *M. catarrhalis* approaching 20 to 30 per cent.[78, 147, 149] Concomitant isolation of two or more organisms occurs in up to 7 per cent of cases. Disparate results of cultures in children with bilateral acute otitis media occur in about 20 per cent of cases.[120]

Relatively few pneumococcal serotypes are responsible for most otitis media caused by *S. pneumoniae*. Studies of about 2000 children indicate that 85 per cent of cases are caused by the following serotypes: 19, 23, 6, 14, 3, 18, 4, 15, 9, 7, and 1.[94, 70] All of these serotypes are included in the currently available pneumococcal vaccines.

Most *H. influenzae* isolated from middle ear fluid are nontypable. Our own experience reveals that type b *H. influenzae* accounts for only 36 per cent of episodes of otitis media attributed to *H. influenzae*, and other investigators have reported as few as 9 per cent type b *H. influenzae* isolates from patients with this disease.[42, 43, 151] About one-quarter of children with otitis media due to *H. influenzae*, type b have concomitant bacteremia or meningitis.[56] Previously thought to be limited to preschool children, *H. influenzae* now is known to cause otitis media in older children and adolescents.[140, 141]

Thirty per cent or more of *H. influenzae*[56] and at least 75 per cent of *M. catarrhalis*[78, 147, 149] isolated from middle ear fluid produce beta-lactamase, which has important implications in the therapy of acute otitis media.

Several clinical situations warrant special consideration: (1) the occurrence of purulent conjunctivitis in association with acute otitis media (conjunctivitis-otitis syndrome) usually is attributable to nontypable *H. influenzae*[14, 20]; (2) acute otitis media is common among children hospitalized in intensive care units, and the bacteriology is more reflective of the hospital environment than of the community[26]; (3) early recurrences of acute otitis media (within 1 month) represent reinfection more often than relapse[25]; and (4) children with tympanostomy tubes may develop acute otitis media caused by organisms more typical of otitis externa (e.g., *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *S. epidermidis*).[137]

The bacteriology of otitis media with effusion mimics that of acute otitis media.[30, 31, 108, 120, 144, 154] In contrast, the etiologic agents of chronic suppurative otitis media are quite distinct. Common isolates include *P. aeruginosa*, *S. aureus*, and enteric gram-negative bacilli.[74, 114] Mixed aerobic and anaerobic bacterial infection is common, particularly when cholesteatoma is present.[21, 114] *Mycobacterium tuberculosis* is a rare, but important cause of chronic suppurative otitis media.[173]

In general, there is a poor correlation between qualitative cultures of the nose and throat and those of the middle ear in patients with otitis media. Several investigators have noted quantitative differences in the nasopharyngeal flora of patients with and without otitis media, and these differences may play a role in the pathogenesis of middle ear disease. Long and colleagues[88] described a significant association between the recovery of abundant *H. influenzae* (≥ 50 per cent total colony count) from the nasopharynx and bacteriologically confirmed otitis media. An additional finding was that a semiquantitative nasopharyngeal culture was sensitive and specific in predicting the middle ear pathogen. Several investigators have reported similar nasopharyngeal colonization rates for *S. pneumoniae* in ill and healthy children.[23, 87, 88] Gray and colleagues[54] have correlated the occurrence of acute otitis media with nasopharyngeal acquisition of new serotypes of *S. pneumoniae*.

Sterile cultures are noted following needle tympanocentesis in about one-third of patients with acute otitis media. This in part may reflect limitations of bacterial culture methods, because antigen detection tests often indicate the presence of pneumococcal capsular polysaccharide in sterile middle ear fluid.[42, 43] Recent studies have focused on the role of viruses, *Mycoplasma*, and *Chlamydia* in acute otitis media. Epidemiologic data support an association between viral respiratory infection and the occurrence of acute otitis media.[57] Infection with respiratory syncytial virus, influenza viruses, and adenoviruses was associated with a greater risk

TABLE 15–1. Bacterial Etiology of Acute Otitis Media in Children* Based Upon Cultures Obtained by Needle Tympanocentesis

Total patients studied	2692
Total episodes of otitis media	2933
Specific bacterial isolates	
Streptococcus pneumoniae	880 (30.0%)†
Haemophilus influenzae	635 (21.7%)
Moraxella catarrhalis (previously *Branhamella catarrhalis*)	198 (6.8%)
Beta-hemolytic streptococci, group A	57 (1.9%)
Enteric bacteria	23 (0.8%)
Staphylococcus aureus	26 (0.9%)
Staphylococcus epidermidis	10 (0.3%)
Pseudomonas aeruginosa	7 (0.2%)
Other	63 (2.1%)

*Summary of 12 studies, children aged 1 month to 6 years.

†Does not equal 100 per cent because many aspirates, in all studies, grew no bacteria.

of otitis media than was infection with other viruses. In contrast to this epidemiologic association is the low viral recovery rate from middle ear fluid in patients with otitis media. A virus was isolated from only 29 of 663 (4.4 per cent) specimens obtained by tympanocentesis and reported by Klein and Teele.[77] A higher virus identification rate has been reported using culture and antigen detection in middle ear fluid.[28, 76, 124] Isolates have included respiratory syncytial virus, influenza viruses, adenoviruses, parainfluenza viruses, enteroviruses, and rhinoviruses. Concomitant isolation of viral and bacterial pathogens from middle ear fluid appears to be common.[28, 124]

A role for *Mycoplasma pneumoniae* in the etiology of otitis media was suggested by the observation of myringitis in nonimmune adults inoculated with the organism.[129] A subsequent study attempted to isolate the organism from middle ear fluid in patients with otitis media but was successful in only 1 of 771 patients.[77] This study suggests that mycoplasmas are not a frequent cause of acute otitis media.

Chlamydia trachomatis has been implicated as a cause of acute otitis media. Tipple and colleagues[105] recovered *C. trachomatis* from 3 of 11 middle ear specimens in infants with chlamydial pneumonia. Each of the patients had clinical findings consistent with acute otitis media. More recently, *C. trachomatis* was isolated from 3 of 26 unselected patients with otitis media.[27] In contrast, Hammerschlag and associates[58] failed to recover the organism from any of 68 patients with otitis media. Further study will be necessary to determine the exact prevalance of *Chlamydia* in middle ear fluid and its role in acute otitis media or otitis media with effusion.

Bacteriology in the Neonate

Clinical investigators have performed needle tympanocentesis to isolate bacterial pathogens causing otitis media in the first 6 weeks of life. A total of 169 infants were included in four of these studies.[11, 13, 105, 106] Bacteria were isolated from middle ear fluid in 68 per cent of cases. As in older children, *S. pneumoniae* and *H. influenzae* were the most frequently isolated organisms. Other than the more frequent occurrence of disease caused by gram-negative enteric organisms (about 20 per cent of cases) and the occasional isolation of other neonatal pathogens (e.g., group B *Streptococcus*), the bacteriology of otitis media in this age group was similar to that in older children.

Persistent otitis media beginning in the neonatal period that fails to resolve spontaneously or with antibiotic therapy should suggest the possibility of a tuberculous etiology.

PATHOGENESIS AND PATHOLOGY

Colonization of the nasopharynx with pathogenic bacteria (e.g., *S. pneumoniae* or *H. influenzae*) is thought to be the initial event in the pathogenesis of acute otitis media.[52] Concomitant viral infection induces respiratory epithelial injury, leading to eustachian tube inflammation and obstruction.[123] This, in turn, causes impairment of middle ear drainage.[18] Acute otitis media develops when there is reflux, aspiration, or insufflation of nasopharyngeal bacteria through the eustachian tube into the middle ear.[17] Bacteria also may reach the middle ear hematogenously or by direct extension through a perforated tympanic membrane, but these routes of infection are unusual. There is experimental evidence that virus-induced impairments in neutrophil migration and bacterial killing also may be important in the pathogenesis of acute otitis media.[2]

PATHOPHYSIOLOGY

Tympanic Membrane

In the presence of otitis media, changes in the tympanic membrane occur quite rapidly. The presence of congested blood vessels, edema (which obscures normal landmarks), and bulging or sagging of Shrapnell membrane indicate not only a myringitis (inflammation of the tympanic membrane) but a deep-seated pathologic condition (otitis media, mastoiditis). Blebs that appear on the surface epithelium are a consequence of edema or hydropic degeneration and are usually associated with conditions of the external ear (myringitis bullosa or external otitis).

Inflammation may occur on either side or on both sides of the fibrous layer (middle layer) of the drum. In severe cases, infection may involve the fibrous layer itself. The membrane becomes thick as a result of edema and the increase of polymorphonuclear leukocytes. The fibrous layer usually is most resilient. All three layers of the drum may undergo dissolution, usually from septic necrosis and thrombophlebitis of tympanic veins, with a resulting perforation. Usually this heals after the infection subsides. In the process of healing, metaplasia of the epithelium, hyaline degeneration, and calcium deposition and scar formation may be noted. Occasionally, when a perforation is close to the margin of the annulus or occurs in Shrapnell membrane, the skin of the external auditory canal and the surface squamous epithelium of the tympanic membrane may grow through the aperture and invade the middle ear. (Shrapnell membrane contains no middle fibrous layer.) This eventually leads to formation of a cholesteatoma (epidermal inclusion cyst). In other cases, even if the perforation heals, a differential in air pressure across the tympanic membrane caused by malfunction of the eustachian tube may result in eventual resorption of air in the middle ear cavity. This causes retraction of Shrapnell membrane or the atrophic scar into the middle ear or mastoid attic. The growth of a cholesteatoma can also be initiated in this way.

Eustachian Tube

The eustachian tube is about 3.8 cm long in the adult. It opens in the fossa of Rosenmüller and then extends upward, backward, and laterally to open in the upper anterior wall of the tympanic cavity (protympanum). In the child, the tube is shorter, straighter, and more patulous. The eustachian tube is composed of two portions: the cartilaginous portion extending into the nasopharynx and the bony portion originating in the middle ear. The upper third of the tube is bony; the middle ear opening is the widest; and the medial end (the part joining the cartilaginous eustachian tube) or isthmus is the narrowest (2.4 mm and 0.3 mm). This bony canal lies below the semicanal for the tensor tympani muscle. Pneumatic peritubal air cells arising from the middle ear cavity surround it and can extend to the petrous apex. The internal carotid artery lies anteromedial to this region.

The lower two-thirds of the eustachian tube is a narrow, slitlike, fibrocartilaginous passage. It makes a 160-degree angle with the bony portion at its junction. The cross section of the tube looks like a shepherd's crook, with a cartilaginous superior and medial surface and a fibrous lateral surface.

Three muscles are associated with the eustachian tube. The tensor tympani muscle lies on top of it; the levator palatini muscle lies under it; and the tensor palatini muscle arises on the tube, scaphoid fossa, and spine of sphenoid, then courses around the hook of the hamulus and forms an

aponeurosis with its mate (from the opposite side) in the soft palate. This is the only muscle that directly acts on the eustachian tube.

The eustachian tube area, protympanum, and hypotympanum are lined by ciliated columnar epithelium with goblet cells or secretory cells (respiratory epithelium, Schneiderian epithelium). The epithelium is continuous with the upper airway system and paranasal sinuses. This area also contains a well-defined subepithelial connective tissue layer, which thins out and may be absent nearing the antrum and mastoid air cell system. The movement of the cilia and "mucous blanket" is always toward the eustachian tube and nasopharynx. Because of this close relationship between the protympanum and the upper airway, most observers feel that otitis media generally arises secondary to infections elsewhere, usually of the upper airway. The tube is surrounded by a plexus of lymphoid channels. It has an arterial supply from a branch of the middle meningeal or accessory meningeal artery and from branches of the artery of the pterygoid canal. The nerve supply is from the tympanic plexus (IX) (sensory) and sphenopalatine ganglion (sympathetics and parasympathetic palatine fiber).

Whereas the bony portion is rigid and patulous, the medial two-thirds is normally held closed by elastic recoil of the fibrocartilaginous tissue. Thus, contraction of the tensor palatini muscle that inserts in the anterolateral wall opens the tube on swallowing. On the average, the adult swallows once per minute awake and once every 5 minutes asleep. Suckling children usually swallow five times per minute.

Mucus and ciliary action flow from the mesotympanum to the eustachian tube. The eustachian tube acts as a unidirectional valve that favors outflow from the middle ear to the pharynx. Reverse flow can be induced by an increase in pressure in the nasopharynx (Valsalva, barotrauma). Thus, during occlusion of the eustachian tube, the oxygen and CO_2 (and other gases) are absorbed from the middle ear by diffusion into the rich vasculature, and a negative pressure is created.

A patent eustachian tube is a critical prerequisite for subsidence of middle ear disease. Obstructions in the bony opening in the protympanum are surgically correctable; obstructions at the isthmus and the cartilaginous portion are not.

In chronic inflammatory states, osteitis develops in pneumatized or partially pneumatized bones, and they are the only mastoids that can coalesce; i.e., coalescent mastoiditis. Chronic inflammation of diploic bones containing marrow spaces and vascular channels produces osteomyelitis.

Chronic inflammation of sclerotic bones results in polypoid mucosal hyperplasia, proliferating granulation tissue, and chronic suppuration. These produce polypoid granulation tissue and sequestration.

CLINICAL PRESENTATION

Acute otitis media is usually self-limiting and runs a characteristic clinical course.

Tubotympanitis

Tubotympanitis is the earliest stage of acute otitis media and is produced by eustachian tube occlusion. Retractions, a diminished light reflex, and poor motility (with application of external pneumatic pressure) of the tympanic membrane are noted. A serous effusion may be present. The handle of the malleus is in a more horizontal position and the lateral process of the malleus is more prominent. At this stage, the light reflex may completely disappear and the drum may be less translucent or opaque. The nasopharyngeal examination demonstrates inflammation of the torus tubarius (eustachian tube orifice) in the fossa of Rosenmüller. The patient will experience muffled hearing, and if audiometric testing is performed a conductive hearing loss, usually in the low frequency range, will be noted. Children may pull at their ears because of the sensation of fullness and general discomfort.

Stage of Hyperemia

At this stage, the patient experiences generalized symptoms of malaise, fever (> 39° C or 102° F), and earache. Injection of vessels around the margin of the tympanic membrane and adjoining external auditory canal skin is noted. Prominent vessels are seen superiorly from the external auditory canal to the handle of the malleus, the manubrium (i.e., the vascular strip). The tympanic membrane landmarks are still present, but the drum is dull and not translucent. The tympanic membrane moves but not without pain. A sensation of fullness and pain associated with muffled hearing persists.

Stage of Exudation

This presuppuration stage is characterized by high fever, nausea and vomiting, loss of appetite, malaise, generalized muscle pain, nasal congestion, a flushed face, and occasional diarrhea and restlessness. Rarely, meningismus may be noted. Pain may be so severe as to awaken the infant from sleep or to prevent sleep entirely and may be accentuated by swallowing. The tympanic membrane, particularly the pars flaccida, is red in appearance. The pars tensa is thick, convex, and bulging. The usual landmarks and the light reflex are lost. A conductive hearing loss at both low and high frequencies may be noted. Occasionally, there may be tinnitus, which is usually pulsatile and throbbing and synchronous with the pulse rate. In young children there may be swelling of the posterosuperior aspect of the adjacent external auditory canal skin.

Stage of Suppuration

Generalized systemic symptoms and toxicity are now maximal. Temperatures may reach very high levels (40° C or 104° F). Pain in the ear is throbbing and pulsatile. Tinnitus is accentuated. The drum is convex, tense, bulging, and whitish in appearance; motility is lacking. Injected, hyperemic vessels are seen in the periphery. There may be small yellowish areas of necrosis on the tympanic membrane. The handle of the malleus is usually in a vertical position, but not very visible. Conductive hearing impairment is greater in both high and low frequencies. There is tenderness over the mastoid (Macewen triangle), suggesting a well-advanced otitis media.

Usually, the tympanic membrane ruptures in the pars tensa with a gush of purulent material, blood, or yellowish serosanginous fluid from the ear. The perforation is generally small and does not enlarge. (This fact helps to differentiate acute otitis media from acute necrotizing otitis media, tuberculous otitis media, or an acute recurrence of otitis media in a chronically infected ear.) Once the pus is drained, general symptoms of toxicity subside.

Stage of Acute Mastoiditis

Signs and symptoms of acute mastoiditis may be subtle, especially if there is partial antibiotic treatment or rupture

of the tympanic membrane. Mastoiditis may be present and progressive despite rupture of the tympanic membrane. The presence of pain (usually nocturnal) and copious purulent discharge associated with a low-grade fever in a patient with acute otitis media suggest mastoiditis. Generally, the presence of profuse discharge from the ear for longer than 2 weeks after the tympanic membrane ruptures indicates mastoiditis. Usually there is mastoid tenderness over the mastoid tip and area of Macewen triangle and edema of the mastoid periosteum with or without postauricular pitting. The involved area is velvety, soft, and thick to palpation. The periosteum does not move over the bone. In the external auditory canal, there is sagging or bulging in the posterosuperior wall. Through the perforation one may see thickened polypoid mucosal projections with a wet, granular, friable mucosa. Occasionally a polyp may protrude through the perforation.

If the infection is trapped in the mastoid from poor drainage, generalized symptoms may reappear. The timing and the duration are more important than the severity of symptoms. This stage is treated by high doses of antibiotics and a simple mastoidectomy to drain trapped purulent material, similar to incision and drainage of any soft tissue abscess.

Relief of pain and other symptoms is usually immediate following drainage through the tympanic membrane. Purulent drainage stops in 1 or 2 days. Usually a dry perforation in the anteroinferior quadrant of the tympanic membrane is noted with no hyperemia. The outer squamous epithelium sheds in sheets and the desquamated products fill the external auditory canal. If the tympanic membrane is intact, it returns to normal, with cessation of inflammation, normal mobility, and normal light reflex reappearing in that order. If the tympanic membrane perforates, it heals last, usually in 3 weeks to 6 months after the onset of infection.

SPECIFIC DIAGNOSIS

The diagnosis of acute otitis media can be made readily by an adequate history and physical examination (with particular reference to inspection of the tympanic membranes).

The general symptoms of acute otitis media are often preceded or masked by predisposing infections such as rhinitis, pharyngitis, or tonsillitis. Occasionally they may be preceded by generalized viral exanthematous illnesses or other diseases such as scarlet fever. Local symptoms usually direct attention to the ear quite early, except in infants or neonates in whom head rolling, tugging at the ear, and increased fretfulness may be the sole manifestations. Older children will complain of a sense of fullness or deafness in the ear, often accompanied by mild tinnitus.

The appearance of the tympanic membrane is most important. All wax, debris, and discharge must be removed for complete visualization of the tympanic membrane. Injection of the tympanic membrane may be observed in an agitated child. This is not evidence, however, of otitis media in the absence of other findings (absent light reflex, decreased motility, retraction, or bulging of the tympanic membrane). In addition, one must differentiate the acute phase of otitis media from an acute systemic illness in a patient with chronic otitis media.

Otoscopy

Adequate magnification and a brilliant source of illumination must be provided for suitable ear inspection by otoscopy. All debris in the canal should be removed mechanically or by irrigation with room temperature saline (only if the tympanic membrane is intact). To evaluate tympanic membrane mobility, one must occlude the external canal completely with a large ear speculum and use pneumatic otoscopy. In the presence of a bulging tympanic membrane this maneuver will elicit pain. Hypomotility of the drum results either from poor eustachian tube function or serum or pus behind the drum.

Tympanometry

Another way to measure the compliance of the tympanic membrane is by tympanometry (Fig. 15–1).[22,32,43,99,127] Under normal circumstances, the pressure in the middle ear is virtually the same as the external ambient pressure; the eustachian tube functions to equate middle ear pressure to atmospheric pressure. If for any reason there is a pressure differential across the tympanic membrane, stress will be applied to the drum. Middle ear compliance therefore varies as a function of the pressure differential across the tympanic membrane. Where there is blockage of the eustachian tube with no fluid in the middle ear, the tympanometry curve will have a shape similar to that of a normal tympanogram, but the point of maximal compliance will be shifted to the negative pressure side. This is because maximal compliance is reached when the tympanic membrane reaches a peak of compliance, i.e., when external canal pressure is reduced to the same level as in the middle ear.

If there is ossicular discontinuity or a flaccid or atrophic tympanic membrane, the drum is highly compliant, and a highly peaked tympanogram is obtained. The most clearly abnormal tympanograms are those obtained in the presence of fluid in the middle ear. These are characterized by three features:

1. The height of the curve is reduced, i.e., the middle ear has reduced compliance.
2. The curve and point of maximal compliance are shifted to the negative pressure side, i.e., eustachian tube blockage.
3. The curve is flat and has no definite peak, the most characteristic feature.

Tympanometry with the electroacoustic impedance bridge has proved to be a highly satisfactory method for detecting the presence of fluid in the middle ear cavity, especially in young children. An intact tympanic membrane is required

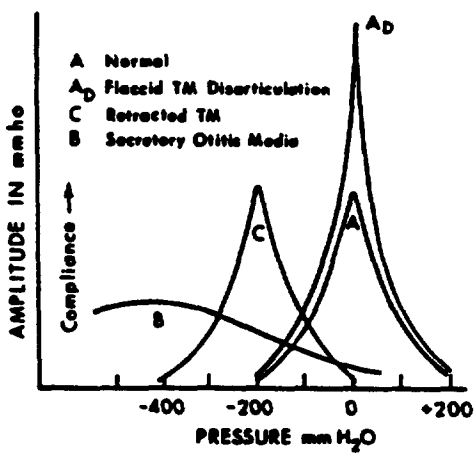

FIGURE 15–1. *Typical idealized tympanograms obtained with an intact tympanic membrane in certain specific middle ear conditions (Jerger 1970, Linden 1974 classification).*

for application of this technique. McCandless and Thomas[90] found a 93 per cent correlation between tympanometry and otoscopy findings and only a 61 per cent correlation between hearing screening tests and otoscopy in children. This has been confirmed by others.[22, 30, 45, 127]

Acoustic Reflectometry

Acoustic otoscopy has been suggested as a noninvasive and objective means for detecting the presence of middle ear fluid.[5, 99, 139] Unlike tympanometry, the instrument need not seal the auditory canal, and it can be effective even in the crying child. The acoustic otoscope measures the amount of sound reflected from the tympanic membrane. Sound reflection is increased by fluid in the middle ear. Studies comparing acoustic reflectometry with pneumo-otoscopy and tympanometry in the diagnosis of otitis media have met with variable results, but the technique appears to hold promise as an additional diagnostic tool.

Audiometric Tests

In addition to otoscopy and tympanometry, audiometric testing may be employed to measure auditory acuity and evaluate conductive hearing losses (Fig. 15–2).[113] Usually there is eustachian tube obstruction early in the clinical course of otitis media. This results in absorption of gases from the middle ear and drum retraction. The reduced compliance of the drum results in increased stiffness in the ossicular chain system. The audiogram reveals a low-frequency conductive hearing loss. As serous effusion appears and the middle ear fills up with serum and pus, the ossicular system has an increased mass applied to it and the audiogram flattens out, giving a high-frequency conductive hearing loss. Usually the discrimination and bone conductive thresholds are not affected.

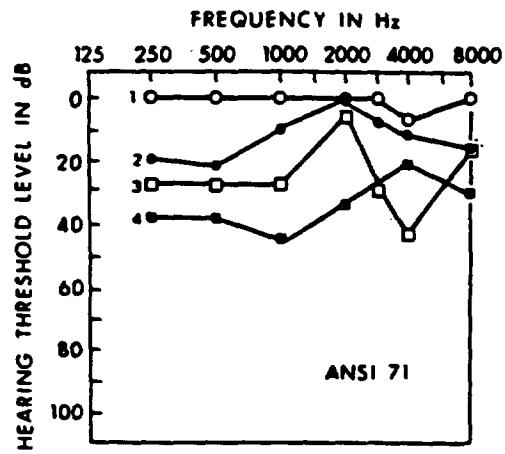

FIGURE 15–2. *Serial air conduction audiogram in a patient who developed eustachian tube malfunction and serous otitis media in the right ear. Curve 1 demonstrates the patient's normal hearing. Curve 2 demonstrates eustachian tube obstruction with a low-frequency air-bone gap, caused by retraction of the tympanic membrane without serous effusions, giving the ossicular system an increased stiffness. Audiograms 3 and 4 denote progressive serous effusion. Since the effusion masses against the ossicular chain, a high-frequency air-bone gap develops. The better hearing at 2000 Hz is a function of the natural resonance frequency in this particular temporal bone.*

Drainage Procedures

Drainage procedures may be required to obtain purulent material for culture. Pediatricians generally use *needle tympanocentesis*. Care must be taken to avoid the posterosuperior quadrant of the tympanic membrane. An aspirate performed incorrectly may cause permanent loss of hearing, bleeding, or other complications. Otolaryngologists generally perform a *myringotomy*, i.e., an incision into the anterior lower quadrant of the drum.[122] This is the most favorable location because (1) it is near the eustachian tube area, (2) it is in a safe zone where trauma will not disturb the ossicles, and (3) it will prevent complications such as cholesteatoma. Needle tympanocentesis and myringotomy do not alter tympanometric values, but aspiration of the effusion is followed by reversion of tympanometric values toward normal.

Radiography

Radiography can be employed to study otitis media. Generally changes in the temporal bone may be observed 10 to 14 days after infection has occurred. Mastoid radiographs may still show opacification or clouding during resolution of the disease process. Radiographic studies are important in the diagnosis and treatment of chronic otitis media and complications of acute or chronic otitis media. In questions of erosion of bone or central nervous system complications of otitis media, polytomography (Fig. 15–3) and computed tomography (Fig. 15–4) may be helpful.

DIFFERENTIAL DIAGNOSIS

The diagnosis of acute otitis media is usually made readily. At times, however, an accurate assessment is difficult. When external otitis or furunculosis of the external canal is present, it is difficult to visualize middle ear disease. In diseases of the external ear there is often a history of itching in the ear canal, pain elicited by manipulation of the pinna, and preservation of hearing. The presence of foreign bodies or cerumen in the external canal may impede a prompt diagnosis. Myringitis bullosa, an inflammation and bullous eruption on the outer layer of the drum, can also be confused with otitis media.

Usually the most difficult problem is differentiating acute otitis media from referred otalgia in infants. In theory, this should be no problem, because the tympanic membrane should appear normal in the latter. However, the child will often cry when examined, and hyperemia of the tympanic membrane will result. A "red drum" may also be produced by trauma, manipulation, or aggressive examination of the external canal. Hyperemia of the tympanic membrane may also be noted in children with mild upper respiratory tract infections. When these are associated with fever, a diagnosis of otitis media may be suggested.

Otalgia also may be associated with infections of the tonsils, adenoids, teeth, nasopharynx, hypopharynx, or larynx. Tumors in those regions can refer pain to the ipsilateral ear along the tenth cranial nerve. Lymphomas, leukemias, and rhabdomyosarcomas involving the palate, nasopharynx, or base of the skull will eventually occlude one or both eustachian tubes, producing serous effusions and otalgia.

Acute otitis media must be differentiated from an acute exacerbation of disease in a patient with chronic otitis media. Generally this can be done readily by adequate visualization of the tympanic membrane. A nonhealed perforation of longer than 2 weeks' duration, middle ear proliferating

FIGURE 15–3. *Posteroanterior polytomograph of a temporal bone. Arrow indicates area of bone destruction in the scutum (i.e., posterior superior aspect of the tympanic bone). In this case, the disease process was cholesteatoma and the malleus and incus are missing.*

granulation tissue, aural polyps, a 40 to 60 dB conductive hearing loss, or persistent foul-smelling discharge should alert the clinician to possible complications or chronic disease.

CHRONIC OTITIS MEDIA

The term chronic otitis media encompasses several entities ... are difficult to differentiate on clinical or pathologic grounds.[94, 144] The disease is often insidious, with few signs or symptoms except for hearing loss. Chronic inflammation of the middle ear may be locally destructive and may result in irreversible sequelae. The fluid behind the tympanic membrane has been described as serous, mucoid, transudative, exudative, or purulent. For our purposes, we will discuss two forms of chronic otitis media separately: (1) chronic suppurative otitis media and (2) otitis media with effusion, formerly known as secretory otitis media.

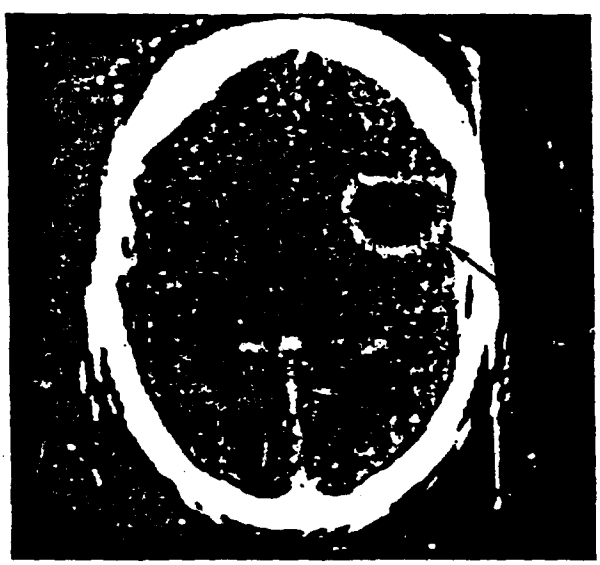

FIGURE 15–4. *Computerized tomogram of a right intracranial temporal lobe abscess secondary to right-sided otitis media and mastoiditis.*

Chronic Suppurative Otitis Media

Chronic suppurative otitis media presents a different problem of diagnosis and management than does the acute disease. The tympanic membrane, which mirrored beautifully the stages of acute otitis media, does not provide a completely accurate picture of chronic disease, the manifestations of which are extremely variable. Acute and chronic otitis media may not be related temporally, since the pathologic changes in the middle ear cleft are essentially different. Thus, the term *chronic* implies a pathologic process of insidious onset that is usually well established prior to the patient's current complaints. The classic symptoms of established chronic suppurative otitis media are *otorrhea* and *deafness* (some form of hearing loss). For purposes of discussion we have classified chronic suppurative otitis media as follows:

I. Tubotympanitis with the following:
   A. Permanent central perforation syndrome
   B. Persistent perforation and tympanic mucosal infection
      1. Tympanic type
      2. Tubotympanic type

II. Atticoantral disease with the following:
   A. Attic retraction—Shrapnell membrane disease
   B. Posterior marginal perforation of the drum and persistent granulation
   C. Cholesteatoma
   D. Chronic mastoiditis

III. End-stage disease
   A. Atelectatic ear
   B. Adhesive otitis media
   C. Tympanosclerosis

In this limited classification the ossicle has not been used as a criterion for staging chronic suppurative otitis media. It has been omitted intentionally to stress that ossicular destruction may occur with many conditions, including acute necrotization, bone resorption, cholesteatoma, and trauma. The physiologic classification of the ossicles is only of importance in the surgical approach to reconstruction of the middle ear.

We have omitted chronic eustachian tube obstruction and chronic secretory otitis media as complications. When these

occur they are probably related closely to tubotympanitis. As such, they may be the forerunners of otitis media.

Tubotympanic Disease

The involvement of the tubotympanic recess (the anterior part of the middle ear) by infection usually is classified as a benign form of otitis media. Presumably this means that complications of this form of disease are infrequent. This area is in direct continuity with the eustachian tube, which controls ventilation of the middle ear cleft and maintains equal pressure on both sides of the tympanic membrane. Involvement is characterized by a central perforation in the pars tensa, persistent or recurrent mucinous or mucopurulent discharge, alterations of the middle ear mucosa, variable eustachian tube malfunction, and mild to moderate conductive hearing loss.

This entity can be subdivided into the following:

PERMANENT PERFORATION SYNDROME. In this entity the eustachian tube functions well except when occluded (e.g., by upper respiratory infection, allergy diathesis, and so on). There is a permanent dry central perforation; the annulus and the manubrium of the malleus remain intact. The ossicular chain is usually normal, and conductive loss is secondary to tympanic membrane perforation. The mucosa of the middle ear loses its cilia, becomes cuboidal or squamous in nature, and forms more goblet cells (metaplasia). The disease has quiescent and acute stages. Recurrent infection of the mucous membrane produces a mucoid and mucopurulent discharge. The lining may become edematous and polypoid with formation of granulation tissue.

Treatment is medical, with appropriate antibiotics during the acute phase and topical antibiotics for chronic persistent mucosal infection. Restoration of eustachian tube function by removal of polyps or adhesions, and surgical closure of tympanic membrane perforation will result in a healthy ear.

PERSISTENT TYMPANIC MUCOSAL INFECTION SYNDROME. In this condition the eustachian tube functions well, but there is a large central perforation. The annulus may be exposed and the handle of the malleus may be missing or medially rotated. This is a permanent mucosal infection, i.e., a disease of the middle ear mucosa. The mucosa appears hyperplastic, granular, and hyperemic. Usually a thin layer of squamous keratinizing epithelium is noted on top of the mucosa. The mastoid air cell system is usually normal, and generally no osteitis of underlying bone is found. The mucosa of the eustachian tube is swollen or polypoid in nature.

Topical antibiotics may be used to dry the ear. Tympanoplasty is performed to remove the abnormal mucosa and close the perforation. Generally, results are excellent with full restoration of middle ear function and hearing.

PERSISTENT TUBOTYMPANIC (PERITUBAL) INFECTION SYNDROME. This disease was classified in the older literature as "catarrhal" otitis media. In this case the eustachian tube is occluded permanently by diseased mucosa or adhesions. It is characterized by a central or anterior perforation with mucopurulent discharge arising usually in the eustachian tube region. The mastoid is normal. The appearance suggests that the focus of infection arises either in the eustachian tube, peritubal lymphatics, or peritubal air cell system. The middle ear mucosa is usually normal or boggy. There may be an increase in goblet cells and loss of cilia. Drainage may be persistent or intermittent.

It is difficult to cure this syndrome surgically because the eustachian tube may be occluded permanently. After a reduction of drainage and surgical closure of the perforation, graft retraction and reperforation may occur. This can be prevented by placing aeration tubes in the ear when surgery is performed. If eustachian tube function can be reconstituted, the prognosis for recovery is significantly improved.

The purulent drainage usually brings the patient to an otologist or pediatrician. The flow of pus may be continuous or intermittent. When purulent drainage is intermittent, prognosis is favorable; this implies some eustachian tube function. If the production of pus stops (for 6 months or more), the disease is termed inactive chronic otitis media; reactivity is still possible. Tympanic membrane perforation is a significant complication of chronic otitis media. Any pathologic opening to the middle ear predisposes it to reinfection.

Persistent perforation leads to infection. The pathogens usually are mixed, and the flora varies from time to time. Most commonly, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Proteus*, *Pseudomonas*, *Escherichia coli*, *S. pneumoniae*, and various fungi (most commonly *Penicillium*, *Aspergillus*, and *Candida albicans*) are recovered. Correlation of culture results obtained from the purulent drainage with those isolated from the site of infection in the middle ear is poor.

Benign chronic otitis media usually does not evolve into acute suppurative otitis media. When acute exacerbations occur, they must be treated as any acute suppurative otitis media.

Atticoantral Disease

Chronic suppurations of the atticoantral region and the posterior superior quadrant of the drum are considered to be significant problems. We have included posterosuperior perforations of the ear drum, marginal perforations near the annular ligament of the drum, and perforations of pars flaccida (Shrapnell membrane) in this category. The underlying mucosa in this region is cuboidal with no goblet cells, and there is minimal submucosal connective tissue. This mucosa responds to infection by proliferation, granulation, tissue formation, and desquamation. There is a high incidence of associated osteonecrosis and osteoneogenesis. This is especially true in the attic and antrum, above the level of the chorda tympani nerve. The anatomic relation of the attic to the middle and posterior cranial fossae, lateral sinus, horizontal semicircular canal, and facial nerve is also an important consideration.

The ventilation of the mastoid system and the antrum may be impeded by the head of the malleus and body of the incus, especially if they are embedded in granulation tissue. Thus, there is a back-up of purulent material into the antrum and mastoid region, with resulting osteitis and further necrosis. Clinically this is seen usually as a bulging of the posterosuperior external canal wall, with drainage through a perforation of scanty amounts of thick offensive-smelling pus.

SHRAPNELL MEMBRANE DISEASE. This is a disease of the epitympanum, or that portion that lies behind Shrapnell membrane, and is a serious condition. When the tympani posticus or tympani anticus isthmuses are blocked by cholesteatoma, granulation tissue, or adhesions, disease is then confined to the epitympanum and Prussak space, with no other communication to the middle ear. Thus, Shrapnell membrane may be involved, whereas the pars tensa may look quite normal. Disease confined solely to the epitympanum is not unusual.

POSTERIOR MARGINAL PERFORATION. When there is a marginal perforation and the annulus tympanicus is destroyed, we have a disease process that usually lies on top of denuded bone, causing osteonecrosis and bone resorption. Skin grows into the middle ear via the perforation.

Once the annulus is destroyed and the tympanic membrane is perforated, the infection can become widespread, producing mastoiditis, facial paralysis, destruction or ankylosis of the ossicles leading to a permanent conductive hearing loss, involvement of the sigmoid sinus producing lateral sinus thrombosis, invasion of the labyrinth causing labyrinthitis, invasion of the petrous apex causing Gradenigo syndrome, and other intra- and extracranial complications.

CHOLESTEATOMA. This term is a misnomer, because a cholesteatoma is not a tumor and does not contain cholesterol by-products. A more appropriate term would be epidermal inclusion cyst or epithelial cyst.

There are three types of cholesteatomas:

1. *Congenital or primary cholesteatoma* is the intracranial or intramastoid dermoid cyst.

2. *Acquired or secondary acquired cholesteatoma* is the classic cystlike mass that usually is seen following infection. Often acute necrotic otitis media with a marginal tympanic perforation near the annulus or sulcus tympanicus occurs. The epidermis then grows into the middle ear cavity.[79] Normal desquamation produces an accumulation of debris in the middle ear. This provides a good culture medium. There usually is a mixed infection, which may involve *S. aureus, P. aeruginosa, Proteus,* nonhemolytic streptococci, *Aspergillus,* and others. The process of alternating infection and healing will cause the advancement of squamous epithelium into the middle ear and antrum.[45, 85, 132] The persistent infection also stimulates proliferation of the mucoperiosteum of the attic region, thus creating an accelerated tissue growth (increased production of collagenase) and a destructive and expansive process. It is characterized by a foul smell, pus, granulomas, and bone destruction.

Attic retraction pocket or primary acquired cholesteatoma is an entity in which there is usually no significant history of previous otitis media. Perforation and cholesteatoma occur in Shrapnell membrane and the epitympanum. The reason for this is a subject of debate.[126] In all cases there is a perforation in the attic portion of the pars flaccida. In many cases this perforation seals after the cholesteatoma gains entrance into the attic. Once the cholesteatoma has entered the middle ear, purulent material also accumulates and causes epithelial metaplasia and fibrosis. Some believe that under negative pressure the pars flaccida forms a pouch in the attic, which expands from this invagination. Squames are shed and retained in the pouch to form a plug of debris that enlarges and expands. This leads to perforation and continued sepsis in the cholesteatoma sac. The negative pressure, which causes a dimple in the tympanic membrane, is thought to be from faulty pneumatization, subclinical attacks of otitis media, undetected serous otitis, chronic eustachian tube obstruction, or closure of both epitympanic isthmuses.[126] This expanding mass follows lines of least resistance to the attic and middle ear. It tends to pass around the long process of the incus to involve the stapes or pyramidal fossa. Thus, we find most commonly the sinus tympani filled with cholesteatoma and necrosis of the long process of the incus and the crura of the stapes. In addition, one may see necrosis of the head of the malleus, malleus ankylosis, and incudomalleolar ankylosis.

Cholesteatoma, therefore, is the presence of skin in an unusual place. It is usually a baglike cystic structure lined by squamous epithelium resting on a fibrous strand of variable thickness. The contents of this sac are the by-products of desquamation, keratinization, and moisture (pus). Cholesteatoma causes osteitis and local bone erosion and results in retention of infected material, which creates a vicious cycle of events. If one aspirates and removes the contents, a period of relative quiescence can be achieved. However, the disease can be cured only if one removes the entire epithelial sac surgically.

OSTEITIS. Acute osteitis manifested as mastoiditis can occur with an acute exacerbation of chronic otitis media. The inflammation extends widely through the mastoid air cells, leaving areas of necrosis and eventual sequestration. These areas usually become surrounded by proliferative granulation tissue. Large perforations of the tympanic membrane and necrosis of the ossicles may be found. The petrous apex may also be involved. In the pneumatized bones, the infection coalesces; in sclerosing bones, it sequesters; and in diploic bones, it produces osteomyelitis. The cardinal sign is a persistent purulent discharge and deep-seated otalgia. Usually, pain, fever, headache, and a cessation of purulent drainage imply a deep infection with poor drainage (petrositis). Radiographic evidence of mastoiditis is helpful in these situations. High-dose antibiotic treatment and surgery are generally required.

End-Stage Disease

The cardinal sign of this state is a conductive hearing loss. Drainage has stopped for longer than 12 months, and clinically the possibility of reactivation of disease is not envisaged.

ATELECTATIC EAR. In this condition almost the entire tympanic membrane is replaced by thin atrophic scar. Usually, the eustachian tube is malfunctioning and the tympanic membrane may be invaginated into the middle ear. Upon positive insufflation, however, the replacement membrane will balloon out. Usually a conductive hearing loss is found. Fixation of the malleus and necrosis of the long process of the incus may be noted. There is no serous effusion or infection in the middle ear, however.

ADHESIVE OTITIS MEDIA. This may develop in the middle ear as a result of the longstanding infectious process, fibrosis, and adhesions. The middle ear mucosa and the remnant of the tympanic membrane are covered by fibrous tissue. Immobilization of ossicles and of the tympanic membrane results in a conductive hearing loss. Eustachian tube function may or may not be normal.

TYMPANOSCLEROSIS. In this disease there is an initial chronic otitis media, but with healing, the collagen and connective tissue in the submucosa of the middle ear become hyalinized. The ossicles are devitalized because of a compromised blood supply. Brittle white plaques that fracture easily without bleeding may be seen in the tympanic membrane. Any or all of the ossicles may be immobile. One must differentiate this entity from otosclerosis, osteopetrosis, and congenital malformations of the ossicles. Following surgery excellent results may be apparent immediately, but subsequently (usually less than 2 years) recurrent tympanosclerosis occurs.

OTITIS MEDIA WITH EFFUSION

The term chronic serous or secretory otitis media implies the presence of persistent middle ear effusion (usually 8 weeks or longer) without signs of inflammation. Recently, the term otitis media with effusion (OME) has been utilized to describe this syndrome. Chronic secretory otitis media may be related to infection, tubal obstruction, nasopharyngeal tumors, allergic or immunologic disorders, or enlarged adenoids.

Bacteria can be recovered from one-third to one-half of specimens obtained at the time of myringotomy or tympanostomy tube insertion in cases of OME.[50, 51, 105, 120, 144] The

bacteriology in such cases has mimicked closely the bacteriology of acute otitis media, with *S. pneumoniae* and *H. influenzae* being the predominant organisms isolated. The significance of this finding at present is unknown. The bacteria may merely colonize middle ear fluid without producing pathogenic changes, or they may play a role in the production or persistence of middle ear fluid. In addition to live bacteria, nonviable bacteria, pneumococcal capsular polysaccharide and endotoxin have been found in chronic middle ear effusions.[20, 59, 82]

Much attention has been given to the nature and composition of the middle ear effusion. The presence of biologic mediators of inflammation in the middle ear fluid has been demonstrated[13, 84, 159]; these include chemotactic factors, macrophage-inhibiting factors, activated complement, histamine, and prostaglandins. There is experimental evidence that arachidonic acid metabolites (prostaglandins and leukotrienes) are important in the pathogenesis of OME.[68, 69] Elevated levels of IgA, IgE, IgM, and IgG have also been noted in serous effusions.[107] Immune complexes have been implicated as possibly playing a role in the persistence of middle ear fluid.[171]

Otitis media with effusion is observed in 10 to 20 per cent of children after an episode of acute otitis media.[64, 92, 162] The overall prevalence of OME in childhood has been estimated at 15 to 20 per cent.[6] Depending on the time of year when the testing is done, as many as 30 per cent of children in the first school year will have middle ear effusions. A substantial portion of these will be transient.[22] The fluctuating hearing loss associated with OME may have an adverse effect on speech, language, and cognitive development during early childhood.[60, 144]

Clinical evaluation depends on otologic examination and audiologic and tympanometric testing.

Symptoms of this disease include conductive deafness, which is usually fluctuant and may be position dependent. The patient may have a dull earache or a sensation of fullness in the ear. The eardrum is usually dull with a poor light reflex and may be retracted. Color may be bluish or pale pink, or the eardrum may be ground glass in appearance.

The treatment of OME is problematic. Several studies have suggested that a 2- to 4-week course of an oral antibiotic may be beneficial.[93, 167] Oral antihistamine-decongestant preparations have not been found to be effective in controlled trials.[24, 93] Because prostaglandins are thought to play a role in the pathogenesis of OME, nonsteroidal anti-inflammatory drugs have been investigated for therapy of this condition. These agents do not appear to be beneficial.[1, 178] Surgical therapy generally is reserved for children with persistent middle ear effusion (usually for at least 2 or 3 months) unresponsive to antibiotic therapy. Myringotomy with tympanostomy tube placement[64] and adenoidectomy[49] have been recommended in the initial surgical treatment of selected children with OME refractory to medical therapy alone. However, the precise indications for surgical intervention of any type in OME remain controversial.[117]

ANTIBIOTIC THERAPY

Antibiotic therapy changes the clinical course of acute otitis media dramatically. Infection generally is arrested prior to tympanic membrane rupture or mastoiditis.

Although antibiotic therapy must be provided for acute otitis media, in the preantibiotic era, many cases of acute suppurative otitis media healed spontaneously. Resolution of the disease in the past, however, frequently required myringotomy or followed spontaneous perforation of the tympanic membrane. Serious intracranial complications developed in about 3 per cent of cases in the preantibiotic era, whereas the incidence of intracranial complications has fallen to about 0.15 per cent following the introduction of antibiotics. Antibiotics have proved effective in reducing morbidity, eliminating the need for myringotomy in many cases, and decreasing significantly the incidence of serious complications.

Appropriate antibiotic therapy for acute otitis media should be based on (1) knowledge of the microorganisms responsible for the disease in children of different ages; (2) the susceptibility to antibiotics of the organisms isolated from patients with acute otitis media; (3) knowledge of the antibiotic concentration that can be achieved at the site of infection; and (4) results of controlled studies of antibiotic therapy in which efficacy has been based on both the clinical results obtained and eradication of pathogens isolated from the middle ear.[2-9, 12, 23, 29, 38, 44, 59, 61, 72, 75, 80, 83, 92, 96, 102, 123, 130, 131, 142, 143, 148, 154, 158, 169]

In formulating specific recommendations, particular attention should be focused on studies that have assessed antibiotic activity within the middle ear. Antibiotics have been measured within purulent material obtained by needle tympanocentesis from children receiving varying doses of different antibiotics. Silverstein and associates[148] demonstrated that use of tetracycline for the treatment of otitis media in children was inappropriate. None of 12 children who received tetracycline for *H. influenzae* otitis media had concentrations of this drug within the middle ear sufficient to equal or to exceed the minimal inhibitory concentration (MIC) of their *H. influenzae* isolates. Moreover, the concentrations of tetracycline within middle ear exudates also failed to inhibit some strains of pneumococci. In contrast to when their study was performed in the 1960s, currently an increasing number of strains of *S. pneumoniae* and streptococci have become resistant to tetracycline. Thus, if the same study were repeated today, tetracycline would prove even less efficacious. Moreover, tetracyclines are not the drugs of choice for any of the pathogens generally associated with otitis media in children. Administration may be followed by dental staining, pseudotumor cerebri, and other complications. These facts clearly indicate that administration of tetracycline for otitis media in children should be avoided.

The concentrations of various penicillins within the middle ear have also been assessed. In general, oral penicillin G and V achieve concentrations within the middle ear sufficient to inhibit most strains of *S. pneumoniae*, *S. pyogenes*, and penicillin-sensitive *S. aureus*. Concentrations of oral penicillin, however, exceed the MIC of *H. influenzae* in only about 50 per cent of cases. Although administration of aqueous penicillin, and even procaine penicillin, produces middle ear concentrations of penicillin sufficient to inhibit gram-positive organisms, administration of benzathine penicillin (Bicillin) does not. Thus, clinical studies of comparisons of single-dose benzathine penicillin with other modes of therapy have been flawed at their inception by use of a form of penicillin that is inappropriate for therapy of otitis media.

Administration of ampicillin at 50 to 75 mg/kg/24 hr has been followed by middle ear concentrations of 1.6 to 12 μg/ml. These levels exceed the MIC of the usual gram-positive organisms, other than penicillin-resistant *S. aureus*, and equal or exceed the MIC of most strains of *H. influenzae*. Amoxicillin, a congener of ampicillin, has been shown to achieve high levels in middle ear fluid following a single oral dose of 15 mg/kg.[89]

Erythromycin administration also is followed by adequate levels of antibiotic within the middle ear for treatment of *S. pneumoniae*, *S. pyogenes*, and *S. aureus* infections but may be inadequate for many cases of *H. influenzae* infection.

Penetration of sulfa into middle ear fluid was studied by Krause and associates,[80] and concentrations were generally ... exceed the MIC of strains of *S. pneumoniae* and *S.* ... and ampicillin-sensitive and ampicillin-resistant ... of *H. influenzae*.

In a comparative study of amoxicillin, cefaclor, erythromycin-sulfisoxazole and trimethoprim-sulfamethoxazole, amoxicillin had the highest ratio of mean peak concentration in middle ear fluid to MIC for three common pathogens of otitis media (*S. pneumoniae*, ampicillin-sensitive *H. influenzae*, and *S. pyogenes*).[80] Trimethoprim-sulfamethoxazole had the highest ratio of mean peak concentration in middle ear fluid to MIC for ampicillin-resistant *H. influenzae*.

Specific Recommendations

Specific recommendations for treatment of children between 1 month and 15 years of age are summarized in Table 15–2, and therapy for children under 1 month of age, in Table 15–3. The recommendations provide a synthesis of information obtained from our own studies and those of other investigators.

The aminopenicillins (ampicillin, amoxicillin, cyclacillin, and bacampicillin) have been used widely in the therapy of acute otitis media. These agents are active *in vitro* against most of the usual pathogens with the exception of β-lactamase–producing strains of *H. influenzae* and *M. catarrhalis*. After equivalent oral doses, mean peak serum concentrations and bioavailability of amoxicillin, cyclacillin, and bacampicillin are superior to that of ampicillin.[101] The addition of a β-lactamase inhibitor (potassium clavulanate) to ... lin expands the drug's spectrum of activity to in... -lactamase–producing strains of *H. influenzae*, *M. ca... ...nalis*, and *S. aureus* without altering its pharmacokinetic properties. All of these agents have been found effective and safe in the treatment of acute otitis media. Ampicillin and amoxicillin-clavulanate potassium have been associated with a somewhat greater incidence of loose stools or frank diarrhea than have the other agents.[38, 75, 103]

Several cephalosporins have been also useful in the treatment of acute otitis media. Cefaclor and cefuroxime axetil are second-generation cephalosporins that are well absorbed orally and achieve concentrations in middle ear fluid sufficient to eradicate most of the pathogens that cause otitis media. These agents possess useful activity against β-lactamase–producing strains of *H. influenzae* and *M. catarrhalis*.

TABLE 15–2. Antimicrobial Therapy for Acute Otitis Media Beyond the Neonatal Period

Drug	Dose
Amoxicillin	40 mg/kg/day in 3 divided doses
Amoxicillin-clavulanate potassium	40 mg/kg/day in 3 divided doses
Cefaclor	40 mg/kg/day in 2 divided doses
Cefuroxime axetil	125 mg (for children less than 2 years of age) or 250 mg (for children aged 2 years or more) twice daily
T... rim-sulfamethoxazole	10 mg/kg/day (trimethoprim) in 2 divided doses
...mycin-sulfisoxazole	50 mg/kg/day (erythromycin) in 4 divided doses

Please see text for additional information. The usual duration of therapy for acute otitis media is 10 days.

TABLE 15–3. Antimicrobial Therapy for Otitis Media in Neonates (< 1 Month)

Initial Therapy	
Ampicillin	200 mg/kg/24 hr IM or IV in 4 divided doses
Cefotaxime	150 mg/kg/24 hr IM or IV in 3 divided doses

If cultures of blood and CSF are sterile at 72 hours, therapy may be completed with an oral antibiotic active against the middle ear isolate obtained by tympanocentesis.

In open trials and in comparative studies with amoxicillin, cefaclor proved to be effective for treatment of acute otitis media.[12, 92, 100, 110]

However, several studies have found cefaclor to be less efficacious than amoxicillin-clavulanate potassium in the treatment of otitis media.[97, 112] Furthermore, at least one published study has suggested that cefuroxime axetil is more efficacious than cefaclor in the therapy of acute otitis media.[3] Both cefaclor and cefuroxime axetil can be administered twice daily for otitis media. Unfortunately, a liquid preparation of cefuroxime axetil is not yet available. Cefaclor may produce a hypersensitivity or serum sickness–like illness in 2 to 3 per cent of patients.[37]

Because of its poor activity against *H. influenzae* and poor penetration into middle ear fluid, cephalexin cannot be recommended for treatment of otitis media.[135]

Trimethoprim-sulfamethoxazole and erythromycin-sulfisoxazole have been useful agents for treatment of acute otitis media, particularly in penicillin or cephalosporin-allergic children, or with disease caused by β-lactamase–producing organisms. Trimethoprim-sulfamethoxazole can be administered twice daily; erythromycin-sulfisoxazole ordinarily is given four times daily. Both drugs generally are well tolerated.

The choice of an antibiotic for acute otitis media must take into account local factors, including the usual antibiotic susceptibility patterns of bacterial isolates, compliance of the patient population with various antibiotic dosing frequencies, and cost of the various agents under consideration.

Antibiotic therapy of otitis media in children less than 1 month of age requires consideration of the frequency with which enteric organisms are recovered. Many neonates with otitis media have concomitant systemic infection, including pneumonia, septicemia, or meningitis. These patients require hospitalization. Parenteral antibiotic therapy must be provided to treat the most significant accompanying infection. As a rule, we admit to the hospital all children under 1 month of age with otitis media. A lumbar puncture and blood cultures are obtained, and middle ear fluid is obtained by tympanocentesis for Gram stain and culture. If the cerebrospinal fluid and blood are sterile after 72 hours and illness is limited to the middle ear, the neonate may be discharged and receive oral therapy.

Ancillary Treatment

MYRINGOTOMY. The literature contains many opinions concerning the indications for myringotomy in acute otitis media, but well-controlled studies are few in number. We consider the indications for myringotomy to be severe persistent pain, failure to respond to initial antibiotic therapy, persistent conductive hearing loss, or a complication of otitis media.

DECONGESTANTS. Vasoconstrictor nose drops have been shown experimentally to increase the patency of the eustachian tube. We have not found a controlled study on the efficacy of nose drops in patients with otitis media.

Oral pseudoephedrine and various oral antihistamines have also been advocated, but in several studies the addition of this agent to the antimicrobial regimen did not affect the number of treatment failures, recurrences, or cases with residual fluid in the middle ear.[26, 106] Because oral or nasal decongestants have been helpful in individual patients, we would utilize vasoconstrictor nose drops (phenylephrine hydrochloride 0.25 per cent) or oral decongestants (pseudoephedrine) for 3 to 5 days in children over 4 months of age.

EAR DROPS.[39] Several authorities have stressed that antibiotic ear drops are of no value in acute suppurative otitis media, even when the ear is draining. In one study, patients treated with ear drops experienced a higher rate of complications. Thus, we would avoid the administration of otic drops to children with acute otitis media.

Supportive Measures

Acetaminophen and local heat generally are sufficient to reduce pain, permitting the patient to rest comfortably. Children may be permitted to determine their own level of activity, but we recommend that children remain at home until their temperature has been normal for 24 hours. Sedation is to be avoided, for it may interfere with the early detection of intracranial complications.

Follow-up Care

All children with otitis media ideally should be re-examined at 72 hours. If symptoms or fever persist, needle tympanocentesis or myringotomy is performed and future antibiotic therapy determined on the basis of cultures and antibiotic sensitivity studies. If the patient has done well, a return visit at 10 to 12 days, when antibiotic therapy has been discontinued, is recommended.

Some children with acute otitis media have persistent or recurrent disease. In addition to treatment of each acute episode, placement of middle ear tubes or adenoidectomy may be considered in selected cases.

PREVENTION

Pneumococcal vaccine has been advocated by some for the prevention of recurrent episodes of acute otitis media. In one study, fewer episodes of otitis media in otitis-prone children were caused by type-specific serotypes contained in an octavalent pneumococcal vaccine in recipients of that vaccine.[161] However, the total number of episodes of otitis media (due to all pathogens) was similar in study and control groups. The same vaccine was studied in Huntsville, Alabama, and statistically significant efficacy for the prevention of otitis media could not be demonstrated.[122] In Finland, a 14-valent pneumococcal vaccine was shown to be efficacious for the prevention of otitis media in the 6 months following its administration to children over 6 months of age.[91] No apparent protection was afforded children less than 6 months of age who received this vaccine.

Several sulfa drugs have been evaluated in the chemoprophylaxis of frequently recurring acute otitis media and have been found to be efficacious.[42, 86, 199, 139] Paradise[115] has suggested that three episodes of otitis media in 6 months or four episodes in 1 year be utilized as a minimum criterion for institution of chemoprophylaxis. Sulfisoxazole at 75 mg/kg/24 hr in two divided doses can be initiated in such cases, particularly if tympanostomy tube insertion is being contemplated. Tympanostomy tubes are of uncertain benefit in the prevention of recurrent otitis media[42, 43, 89, 91, 121] and the potential adverse anatomic and audiologic sequelae of tube placement must be considered.[121]

COMPLICATIONS

Otitis media is a potentially serious disease because of its complications. Originally, surgery was the only mode of therapy, and the results were not predictable. In the past, the relative success of surgery for mastoiditis remained in sharp contrast to the almost invariably fatal outcome for patients with purulent otitic meningitis.[111] This was the most dreaded complication of otitis media and the most frequent cause of death. Thus, surgery was aimed at prevention of this complication.

Infection may spread from the temporal bone along preformed vascular channels, usually following a thrombophlebitis of emissary or perforating veins. This causes early complications with few prodromal signs and no bone destruction. Infection may also spread along the usual anatomic openings, suture lines, anatomic dehiscences of bone (patent petrosquamous suture line, dehiscent jugular bulb, and so on), fracture lines, or by way of surgically created defects.

Infection can also spread by contiguity. When bone destruction or erosion occurs, infection can spread via the necrotic area to an adjacent structure. This mode of spread is most common today and is associated primarily with chronic otitis media. Complications are delayed and generally are associated with prodromal symptoms.

The complications of otitis media usually are subdivided into intracranial and extracranial problems. The intracranial group is further subdivided into meningeal and extrameningeal complications.

I. Intracranial complications
  A. Meningeal complications
    1. Epidural abscess
      a. Perisinus (lateral or sigmoid) abscess
    2. Focal meningitis
    3. Generalized meningitis
    4. Lateral sinus thrombosis
    5. CSF otorrhea
    6. Otitic hydrocephalus
    7. Subdural abscess
  B. Extrameningeal complications
    1. Brain abscess
      a. Cerebellar
      b. Temporal
      c. Other—usually parietal and occipital lobe
    2. Petrositis
    3. Extradural abscess in the tegmen (floor of middle cranial fossa), mastoid, or sinodural angle (floor of posterior fossa)
    4. Focal encephalitis
II. Extracranial complications
  A. Serous labyrinthitis
  B. Purulent labyrinthitis
  C. Mastoiditis
  D. Subperiosteal abscess
    1. Bezold abscess
  E. Facial nerve paralysis
  F. Horizontal canal fistula (other labyrinthine fistulas)
  G. Paralabyrinthitis—osteitis of otic capsule
  H. Ossicular destruction
  I. Cholesteatoma
  J. Osteitis or osteomyelitis of the temporal bone

Bacterial meningitis is the most common intracranial complication of otitis media.[174] *H. influenzae*, type b is the most causative organism.[66]

Lateral sinus thrombosis is usually caused by *S. aureus*, beta-hemolytic streptococci, or pneumococci. It is associated with septicemia, septic embolization of viscera, and occlusion of the sigmoid sinus; on occasion, it may extend and cause cavernous sinus, superior petrosal sinus, or internal jugular vein thrombosis. Death is caused by septicemia and embolization, with multiple brain abscesses and meningitis. The mortality rate is about 25 per cent. The fever is characteristically "picket fence" in occurrence and is preceded by chills and diaphoresis. Between these episodes patients may appear well. Other findings include anemia, cervical adenopathy, rapid emaciation, and persistent headache. Increased intracerebral pressure with papilledema may be noted in 50 per cent of cases. Papilledema may be unilateral and is usually ipsilateral. The Tobey-Ayer or Queckenstedt test is usually negative. Positive blood cultures are frequently obtained. Contrast studies such as retrograde jugular phlebogram indicate jugular bulb thrombosis. An interesting clinical finding is a positive Griesinger sign. There is edema and pain over the posterior aspect of the mastoid due to thrombosis of the mastoid emissary vein. This is secondary to sigmoid sinus thrombosis, which extends into this tiny vessel. Dawes[34] found that lateral sinus thrombosis is preceded by an extradural abscess in over half the cases. Treatment consists of antibiotic therapy and surgery. The latter includes mastoidectomy and sinus drainage.

A communicating hydrocephalus, *otitic hydrocephalus*, may follow acute otitis media by several weeks. This occurs in children and adolescents. It is usually associated with lateral sinus thrombosis that has impaired intracranial venous drainage and with the resorptive function of the arachnoidal villi in the superior sagittal sinus. If both lateral sinuses are thrombosed, the hydrocephalus may be permanent. Cultures of cerebrospinal fluid are negative. The hydrocephalus generally subsides spontaneously within a few months.

Suppurative labyrinthitis may occur with both acute and chronic otitis media. In acute otitis media it presumably is caused by extension through round and oval windows. In chronic otitis media it also may follow a pathologic fistula of the bony labyrinth or osteitis of the capsule. Labyrinthitis may also occur in retrograde fashion from infections of the meninges with involvement of the subarachnoid space. Infection extends through the cochlear aqueduct and internal auditory canal. Shambaugh[165] noted that meningitis was responsible for 20 per cent of the cases of deafness in 500 children in special schools for the deaf.

Suppurative labyrinthitis is characterized by severe nausea and vomiting, associated with complete hearing loss and absent caloric responses.

Serous labyrinthitis usually is secondary to osteitis of the otic capsule or secondary to meningeal infection. It is characterized by vestibular symptoms (spontaneous nystagmus to the opposite side, nausea and vomiting, vertigo, ataxia), and cochlear symptoms (neurosensory hearing loss, diplacusis, disturbed speech).

Petrositis is an inflammation of the pneumatized areas of the perilabyrinthine and apical portions of the temporal bone. Because in children the petrous apex contains air cells and bone marrow spaces, most of these cases involve osteomyelitis. They usually extend intracranially, resulting in meningitis or cerebellar abscesses. The symptoms are pain around the ipsilateral eye (gasserian ganglion [V] infection), persistent discharge (otitis media), and diplopia (paresis of nerve VI in Corello canal or paralysis of the ipsilateral external rectus muscle). These signs constitute Gradenigo syndrome.

These infections can extend to the lateral pharyngeal and retropharyngeal spaces, meninges, CNS, or venous sinuses.

Facial paralysis[49] secondary to otitis media is usually peripheral in origin. Cranial nerve VII is involved most frequently, presumably because it has the longest course in a bony canal (27 mm). Facial nerve paralysis is associated more commonly with chronic otitis media.

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16
MASTOIDITIS

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Mastoiditis, a suppurative infection of the mastoid air cells, is a potential complication of all cases of otitis media due to the continuity of the mucoperiosteal lining of the mastoid with that of the middle ear.[49] The spectrum of disease in mastoiditis ranges from asymptomatic cases with apparent spontaneous resolution[53] to progressive disease with life-threatening complications.[10, 12] Since the advent of antibiotic therapy, mastoiditis is seen much less frequently, but the frequency of complications remains the same.[20, 66] With mastoiditis occurring less commonly, physicians are less apt to consider the diagnosis, especially when the clinical picture has been masked by antibiotic therapy or when the process is chronic and low grade. Proper antibiotic therapy, often accompanied by surgical drainage, can halt and prevent serious complications if mastoiditis is diagnosed early enough.

HISTORY

Prior to the advent of antibiotics, mastoiditis was a frequent complication of otitis media that could only be treated by expectant waiting or surgery.[27, 28] When surgery was used, many patients with mastoiditis were able to be cured by simple mastoid drainage alone, with a mortality rate quoted at 2 per cent.[28] However, intracranial complications of mastoiditis carried a very grave prognosis. In the preantibiotic era, between 1928 and 1933, 25 of every 1000 deaths at Los Angeles County Hospital were caused by intracranial complications of otitis media such as meningitis, venous sinus thrombosis, or brain abscess. In contrast, between 1949 and 1954, only 2.5 per 1000 deaths at the same hospital were caused by complications of otitis or mastoiditis.[28] The use of antibiotics in treating mastoiditis at first led to a marked decrease in the surgical approach to treatment of this illness.[12, 21, 66] However, the realization that infection can persist and complications of mastoiditis can occur even while the patient is receiving antibiotic therapy has resulted in the present day combined approach of antibiotics and surgery.[21, 66, 82]

BACTERIOLOGY

The bacteriology of acute mastoiditis differs somewhat from that of acute otitis media (Table 16–1). In acute otitis media, *Streptococcus pneumoniae* is the most frequent pathogen isolated (31 per cent), with *Haemophilus influenzae* being the second most common (22 per cent), *Moraxella catarrhalis* being the third most common (7 per cent), and group A beta-hemolytic streptococci being a distant fourth (2 per cent).[17] However, studies on acute mastoiditis (defined as symptoms of less than 1 month's duration) show that *Streptococcus pyogenes* (group A beta-hemolytic streptococci) and *S. pneumoniae* are the two most frequently isolated organisms from the middle ear and mastoid, with *Staphylococcus aureus* being the third most common isolate.[20, 23, 66, 69] *H. influenzae* has been isolated from the middle ear of patients with mastoiditis, but less often than one would expect given its frequent recovery in acute otitis media without mastoiditis. Gram-negative bacteria, enterococci, anaerobes, and *Mycobacterium tuberculosis* have also been isolated occasionally in patients with acute mastoiditis.

Chronic mastoiditis has a different bacteriologic spectrum than acute mastoiditis. Aerobic cultures of chronic mastoiditis and chronic otitis media both show predominantly *S.*