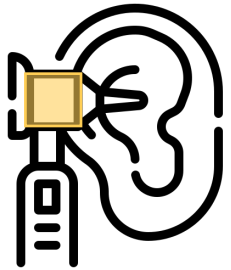
Journal Reading

The NEW ENGLAND JOURNAL of MEDICINE

Tympanostomy Tubes or Medical Management for Recurrent Acute Otitis Media

May 13, 2021

Hoberman A, Preciado D, Paradise JL, et al.



Presenter: Clerk 2 張雅筑

Supervisor: VS 洪偉誠 醫師

Date: 2025/07/16

Background- Acute otitis media (AOM)

- predominant causes
  - Streptococcus pneumoniae
  - non-typeable Haemophilus influenzae

in Taiwan:
- Streptococcus pneumoniae
- Haemophilus influenzae
- Moraxella catarrhalis

- leading indication for antimicrobial treatment in children

Background- Acute otitis media (AOM)

- recurrent acute otitis media
  - at least 3 episodes in 6 months or
  - at least 4 episodes in 12 months with at least 1 episode within the preceding 6 months

→ principal indication for **tympanostomy tube placement**

AAO-HNSF Clinical Practice Guideline: Tympanostomy Tubes in Children

(2013)

to treat
- persistent middle ear effusion
- frequent ear infections
- ear infections despite antibiotic therapy

By age 3, nearly 1 in 15 children have tubes.

Background

tympanostomy tube placement

✓
- varying duration of AOM-free periods

✗
- cost
- possible late sequelae of anesthesia
- occurrence of refractory tube otorrhea
- tube blockage
- premature extrusion or dislocation of the tube
- progressive reduction in incidence with increasing age

Aim of study

- to determine:

  tympanostomy tube placement v.s. medical management

  which has greater reduction in

  the rate of recurrence of acute otitis media during 2-year period

Methods- Participants

- conducted between December 2015 and March 2020
- children 6 to 35 months with recurrent AOM

  + provided at least one AOM confirmed by trial clinician

    - required a history of acute symptoms with a score of ≥ 2 on the five-item Acute Otitis Media Severity of Symptoms (AOM-SOS) scale, version 4.0
    - presence of either middle-ear effusion with specified combinations of otalgia, tympanic membrane bulging, and tympanic membrane erythema or purulent otorrhea

Acute Otitis Media Severity of Symptoms (AOM-SOS) scale, version 4.0

How has your child been doing?

We are interested in finding out how your child has been doing. For each question, please place a check (✓) in the box corresponding to your child's symptoms. Please answer all questions.

	No	A Little	A Lot
Over the past 12 h, has your child been tugging, rubbing, or holding the ear(s) more than usual?	☐	☐	☐
Over the past 12 h, has your child been crying more than usual?	☐	☐	☐
Over the past 12 h, has your child been more irritable or fussy than usual?	☐	☐	☐
Over the past 12 h, has your child been having more difficulty sleeping than usual?	☐	☐	☐
Over the past 12 h, has your child been having fever or feeling warm to touch?	☐	☐	☐

Methods- Participants

- exclusion criteria
  - children who had undergone tympanostomy tube placement, adenoidectomy, or tonsillectomy
  - chronic illness
  - congenital anomaly that increased the risk of otitis media (e.g., cleft palate)
  - otitis media with effusion in both ears of at least 3 months' duration
  - sensorineural hearing loss

Methods- Randomization

- stratification
  - age: 6 to 11 months, 12 to 23 months, or 24 to 35 months
  - exposure or non-exposure to at least three children for at least 10 hours per week
- 2 groups
  - undergo tympanostomy tube placement
    - usually performed within 2 weeks; Teflon Armstrong-type tympanostomy tubes were inserted in both ears
  - receive nonsurgical medical management, with the option of tympanostomytube placement in the event of treatment failure

Methods- Follow up

- assessments at 8-week intervals
- bring children for evaluation if
  - any respiratory symptoms for at least 5 days
  - bring children within 48 hours if they had any symptom suggestive of AOM or had received a diagnosis of AOM at a non-trial site

Methods- Examination and assessment

- when episodes occurred
  - culture: nasopharyngeal specimen/ throat swab
  - AOM-SOS scale
  - any instance of protocol-defined diarrhea or diaper dermatitis
- at each visit
  - recorded all use of other health care resources
  - obtained nasopharyngeal or throat specimens for culture
  - Otitis Media–6 Survey
  - Caregiver Impact Questionnaire
  - score level of satisfaction

Methods- Treatment

- with tympanostomy tubes in place
  - otorrhea accompanied by at least one AOM-SOS scale symptom (except immediately postoperatively)

    → acute infection
    - obtained a specimen for culture from the tube lumen
    - 5 drops of 0.3% ofloxacin (Floxin) ototopically twice daily for 10 days
    - if otorrhea persisted > 7 days: prescribed amoxicillin– clavulanate or culture-directed antimicrobial treatment

Methods- Treatment

- with tympanostomy tubes in place
  - tube extrusion
    - within 6 months: replaced if had at least two episodes of AOM within 3 months
    - beyond 6 months: tubes were reinserted if recurrent AOM

Methods- Treatment

- medical management group
  - if AOM
    - oral amoxicillin–clavulanate at a dose of 90 mg of amoxicillin and 6.4 mg of clavulanate per kilogram of body weight per day for 10 days
    - if response inadequate: ceftriaxone at a dose of 75 mg per kilogram intramuscularly, repeated in 48 hours

Methods- Treatment failure

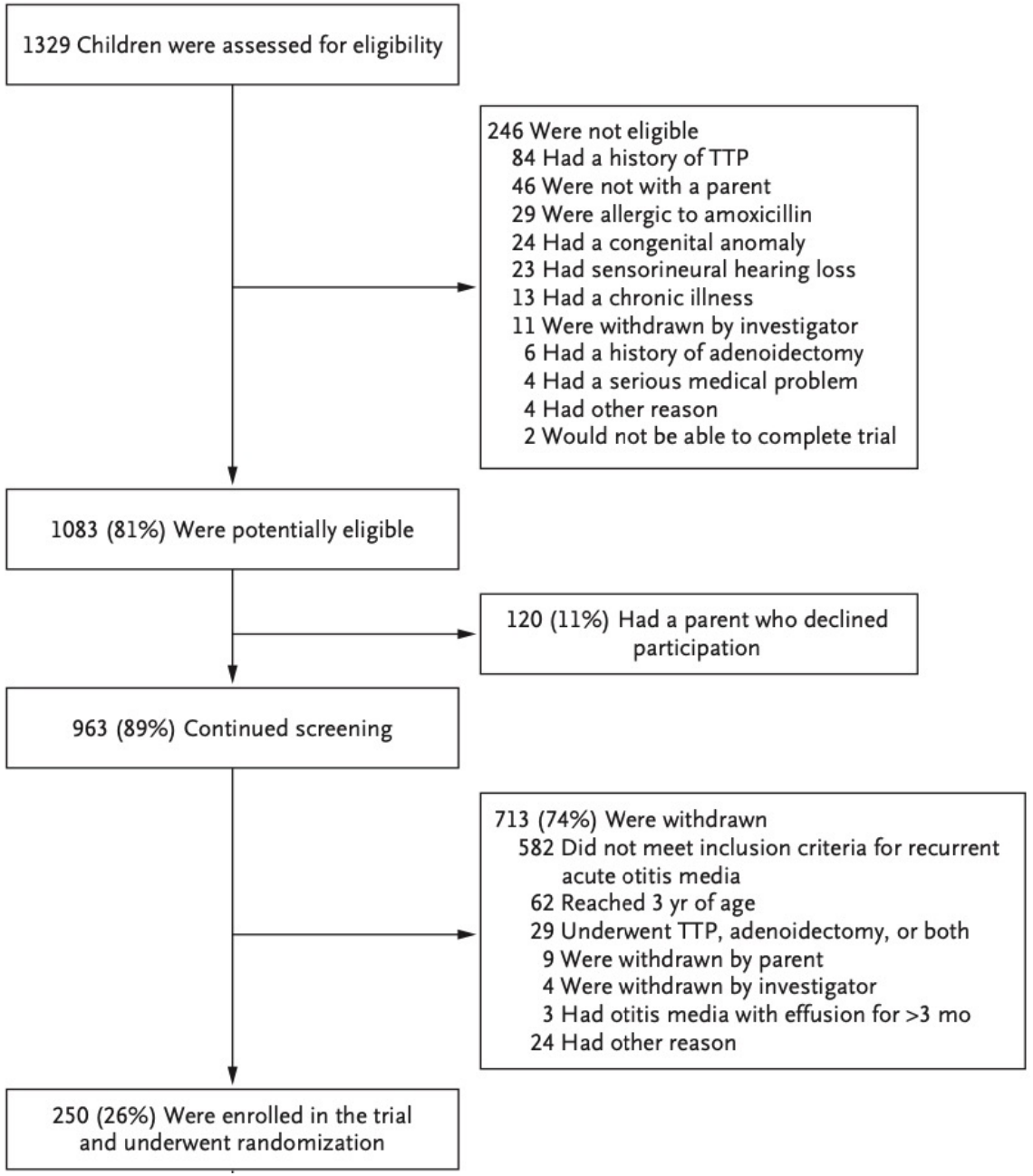
- the development of any of the following
  - long cumulative periods of systemic antimicrobial treatment
  - persistent otorrhea
  - otitis media with effusion
  - tympanic membrane perforation
  - antimicrobial-associated protocol-defined diarrhea
  - AOM–related hospitalization
  - untoward reaction to anesthesia

Methods- Treatment failure

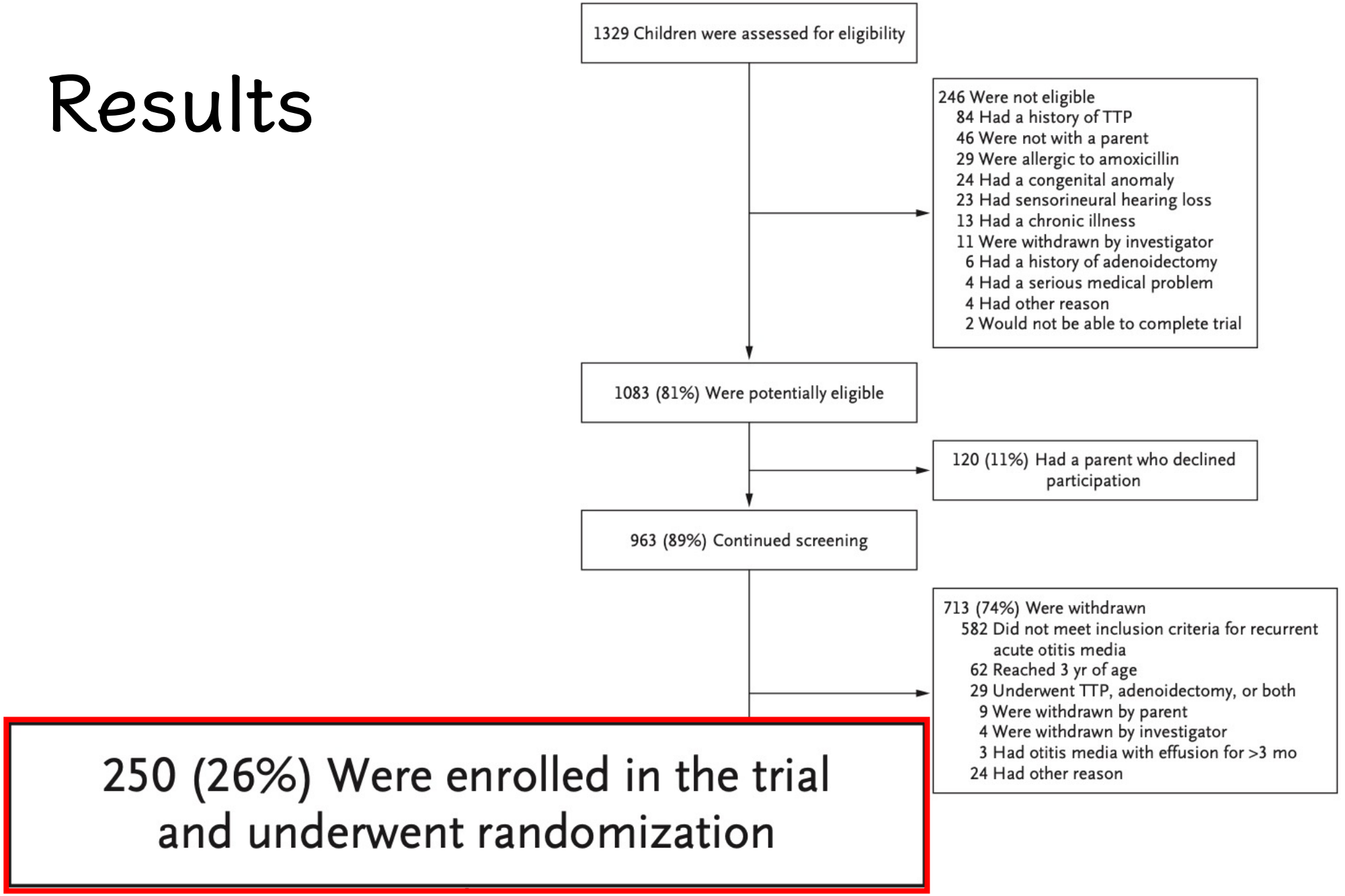
- in medical management group
  - recurrences of AOM at the frequency originally required for trial entry

    → resulting in referral for tympanostomy tube placement
  - receipt of tympanostomy tube placement at parental request

Results


1329 Children were assessed for eligibility
246 Were not eligible
84 Had a history of TTP
46 Were not with a parent
29 Were allergic to amoxicillin
24 Had a congenital anomaly
23 Had sensorineural hearing loss
13 Had a chronic illness
11 Were withdrawn by investigator
6 Had a history of adenoidectomy
4 Had a serious medical problem
4 Had other reason
2 Would not be able to complete trial
1083 (81%) Were potentially eligible
120 (11%) Had a parent who declined participation
963 (89%) Continued screening
713 (74%) Were withdrawn
582 Did not meet inclusion criteria for recurrent acute otitis media
62 Reached 3 yr of age
29 Underwent TTP, adenoidectomy, or both
9 Were withdrawn by parent
4 Were withdrawn by investigator
3 Had otitis media with effusion for >3 mo
24 Had other reason
250 (26%) Were enrolled in the trial and underwent randomization

Results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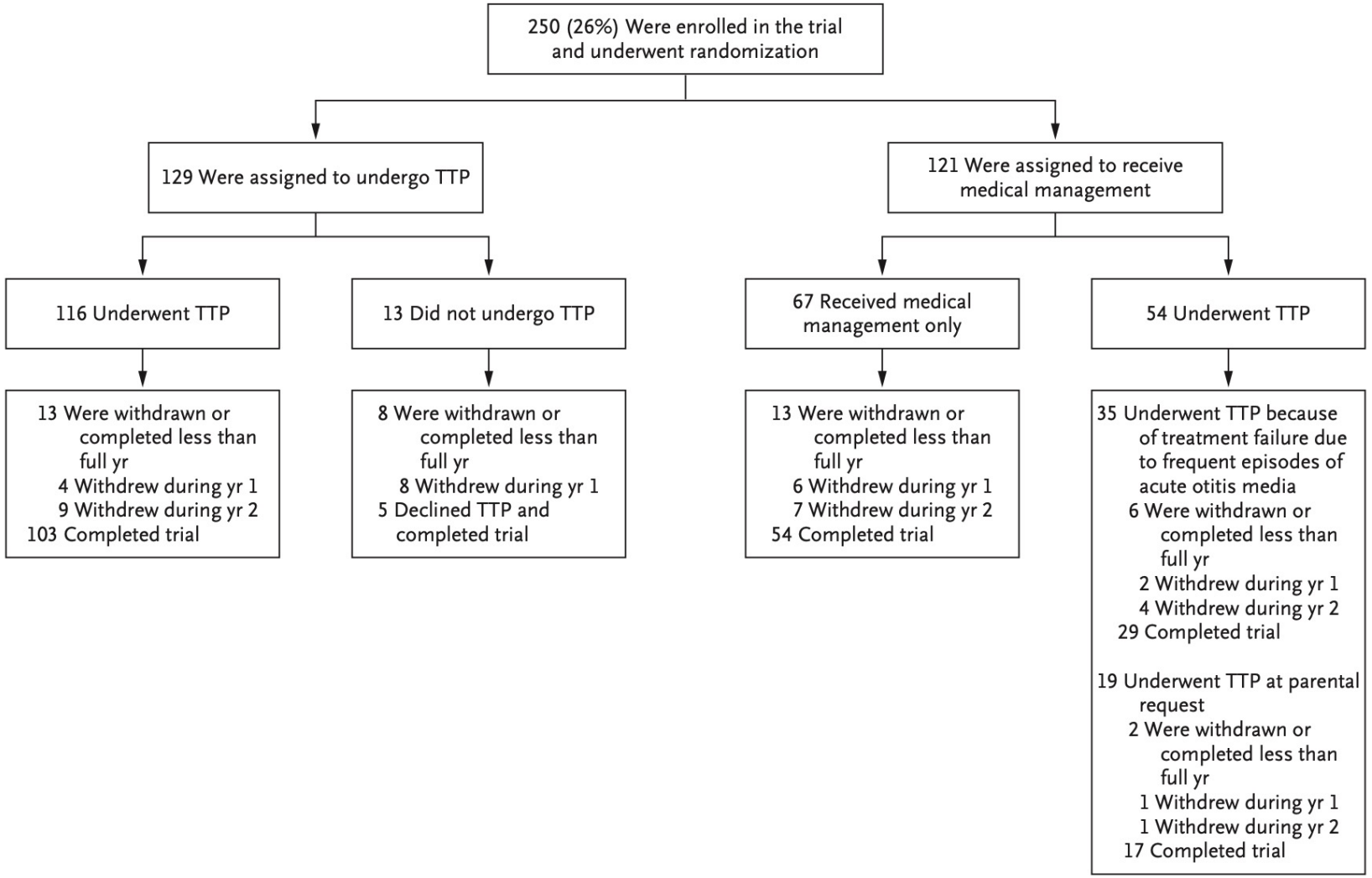
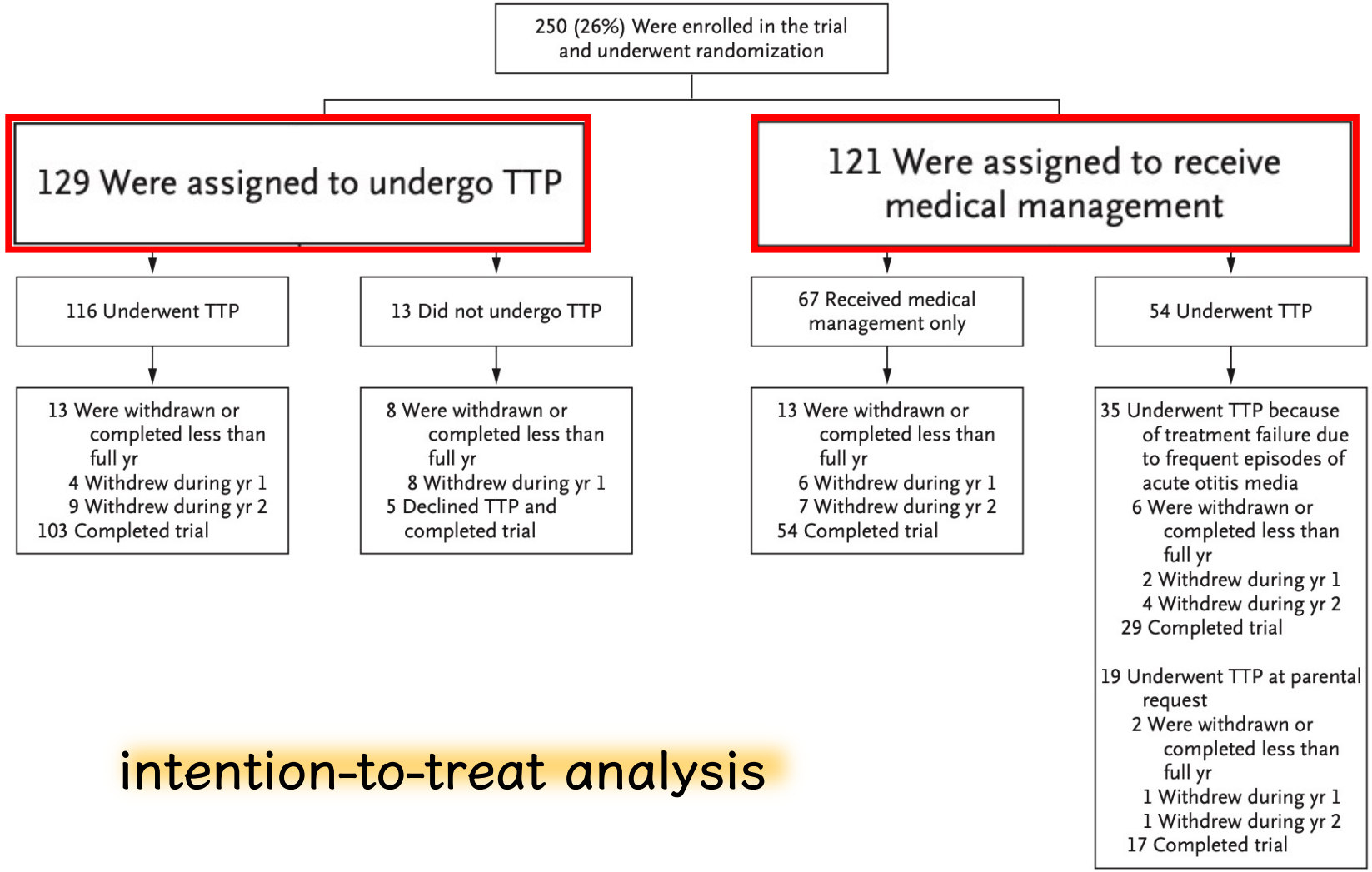
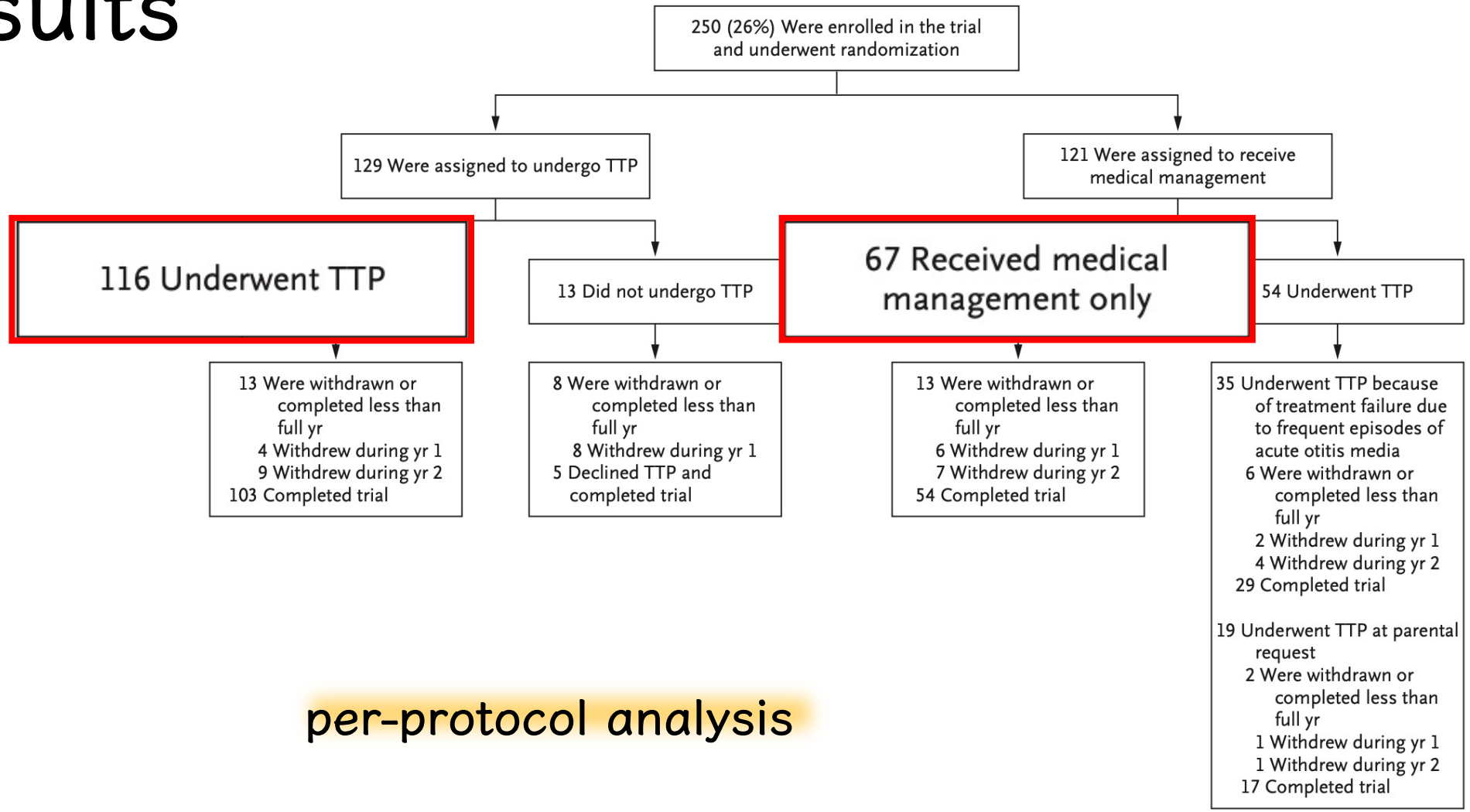

250 (26%) Were enrolled in the trial and underwent randomization
129 Were assigned to undergo TTP
121 Were assigned to receive medical management
116 Underwent TTP
13 Did not undergo TTP
67 Received medical management only
54 Underwent TTP
13 Were withdrawn or completed less than full yr
4 Withdrew during yr 1
9 Withdrew during yr 2
103 Completed trial
8 Were withdrawn or completed less than full yr
8 Withdrew during yr 1
5 Declined TTP and completed trial
13 Were withdrawn or completed less than full yr
6 Withdrew during yr 1
7 Withdrew during yr 2
54 Completed trial
35 Underwent TTP because of treatment failure due to frequent episodes of acute otitis media
6 Were withdrawn or completed less than full yr
2 Withdrew during yr 1
4 Withdrew during yr 2
29 Completed trial
19 Underwent TTP at parental request
2 Were withdrawn or completed less than full yr
1 Withdrew during yr 1
1 Withdrew during yr 2
17 Completed trial

Results



intention-to-treat analysis

Results



per-protocol analysis

Results

Selected demographic and clinical characteristics

Table 1. Selected Demographic and Clinical Characteristics of the Children, According to Treatment Assignment.*

Characteristic	Tympanostomy-Tube Group (N=129)	Medical-Management Group (N=121)	All Children (N=250)
	number of children (percent)		
Site of enrollment†			
Pittsburgh	92 (71)	91 (75)	183 (73)
Washington, DC	20 (16)	16 (13)	36 (14)
Bardstown, KY	17 (13)	14 (12)	31 (12)
Age at enrollment			
6–11 mo	46 (36)	45 (37)	91 (36)
12–23 mo	70 (54)	67 (55)	137 (55)
24–35 mo	13 (10)	9 (7)	22 (9)
Sex			
Female	42 (33)	48 (40)	90 (36)
Male	87 (67)	73 (60)	160 (64)
Race‡			
White	70 (54)	70 (58)	140 (56)
Black	41 (32)	42 (35)	83 (33)
Asian	3 (2)	2 (2)	5 (2)
Multiracial	10 (8)	7 (6)	17 (7)
Other	5 (4)	0	5 (2)
Ethnic group‡			
Not Hispanic or Latino	110 (85)	111 (92)	221 (88)
Hispanic or Latino	19 (15)	10 (8)	29 (12)
Exposure to other children§			
No	26 (20)	22 (18)	48 (19)
Yes	103 (80)	99 (82)	202 (81)
Otitis media with effusion present at randomization¶			
No	85 (66)	71 (59)	156 (62)
Yes	44 (34)	50 (41)	94 (38)
Estimated risk of recurrences of acute otitis media‖			
Probably lesser	63 (49)	72 (60)	135 (54)
Probably greater	66 (51)	49 (40)	115 (46)

Results

Table 2. Two-Year Primary and Secondary Outcomes, According to Treatment Assignment.*

Outcome Measure or Child Characteristic	Tympanostomy-Tube Group (N=129)	Medical-Management Group (N=121)	All Children (N=250)	Estimated Between-Group Difference (95% CI); P Value†
Two-year occurrence of episodes of acute otitis media				
No. of episodes; no. of child-yr‡	384; 259.5	378; 242.6	762; 502.1	
Yr 1 and 2 combined — rate per child-yr§	1.48±0.08	1.56±0.08	1.52±0.08	0.97 (0.84 to 1.12); P=0.66
Yr 1	1.94±0.12	2.20±0.14	2.07±0.13	
Yr 2	1.06±0.09	0.97±0.09	1.01±0.09	

In the per-protocol analysis,
tympanostomy tube group: 1.47±0.08
medical management group: 1.72±0.11
(risk ratio, 0.82; 95% CI, 0.69 to 0.97).

no significant difference in reducing the subsequent occurrence of episodes of AOM

Results

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Yr 2	1.06±0.09	0.97±0.09	1.01±0.09	

the rate among children 6 to 11 months was 2.63 times the rate among those 24 to 35 months
the rate among children 12 to 23 months was 1.80 times the rate among the older children

related to age at enrollment:
the younger, the higher

not related to:

- initial estimates of risk of recurrences of acute otitis media
- degree of exposure to other children
- otitis media with effusion at trial entry

Results

Treatment failure — no. of children/total no. (%)**				
Had failure	56/124 (45)	74/120 (62)	130/244 (53)	0.73 (0.58 to 0.92)
Did not have failure	68/124 (55)	46/120 (38)	114/244 (47)	
Total days with otitis-related symptoms or signs — no. of days per yr (range)				
Tube otorrhea	7.96±1.10 (0 to 81)	2.83±0.78 (0 to 76)	5.44±0.70 (0 to 81)	5.21 (2.60 to 7.82)
Other symptoms of acute otitis media	2.00±0.29 (0 to 17)	8.33±0.59 (0 to 35)	5.11±0.38 (0 to 35)	−6.32 (−7.55 to −5.10)
Total days of antimicrobial treatment — no. of days per yr (range)	8.76±0.94 (0 to 119)	12.92±0.90 (0 to 56)	10.80±0.67 (0 to 119)	−4.50 (−6.82 to −2.18)

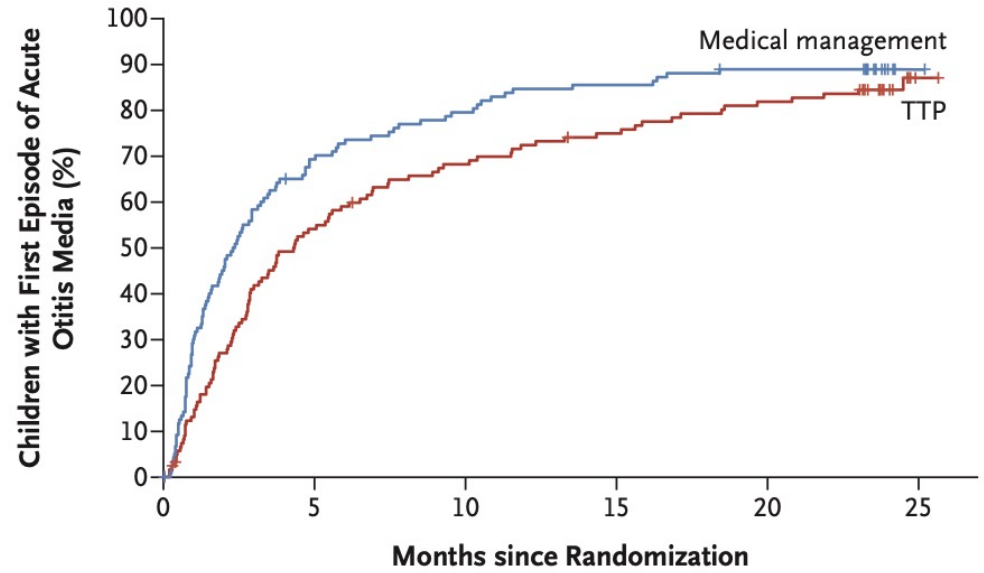
tympanostomy tube group superior in:

- less treatment failure
- less total days with otitis-related symptoms or signs other than tube otorrhea
- less total days of antimicrobial treatment

Results

tympanostomy tube group	medical management group
4.34 months	2.33 months

(hazard ratio, 0.68; 95% CI, 0.52 to 0.90)



No. at Risk						
Medical	121	36	24	17	12	1
TTP	129	56	38	29	21	1
No. of Events						
Medical	0	83	95	102	106	106
TTP	0	66	83	91	99	103
No. with Censored Data						
Medical	0	2	2	2	3	14
TTP	0	7	8	9	9	25

Figure 2. Time to First Recurrent Episode of Acute Otitis Media.
Shown are one minus Kaplan–Meier survival estimates of the cumulative percentage of children who had a recurrent episode of acute otitis media, according to trial group. The median time to a first occurrence of acute otitis media was longer in the tympanostomy-tube group than in the medical-management group (4.34 months vs. 2.33 months; hazard ratio, 0.68; 95% confidence interval, 0.52 to 0.90).

Results

- in medical management group

55 children	46 children
met clinical criteria for treatment failure on the basis of continuing recurrent AOM	neither met the criteria nor underwent tympanostomy tube placement at parental request

younger

→ differed significantly only with respect to the age at trial enrollment

Results

Frequency distribution of episodes of acute otitis media, yr 1 and 2 combined¶				
No. of episodes — no. of children/total no. (%)				
0	17/108 (16)	12/100 (12)	29/208 (14)	
1 or 2	41/108 (38)	41/100 (41)	82/208 (39)	
3 or 4	24/108 (22)	29/100 (29)	53/208 (25)	
≥5	26/108 (24)	18/100 (18)	44/208 (21)	
Range — no. of episodes	0 to 13	0 to 16	0 to 16	
Estimated severity of episodes of acute otitis media — no. of episodes/total no. (%)‖				
Probably nonsevere	180/336 (54)	168/333 (50)	348/669 (52)	
Probably severe	156/336 (46)	165/333 (50)	321/669 (48)	0.91 (0.76 to 1.09)
Child and parent QOL assessments				
Score on the Otitis Media–6 Survey††	1.50±0.03	1.55±0.03	1.52±0.02	–0.05 (–0.13 to 0.02)
Score on the Otitis Media–6 Survey — children's overall QOL‡‡	8.45±0.07	8.37±0.07	8.42±0.05	0.06 (–0.13 to 0.24)
Score on the Caregiver Impact Questionnaire§§	10.82±0.53	10.93±0.55	10.87±0.38	–0.04 (–1.55 to 1.47)
Score on the Caregiver Impact Questionnaire — caregivers' overall QOL‡‡	8.55±0.06	8.50±0.06	8.53±0.04	0.03 (–0.14 to 0.20)
Parental satisfaction with treatment assignment¶¶	4.64±0.10	4.43±0.13	4.54±0.08	0.25 (–0.06 to 0.56)
Use of medical resources other than trial visits — no. of parent reports/no. of parental questionnaires (%)‖‖	738/1635 (45)	672/1628 (41)	1410/3263 (43)	1.07 (0.98 to 1.18)
Use of nonmedical resources — no. of reported occurrences/no. of parental questionnaires (%)***				
Missed work owing to child's illness	286/1635 (17)	256/1628 (16)	542/3263 (17)	1.11 (0.88 to 1.41)
Special child care arrangements owing to child's illness	231/1635 (14)	195/1628 (12)	426/3263 (13)	1.15 (0.89 to 1.48)

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0	17/108 (16)	12/100 (12)	29/208 (14)	
1 or 2	41/108 (38)	41/100 (41)	82/208 (39)	
3 or 4			208 (25)	
≥5			208 (21)	
Range — no. of epis			to 16	
Estimated severity of ep no. (%)‖				
Probably nonsevere			669 (52)	
Probably severe			669 (48)	0.91 (0.76 to 1.09)
Child and parent QOL a				
Score on the Otitis M			2±0.02	−0.05 (−0.13 to 0.02)
Score on the Otitis M			2±0.05	0.06 (−0.13 to 0.24)
Score on the Caregiv			87±0.38	−0.04 (−1.55 to 1.47)
Score on the Caregiv			3±0.04	0.03 (−0.14 to 0.20)
Parental satisfaction wit			4±0.08	0.25 (−0.06 to 0.56)
Use of medical resource parental questionnaires (%)‖‖			3263 (43)	1.07 (0.98 to 1.18)
Use of nonmedical resources — no. of reported occurrences/no. of parental questionnaires (%)***				
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no significant difference in:

- frequency distribution of episodes of AOM
- estimated severity of episodes of AOM
- child and parent QOL assessments
- parental satisfaction with treatment assignment
- use of medical and non-medical resources

Results

Table 3. Adverse Events, According to Treatment Assignment.

Adverse Event	Tympanostomy-Tube Group (N=129)		Medical-Management Group (N=121)		All Children (N=250)		Risk Ratio (95% CI)
	No. of children (%)	No. of Events	No. of children (%)	No. of Events	No. of children (%)	No. of Events	
Nonserious events							
Protocol-defined diarrhea*	21 (16)	43	34 (28)	59	55 (22)	102	0.67 (0.44–1.03)
Diaper dermatitis†	25 (19)	46	33 (27)	56	58 (23)	102	0.79 (0.51–1.22)
Tube otorrhea‡	94 (73)	320	34 (28)	119	128 (51)	439	2.57 (1.91–3.48)
Otorrhea, not tube-associated	0	0	8 (7)	8	8 (3)	8	—
Serious events: miscellaneous§	3 (2)	3	7 (6)	8	10 (4)	11	0.40 (0.11–1.52)

* Protocol-defined diarrhea was the occurrence of at least three watery stools on 1 day or at least two watery stools on 2 consecutive days.
† Diaper dermatitis was defined as dermatitis resulting in topical antifungal treatment.
‡ Three children in the tympanostomy-tube group and two in the medical-management group received placement of an ear wick in treating refractory tube otorrhea.
§ In the tympanostomy-tube group, there was one serious adverse event each involving intussusception, asthma exacerbation, and gastroenteritis. In the medical-management group, there were three serious adverse events involving asthma exacerbation and one serious adverse event each involving complex febrile seizure, respiratory insufficiency, bronchiolitis, dehydration, and protocol-defined diarrhea resulting in hospitalization.

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Serious events: miscellaneous§	3 (2)	3	7 (6)	8	10 (4)	11	0.40 (0.11–1.52)

no significant difference in:

- non-serious adverse events
- serious adverse events

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Results- Bacterial resistance

- no significance difference in
  - the percentage of children colonized with any penicillin-non-susceptible pathogen
  - the percentages of isolates that were non-susceptible or in conditional odds ratios

Discussion- Strengths of trial

- a diverse participant population in the age group most prone to recurrences of AOM
- otoscopic diagnoses by validated otoscopists
- pretrial confirmation in each child of at least one episode of AOM
- a standardized protocol for treating episodes
- validated scales for rating the severity of symptoms and functional outcomes
- monitoring for antimicrobial resistance
- follow-up of children for 2 full years
- modest attrition

Discussion- Limitation of trial

- receipt of tympanostomy tubes, for differing reasons and at differing times, by certain children in the medical management group

  → thereby complicating the task of analysis

Conclusion

- no significant difference between groups in the rate of episodes of AOM during the ensuing 2-year period
- despite their greater use of antimicrobial treatment in medical management group, no evidence was founded of increased antimicrobial resistance
- **favor tympanostomy tube group**
  - the time to a first episode of AOM
  - the time with otitis-related symptoms or signs
  - the percentage of meeting specified criteria for treatment failure

overall complication rate: 17%

Ahmed, I., Tunkel, D. E., & Eagle, C. A. (2006). *Medial migration of tympanostomy tubes: An overlooked complication. International Journal of Pediatric Otorhinolaryngology, 70*(5), 889–892.

→ **thorough assessment necessary**

Clinical Practice Guideline: Tympanostomy Tubes in Children (Update)

Rosenfeld RM, Tunkel DE, Schwartz SR, et al. Clinical Practice Guideline: Tympanostomy Tubes in Children (Update). *Otolaryngol Head Neck Surg*. 2022;166(1_suppl):S1-S55.

Table 5. Summary of Guideline Key Action Statements.

Statement	Action	Strength	Comment
1. OME of short duration	Clinicians should *not* perform tympanostomy tube insertion in children with a single episode of OME of less than 3 months' duration, from the date of onset (if known) or from the date of diagnosis (if onset is unknown).	Recommendation (against)	KAS unchanged
6. Recurrent AOM without MEE	Clinicians should *not* perform tympanostomy tube insertion in children with recurrent AOM who do not have MEE in either ear at the time of assessment for tube candidacy.	Recommendation (against)	KAS unchanged; new patient information sheet
7. Recurrent AOM with MEE	Clinicians should offer bilateral tympanostomy tube insertion in children with recurrent AOM who have unilateral or bilateral MEE at the time of assessment for tube candidacy.	Recommendation	KAS unchanged

Thank you for your listening

OM-6 Survey[4]

Instructions: Please help us understand the impact of ear infections or fluid on your child's quality of life by checking one box [X] for each question below. Thank you.

Physical Suffering: Ear pain, ear discomfort, ear discharge, ruptured ear drum, high fever, or poor balance. How much of a problem for your child during the past 4 weeks?

[ ] Not present/no problem
[ ] Hardly a problem at all
[ ] Somewhat of a problem
[ ] Moderate problem
[ ] Quite a bit of a problem
[ ] Very much a problem
[ ] Extreme problem

Hearing Loss: Difficulty hearing, questions must be repeated, frequently says "what," or television is excessively loud. How much of a problem for your child during the past 4 weeks?

[ ] Not present/no problem
[ ] Hardly a problem at all
[ ] Somewhat of a problem
[ ] Moderate problem
[ ] Quite a bit of a problem
[ ] Very much a problem
[ ] Extreme problem

Speech Impairment: Delayed speech, poor pronunciation, difficult to understand, or unable to repeat words clearly. How much of a problem for your child during the past 4 weeks?

[ ] Not present/no problem (or not applicable)
[ ] Hardly a problem at all
[ ] Somewhat of a problem
[ ] Moderate problem
[ ] Quite a bit of a problem
[ ] Very much a problem
[ ] Extreme problem

Emotional Distress: Irritable, frustrated, sad, restless, or poor appetite. How much of a problem for your child during the past 4 weeks as a result of ear infections or fluid?

[ ] Not present/no problem
[ ] Hardly a problem at all
[ ] Somewhat of a problem
[ ] Moderate problem
[ ] Quite a bit of a problem
[ ] Very much a problem
[ ] Extreme problem

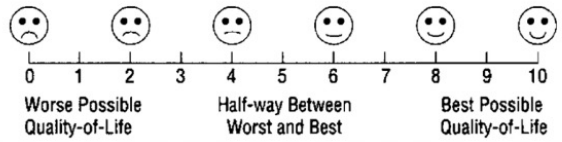
Activity Limitations: Playing, sleeping, doing things with friends/family, attending school or day care. How limited have your child's activities been during the past 4 weeks because of ear infections or fluid?

[ ] Not limited at all
[ ] Hardly limited at all
[ ] Very slightly limited
[ ] Slightly limited
[ ] Moderately limited
[ ] Very limited
[ ] Severely limited

Caregiver Concerns: How often have you, as a caregiver, been worried, concerned, or inconvenienced because of your child's ear infections or fluid over the past 4 weeks?

[ ] None of the time
[ ] Hardly any time at all
[ ] A small part of the time
[ ] Some of the time
[ ] A good part of the time
[ ] Most of the time
[ ] All of the time

Overall, how would you rate your child's quality of life as a result of ear infections or fluid? (Circle one number)



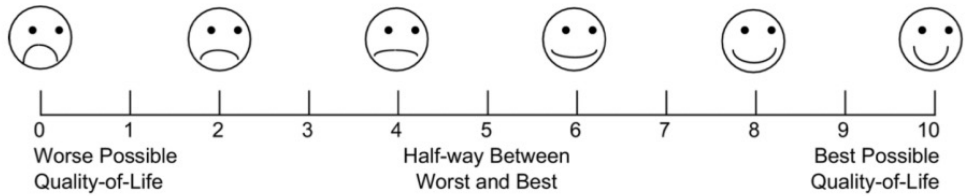
The 6-item health-related quality-of-life survey (OM-6) for chronic and recurrent otitis media.

CAREGIVER IMPACT QUESTIONNAIRE

How often did you or your partner experience the following problems during the past 3 months as a consequence of ear infections or ear fluid in your child? Please circle one number for each question.

	None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
1. Lack of sleep	1	2	3	4	5	6	7
2. Absence from work or education	1	2	3	4	5	6	7
3. Cancelling of family activities, such as trips, play dates, vacations	1	2	3	4	5	6	7
4. Changing daily activities, such as housework, shopping, or time with other siblings	1	2	3	4	5	6	7
5. Feeling nervous, agitated, or irritable	1	2	3	4	5	6	7
6. Feeling helpless or frustrated	1	2	3	4	5	6	7

7. Overall, how would you rate *your* quality of life during the past 3 months as a result of your child's ear infections or fluid (circle one number):



8. Are there other children in your family?

[ ] Yes [ ] No → skip questions 9 and 10

If there are other children in your family, then please indicate to what extent your agree or disagree with the statements below. Please circle one number for each question.

	Strongly agree	Agree	Not certain	Disagree	Strongly disagree
9. Our other children felt neglected or excluded when our child had an ear infection or fluid during the past 3 months	1	2	3	4	5
10. Our other children demanded extra attention when our child had an ear infection or fluid during the past 3 months	1	2	3	4	5

‖ Risk of recurrences of acute otitis media was categorized, with the use of a 16-point scale, as probably lesser (<8 points) or probably greater (≥8 points) on the basis of the following known or presumed risk factors: early age of onset of acute otitis media, numerous or frequent previous episodes of acute otitis media, receipt of multiple courses of antibiotic treatment (suggesting a higher risk of acute otitis media caused by resistant pathogens), eligibility for enrollment first evident during warm-weather months, parental characterization of previous episodes of acute otitis media as severe, eligibility for enrollment despite nonexposure to other young children, moderate or marked tympanic-membrane bulging during previous episodes of acute otitis media, most previous episodes of acute otitis media in both ears, and a high score on the Acute Otitis Media–Severity of Symptom scale during screening, at enrollment, or both. (Details are provided in the final version of the protocol.)