

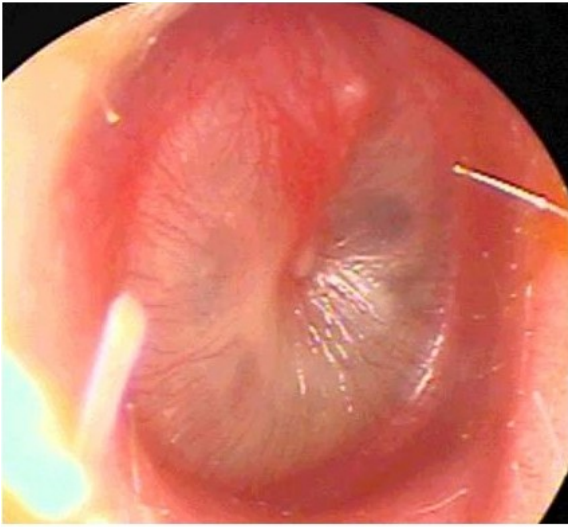
## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

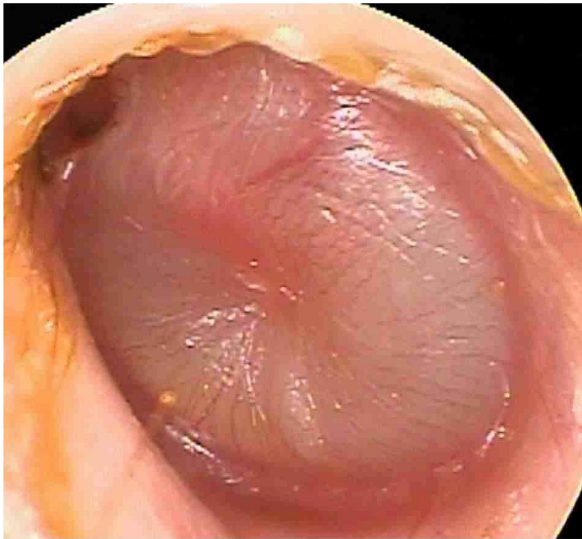
Supplement to: Hoberman A, Paradise JL, Rockette HE, et al. Shortened antimicrobial treatment for acute otitis media in young children. *N Engl J Med* 2016;375:2446-56. DOI: 10.1056/NEJMoa1606043

## TABLE OF CONTENTS

	<b>Pages</b>
<b>FIGURES S1-S3</b> .....	<b>2</b>
<b>TABLE S1</b> .....	<b>3-5</b>
<b>TABLE S2</b> .....	<b>6</b>
<b>TABLE S3</b> .....	<b>7-8</b>



**Figure S1.** Slight bulging of the tympanic membrane.



**Figure S2.** Moderate bulging of the tympanic membrane.



**Figure S3.** Marked bulging of the tympanic membrane

<b>Table S1. Selected Demographic and Clinical Characteristics of Children According to Treatment Group</b>			
<b>Characteristic</b>	<b>10-Day Treatment Group (N=257)</b>	<b>5-Day Treatment Group (N=258)</b>	<b>All Children (N=515)</b>
Site of enrollment -- no. (%) *			
CHP	163 (63)	163 (63)	326 (63)
Pediatric PittNet	47 (18)	47 (18)	94 (18)
KPAR	47 (18)	48 (19)	95 (18)
Age at entry -- no. (%)			
6-11 mo	129 (50)	132 (51)	261 (51)
12-17 mo	80 (31)	77 (30)	157 (30)
18-23 mo	48 (19)	49 (19)	97 (19)
Sex -- no. (%)			
Female	115 (45)	123 (48)	238 (46)
Male	142 (55)	135 (52)	277 (54)
Race -- no. (%) †			
White	116 (45)	110 (43)	226 (44) ‡
Black/African-American	110 (43)	118 (46)	228 (44)
Asian	7 (3)	5 (2)	12 (2)
Multiracial	21 (8)	21 (8)	42 (8)
Other	3 (1)	4 (2)	7 (1)
Ethnicity -- no. (%) †			
Not Hispanic or Latino	233 (91)	235 (91)	468 (91)
Hispanic or Latino	24 (9)	23 (9)	47 (9) §
Maternal level of education -- no. (%)			
Less than high school	31 (12)	26 (10)	57 (11)
High school graduate or equivalent	150 (58)	169 (66)	319 (62)
College graduate	76 (30)	62 (24)	138 (27)
Unknown	0	1 (0)	1 (0)

Type of health insurance -- no. (%)			
Private	84 (33)	75 (29)	159 (31)
Public	171 (67)	179 (69)	350 (68)
None	2 (1)	4 (2)	6 (1)
Exposure to other children -- no. (%)			
No	109 (42)	105 (41)	214 (42)
Yes	148 (58)	153 (59)	301 (58)
AOM-SOS score at entry -- no. (%) ¶			
3-5	43 (17)	59 (23)	102 (20)
6-8	75 (29)	70 (27)	145 (28)
9-11	98 (38)	95 (37)	193 (37)
12-14	41 (16)	34 (13)	75 (15)
AOM-SOS score at entry -- mean (SD)	8.6 (3)	8.2 (3)	8.4 (3)
Estimated severity of illness from pain and fever history only-- no. (%) **			
Likely nonsevere	111 (43)	121 (47)	232 (45)
Likely severe	146 (57)	137 (53)	283 (55)
Laterality of acute otitis media -- no. (%)			
Unilateral	136 (53)	126 (49)	262 (51)
Bilateral	121 (47)	132 (51)	253 (49)
Degree of tympanic membrane bulging in worse ear -- no. (%)			
Slight	35 (14)	45 (17)	80 (16)
Moderate	137 (53)	135 (52)	272 (53)
Marked	85 (33)	78 (30)	163 (32)

\* CHP denotes Children's Hospital of Pittsburgh; Pediatric PittNet is a CHP-affiliated practice-based research network; KPAR denotes Kentucky Pediatric and Adult Research.

† Race and ethnicity were reported by the parents.

‡ By comparison, of the children whose parents withheld consent for randomization, white children comprised 82% (P<0.001).

§ By comparison, of the children whose parents withheld consent for randomization, Hispanic or Latino children comprised 1% (P<0.001).

|| Exposure to other children was defined as exposure to at least three children for at least 10 hours per week.

¶ The Acute Otitis Media Severity of Symptoms (AOM-SOS) scale consists of seven discrete items -- tugging of ears, crying, irritability, difficulty sleeping, diminished activity, diminished appetite, and fever. Parents are asked to rate these symptoms, in comparison with the child's usual state, as "none," "a little," or "a lot," with corresponding scores of 0, 1, and 2. Thus, total scores range from 0 to 14, with higher scores indicating greater severity of symptoms.

\*\* The current American Academy of Pediatrics clinical practice guideline concerning the management of acute otitis media refers to children with "severe signs or symptoms" as those with "moderate or severe otalgia or otalgia for at least 48 hours or temperature 39°C (102.2°F) or higher."<sup>3</sup> In an effort to simulate that definition using scores on only two of the AOM-SOS items, we categorized the acute otitis media episode as "likely severe" if the parent described the child as having had "a lot" of ear tugging or "a lot" of fever during the preceding 24 hours.

**Table S2. Distribution of AOM-SOS Scores for the Index Acute Otitis Media Episode at the Times of Treatment Failure According to Treatment Group\***

	Treatment group		All
	10-Day	5-Day	
	N	N	N
<b>AOM-SOS scores at the Day 12-14 clinical assessment</b>			
<b>Missing</b>	5	1	6
<b>0</b>	11	25	36
<b>1</b>	5	6	11
<b>2</b>	4	11	15
<b>3</b>	5	5	10
<b>4</b>	3	9	12
<b>5</b>	3	5	8
<b>6</b>	3	1	4
<b>7</b>	.	4	4
<b>8</b>	.	4	4
<b>9</b>	.	1	1
<b>10</b>	.	1	1
<b>11</b>	.	1	1
<b>12</b>	.	2	2
<b>14</b>	.	1	1
<b>All</b>	39	77	116

AOM-SOS scores >8, 10-day vs. 5-day treatment group, P=0.17

\* The Acute Otitis Media Severity of Symptoms (AOM-SOS) scale consists of seven discrete items -- tugging of ears, crying, irritability, difficulty sleeping, diminished activity, diminished appetite, and fever. Parents are asked to rate these symptoms, in comparison with the child’s usual state, as “none,” “a little,” or “a lot,” with corresponding scores of 0, 1, and 2. Thus, total scores range from 0 to 14, with higher scores indicating greater severity of symptoms.

**Table S3. Distribution of AOM Recurrences Within the Entire Respiratory Season (Oct 1<sup>st</sup> - May 31<sup>st</sup>) According to Treatment Group, Clinical Assessment at Day 12-14 and Middle-Ear Effusion at the End-of-Treatment Visit\* (Restricted to Subjects Completing the Study)**

(\*If clinical success, then middle-ear effusion at the Day 12-14 end-of-treatment visit; if clinical failure, then middle-ear effusion at Day 16-30)

		Treatment group												All					
		10-Day						5-Day											
		MEE at the end-of-treatment visit						MEE at the end-of-treatment visit						MEE at the end-of-treatment visit					
		Unknown		No MEE		MEE		Unknown		No MEE		MEE		Unknown		No MEE		MEE	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
<b>Treatment failure by Day 12-14 visit</b>	<b>Cumulative No. of AOM recurrences</b>																		
	<b>0</b>	.	.	55	70.5	54	48.6	.	.	38	71.7	55	64.0	.	.	93	71.0	109	55.3
	<b>1</b>	.	.	12	15.4	36	32.4	.	.	12	22.6	18	20.9	.	.	24	18.3	54	27.4
	<b>≥ 2</b>	.	.	11	14.1	21	18.9	.	.	3	5.7	13	15.1	.	.	14	10.7	34	17.3
	<b>All</b>	.	.	78	100.0	111	100.0	.	.	53	100.0	86	100.0	.	.	131	100.0	197	100.0
<b>Treatment failure</b>	<b>Cumulative No. of AOM recurrences</b>																		
	<b>0</b>	9	75.0	4	66.7	6	30.0	1	14.3	11	68.8	20	45.5	10	52.6	15	68.2	26	40.6
	<b>1</b>	1	8.3	.	.	9	45.0	5	71.4	4	25.0	16	36.4	6	31.6	4	18.2	25	39.1
	<b>≥ 2</b>	2	16.7	2	33.3	5	25.0	1	14.3	1	6.3	8	18.2	3	15.8	3	13.6	13	20.3
	<b>All</b>	12	100.0	6	100.0	20	100.0	7	100.0	16	100.0	44	100.0	19	100.0	22	100.0	64	100.0
<b>Not seen for clinical assessment</b>	<b>Cumulative No. of AOM recurrences</b>																		
	<b>0</b>	7	63.6	.	.	.	.	8	61.5	.	.	.	.	15	62.5	.	.	.	.
	<b>1</b>	3	27.3	.	.	.	.	4	30.8	.	.	.	.	7	29.2	.	.	.	.
	<b>≥ 2</b>	1	9.1	.	.	.	.	1	7.7	.	.	.	.	2	8.3	.	.	.	.
	<b>All</b>	11	100.0	.	.	.	.	13	100.0	.	.	.	.	24	100.0	.	.	.	.
<b>All</b>	<b>Cumulative No. of AOM recurrences</b>																		
	<b>0</b>	16	69.6	59	70.2	60	45.8	9	45.0	49	71.0	75	57.7	25	58.1	108	70.6	135	51.7
	<b>1</b>	4	17.4	12	14.3	45	34.4	9	45.0	16	23.2	34	26.2	13	30.2	28	18.3	79	30.3
	<b>≥ 2</b>	3	13.0	13	15.5	26	19.8	2	10.0	4	5.8	21	16.2	5	11.6	17	11.1	47	18.0
	<b>All</b>	23	100.0	84	100.0	131	100.0	20	100.0	69	100.0	130	100.0	43	100.0	153	100.0	261	100.0

**Treatment success + Treatment failure**

10-day vs. 5-day: There is no difference in the proportion of subjects with at least one AOM recurrence within the entire respiratory season (p=0.09, adjusting for site, age, exposure and MEE status at the end-of-treatment visit).

MEE vs. no MEE at the end-of-treatment visit: There is a significant difference in the proportion of subjects with at least one AOM recurrence within the entire respiratory season (p<0.001, adjusting for site, age, exposure and treatment group).

There is no significant interaction between treatment group and MEE status at the end-of-treatment visit (p=0.64).



**Treatment success**

10-day vs. 5-day: There is no difference in the proportion of subjects with at least one AOM recurrence within the entire respiratory season ( $p=0.06$ , adjusting for site, age, exposure and MEE status at the end-of-treatment visit).

MEE vs. no MEE at the end-of-treatment visit: There is a significant difference in the proportion of subjects with at least one AOM recurrence within the entire respiratory season ( $p=0.01$ , adjusting for site, age, exposure and treatment group).

There is no significant interaction between treatment group and MEE status at the end-of-treatment visit ( $p=0.52$ ).

**Treatment failure**

10-day vs. 5-day: There is no difference in the proportion of subjects with at least one AOM recurrence within the entire respiratory season ( $p=0.35$ , adjusting for site, age, exposure and MEE status at the end-of-treatment visit).

MEE vs. no MEE at the end-of-treatment visit: There is a significant difference in the proportion of subjects with at least one AOM recurrence within the entire respiratory season ( $p=0.008$ , adjusting for site, age, exposure and treatment group).

There is no significant interaction between treatment group and MEE status at the end-of-treatment visit ( $p=0.87$ ).

**AOM:** denotes acute otitis media

**MEE:** denotes middle-ear effusion