

Original Article



Allergy is not a risk factor for recurrent acute otitis media: a real-life clinical experience

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Conflict of Interest

The authors have no financial conflicts of interest.

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ABSTRACT

Background: Acute otitis media (AOM) is the most common bacterial infection in children. Some children with AOM tend to be otitis-prone, such as to have frequent recurrence of AOM (RAOM). The possible RAOM risk factors are widely debated.

Objective: The aim was to identify predictive factors, including clinical data and endoscopic findings, for RAOM in children.

Methods: The current study was performed in a real-life setting, such as an otorhinolaryngologic (ORL) clinic. In this study, 1,002 children (550 males, 452 females; mean age, 5.77 ± 1.84 years), complaining upper airway symptoms, were consecutively visited. Detailed clinical history and nasal endoscopy were performed.

Results: Throughout the ORL visit, it was possible to define some factors involved in the recurrence of AOM, including female sex, artificial feeding, tonsillar and adenoid hypertrophy, whereas male sex and recurrent respiratory infections could protect from RAOM.

Conclusion: Allergy was not associated with RAOM. In addition, this real-life study identified some predictive factors of RAOM, thus also in a primary care setting it is possible to achieve important information that is relevant in clinical practice.

Keywords: Recurrent acute otitis media; Allergy; Real-life; Predictive factors; Child

INTRODUCTION

Acute otitis media (AOM) is an ear disease defined by signs or symptoms of acute infection [1]. AOM is the most common bacterial infection in children [2-6]. Consequently, AOM is the most common reason for antibiotic prescription in the pediatric age [7, 8]. Almost all children experience at least one episode of AOM during childhood. Therefore, the burden of AOM is relevant both concerning the direct (healthcare expense) and indirect cost (loss of school and work days) and the impact on quality of life of children and their parents. Moreover, antibiotic overuse is the main cause of the increase of multidrug-resistant microbes as well as for the occurrence of adverse reactions [9, 10]. For these reasons, several guidelines on AOM management were performed to optimize therapy [2-4].

Notably, some children with AOM tend to be otitis-prone, such as to have frequent recurrence of AOM (RAOM). International guidelines on AOM management define RAOM when at least

3 episodes occur in the preceding 6 months or at least 4 episodes in the preceding year [3-6]. So, the identification of factors involved in the recurrence may have a practical interest. In particular, allergy is still a controversial and debated risk factor for RAOM.

Therefore, the current study was performed in a real-life setting, such as an otorhinolaryngologic (ORL) clinic, with the aim to identify predictive factors, including clinical data, allergy, and endoscopic findings, for RAOM in children.

MATERIALS AND METHODS

Patients

A total of 1,002 children (550 males, females; mean age, 5.77 ± 1.84 years), complaining upper airway symptoms, were consecutively referring to an ORL clinic during the period 2015–2017. They were consecutively enrolled in the study. Inclusion criteria were: age between 3 and 10 years and complaints of upper airways. Exclusion criteria were: current disorder(s) and treatment(s) able to interfere with the findings. The current study complied with the principles of the Declaration of Helsinki and its recommendations guiding physicians in biomedical research involving human subjects (adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964 and amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975; the 35th Asia Pacific allergy World Medical Assembly, Venice, Italy, October 1983; and the 41st World Medical Assembly, Hong Kong, September 1989). The study was approved by the local Review Board (Villa Montallegro, 08/2014) and informed written consent was obtained by the parents.

All children were evaluated by detailed medical history (concerning RAOM, premature birth, feeding type [breastfeeding or artificial], familiar atopy, passive smoking, wheezing, recurrent respiratory infections); clinical visit; nasal endoscopy (assessing turbinate, tonsillar, and adenoid hypertrophy); and skin prick test.

Tonsil hypertrophy was defined according to Friedman's classification [11]. The adenoids hypertrophy was defined according to Parikh classification [12]. Turbinate Hypertrophy was considered as previously described and validated [13].

Skin prick test was performed as stated by the European Academy of Allergy and Clinical Immunology [14]. The panel of tested allergens included: grasses mix, *Parietaria officinalis*, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, olive tree, birch, cat, dog, *Alternaria alternata*, and cypress, using the extracts of Stallergenes-Greer (Milan, Italy).

The definition of allergy was the consistency between symptom occurrence and the exposure to the sensitizing allergen, such as the demonstration of a cause/effect relationship.

The definition of prematurity was a birth occurred between the 22nd week and the 37th complete week of gestation. Family atopy was the presence of at least a parent with allergic disease. Wheezing was considered as present in the last year.

Statistical analysis

Continuous variables were expressed as means with standard deviations (SDs) and categorical variables as the number of subjects and percentage values. The univariate

logistic regression models were performed to screen the effect of clinical and demographic variables on the RAOM. The odds ratios associated with RAOM were calculated with their 95% confidence interval for each factor from the logistic model. The likelihood ratio test was used as a test of statistical significance and the estimated p values were adjusted for multiple comparisons by the Bonferroni correction method. The covariates with a p value <0.05 were then selected for the multivariate analysis, where the RAOM was the dependent variable. Possible multicollinearity was assayed using intraclass correlation coefficient (ICC) and the variables with an ICC >0.5 were considered associated. Multivariate analysis was performed using again the logistic regression model and the model selection was done by the Akaike Information Criterion. Moreover, multiplicative interaction terms were used to test whether the feeding type was different according to the risk factors.

The multivariate model performance was assayed using K-fold cross-validation. In particular, the dataset was split into a training set (95% of the data) and a test set (5% of the data) randomly for k different times and then the percentage of total items classified correctly, false positive and false negative rate were estimated using confusion matrix.

For the results suggestive of an interaction with the feeding type factor ($p < 0.05$), a stratified analysis was then performed based on that variable using the penalised logistic model.

Differences, with a p value less than 0.05, were selected as significant and data were acquired and analyzed in R v3.5.3 (R Foundation for Statistical Computing, Vienna, Austria) environment [15].

RESULTS

A total of 1,002 (550 males) children were consecutively visited and included in this study. The demographic and clinical characteristics of the study participants are summarised in **Table 1**. Briefly, the mean age was 5.77 years (SD, 1.84). The majority of children ($N = 765$) received breastfeeding, while 236 received artificial feeding time. About the primary outcome, 210 children (20.96%) had RAOM, while 792 (79.04%) had no RAOM, so children were subdivided into 2 groups: with and without RAOM.

Descriptive statistics of demographic and clinical factors in comparison to RAOM are reported in **Table 2**. The mean age of children in the 2 groups was quite similar (5.84 and 5.52 years, respectively). In patients without RAOM, artificial feeding time was received by 169 children (71.61%) while 623 children (81.44%) received breastfeeding. Instead, in children with RAOM, 67 (28.39%) and 142 (18.56%) had artificial feeding and breastfeeding respectively.

The univariate logistic regression analysis (**Table 2**), using the complete set of data, demonstrated a significant association among sex, feeding type, wheezing, recurrent respiratory infections, turbinate hypertrophy, tonsillar hypertrophy, adenoid hypertrophy, and RAOM ($p < 0.05$). Multicollinearity presence was not observed among covariates (**Table 3**; ICCs < 0.50).

The multivariate analysis (**Table 4**), confirmed a statistically significant effect of sex, feeding type, recurrent respiratory infections, tonsillar hypertrophy, and adenoid hypertrophy, on RAOM ($p \leq 0.001$, $p \leq 0.01$, $p < 0.0001$, $p < 0.0001$, and $p \leq 0.05$, respectively).

Table 1. Demographic and clinical characteristics of study participants (n = 1,002)

Characteristic	Value
Recurrent acute otitis media	
Absence	792 (79.04)
Presence	210 (20.96)
Age (yr)	5.77 ± 1.84
Sex	
Female	450/1,000 (45.00)
Male	550/1,000 (55.00)
Prematurity	
No	924/1,001 (92.31)
Yes	77/1,001 (7.69)
Feeding type	
Artificial	236/1,001 (23.58)
Breastfeeding	765/1,001 (76.42)
Passive smoking	
No	929 (92.71)
Yes	73 (7.29)
Family atopy	
No	273/999 (27.33)
Yes	726/999 (72.67)
Allergic rhinitis	
No	453/997 (45.44)
Yes	544/997 (54.56)
Wheezing	
No	872/1,001 (87.11)
Yes	129/1,001 (12.89)
Recurrent respiratory infections	
No	364/997 (36.51)
Yes	633/997 (63.49)
Turbinate hypertrophy	
No	288 (28.74)
Yes	714 (71.26)
Tonsillar hypertrophy	
No	233/1,000 (23.3)
Yes	767/1,000 (76.7)
Adenoid hypertrophy	
No	370/1,001 (36.96)
Yes	631/1,001 (63.04)

Values are presented as number (%) or mean ± standard deviation.

In particular, in males, the chance of having RAOM was about 45% less likely than that in females, keeping constant the other covariates (odds ratio [OR], 0.55). A 38% decrease in RAOM chance was shown in children with breastfeeding compared to children that received artificial feeding (OR, 0.62). Moreover, children with recurrent respiratory infections had about 67% less likely to have RAOM than children without recurrent respiratory infections, keeping constant the other covariates (OR, 0.33).

Children with tonsillar hypertrophy had a chance 3 times more likely of having RAOM than children without tonsillar hypertrophy, maintaining constant the other covariates (OR, 2.97). Consistently, children with adenoid hypertrophy had a chance of having RAOM about 1.4 times more likely than children without adenoid hypertrophy, maintaining constant the other covariates (OR, 1.36).

Finally, the multivariate model performance showed an excellent model average accuracy (accuracy = 0.81). All the accuracy scores are greater than 0.66 and they ranged from 0.66 to 0.96. Moreover, low false positive and negative rates were 0.01 and 0.18, respectively.

Table 2. Contingency tables and summary output of the univariate analysis

Characteristic	Descriptive statistic		Univariate analysis	
	Recurrent acute otitis media		OR (95% CI)	p value [†]
	Absence, 792 (79.04)	Presence, 210 (20.96)		
Age (yr)	5.84 ± 1.87	5.52 ± 1.69	0.93 (0.85–1.01)	0.9407
Sex*				<0.01
Female	333 (74)	117 (26)	1	
Male	457 (83.09)	93 (16.91)	0.56 (0.41–0.77)	
Prematurity				0.8649
No	736 (79.65)	188 (20.35)	1	
Yes	56 (72.73)	21 (27.27)	1.66 (0.95–2.78)	
Feeding type*				<0.01
Artificial	169 (71.61)	67 (28.39)	1	
Breastfeeding	623 (81.44)	142 (18.56)	0.54 (0.39–0.77)	
Passive smoking				0.9999
No	739 (79.55)	190 (20.45)	1	
Yes	53 (72.6)	20 (27.4)	1.51 (0.85–2.58)	
Family atopy				0.8737
No	207 (75.82)	66 (24.18)	1	
Yes	583 (80.3)	143 (19.7)	0.73 (0.53–1.03)	
Wheezing*				<0.05
No	676 (77.52)	196 (22.48)	1	
Yes	115 (89.15)	14 (10.85)	0.46 (0.25–0.79)	
Allergic rhinitis				0.1039
No	341 (75.28)	112 (24.72)	1	
Yes	451 (82.9)	93 (17.1)	0.66 (0.48–1.01)	
Recurrent respiratory infections*				<0.0001
No	254 (69.78)	110 (30.22)	1	
Yes	538 (84.99)	95 (15.01)	0.42 (0.3–0.57)	
Turbinate hypertrophy*				<0.01
No	207 (71.88)	81 (28.12)	1	
Yes	585 (81.93)	129 (18.07)	0.56 (0.4–0.77)	
Tonsillar hypertrophy*				<0.0001
No	213 (91.42)	20 (8.58)	1	
Yes	579 (75.49)	188 (24.51)	2.32 (1.67–3.34)	
Adenoid hypertrophy*				<0.0001
No	325 (87.84)	45 (12.16)	1	
Yes	466 (73.85)	165 (26.15)	1.84 (1.44–2.4)	

Values are presented as number (%) or mean ± standard deviation.

OR, odd ratio; CI, confidence interval.

*Variables entering in the multivariate analysis (see the text for abbreviations and further details). [†]Likelihood ratio p value.

Table 3. Intraclass correlation matrix

	Sex	Feeding	Wheezing	Recurrent respiratory infections	Turbinate hypertrophy	Tonsillar hypertrophy	Adenoid hypertrophy
Sex	1	-	-	-	-	-	-
Feeding	0.03 (-0.03 to 0.09)	1	-	-	-	-	-
Wheezing	-0.20 (-0.26 to -0.14)	-0.41 (-0.46 to -0.36)	1	-	-	-	-
Recurrent respiratory infections	0.13 (0.07–0.19)	0.05 (-0.01 to 0.11)	-0.28 (-0.33 to -0.22)	1	-	-	-
Turbinate hypertrophy	-0.03 (-0.09 to 0.03)	0.02 (-0.04 to 0.09)	-0.25 (-0.31 to -0.19)	-0.01 (-0.07 to 0.06)	1	-	-
Tonsillar hypertrophy	0.08 (0.02–0.14)	0.03 (-0.03 to 0.10)	-0.41 (-0.46 to -0.36)	0.25 (0.19 to 0.31)	0.00 (-0.07 to 0.06)	1	-
Adenoid hypertrophy	0.09 (0.03–0.16)	-0.02 (-0.08 to 0.04)	-0.27 (-0.32 to -0.21)	0.00 (-0.06 to 0.06)	-0.01 (-0.07 to 0.06)	0.31 (0.25 to 0.36)	1

Results are expressed as the intraclass correlation coefficient with 95% confidence interval.

Table 4. Multivariate analysis, the predictor effects on the recurrent acute otitis media (N = 986)

Characteristic	Multivariate analysis	
	OR (95% CI)	p value [†]
(Intercept)	0.52 (0.35–0.77)	<0.01
Sex		<0.001
Female	1	
Male	0.55 (0.39–0.77)	
Feeding type		<0.05
Artificial	1	
Breastfeeding	0.62 (0.43–0.9)	
Recurrent respiratory infections		<0.0001
No	1	
Yes	0.33 (0.24–0.47)	
Tonsillar hypertrophy		<0.0001
No	1	
Yes	2.97 (2.05–4.45)	
Adenoid hypertrophy		<0.05
No	1	
Yes	1.36 (1.03–1.81)	

OR, odd ratio; CI, confidence interval.

*Variables entering in the multivariate analysis (see the text for abbreviations and further details). [†]Likelihood ratio p value.

DISCUSSION

RAOM represents an intriguing challenge in the clinical practice for both the pediatrician and the ORL specialist. The AOM diagnosis requires adequate procedure and precise differential diagnosis, mainly concerning otitis media with effusion. There is current debate concerning the identification of risk factors associated with RAOM. Allergy is a controversial candidate. Moreover, AOM therapy is controversial as many guidelines suggest watchful waiting for mild-moderate episodes in children > 2 years aged. Moreover, the prevention of RAOM is overwhelmingly desirable, even though it is debated. At present, there is no convincing evidence of preventing RAOM by the proposed treatments both conventional and not [2–6]. Therefore, as there is no convincing preventing and effective preventive treatment for RAOM, to know predictive factors for RAOM could be fruitful from a pragmatic point of view.

Therefore, this real-life study aimed to evaluate whether some clinical data and/or endoscopic findings may be a predictive marker of RAOM in children during an ORL visit. In other words, the current study would identify easy and simple factors that could be achieved during an ORL consultation.

The analysis of data allowed to define some variables able to predict RAOM in children with upper respiratory complaints. In particular, male sex, breastfeeding, and recurrent respiratory infections were a protective factor for RAOM, whereas adenoid and tonsillar hypertrophy were promoting factors.

These outcomes confirm partially known mechanisms involved in RAOM, even though they reinforce the value of a thorough ORL visit, including endoscopy. In particular, anatomic and mechanic features play a relevant pathogenic role in favouring the recurrence of AOM. Actually, tuba compression/obstruction is a crucial factor in promoting infections in the middle ear.

Interestingly, recurrent respiratory infections seem to be negatively associated with RAOM. This finding confirms the dichotomy between respiratory and ear infective recurrence as it is a common experience to observe children with RAOM without recurrent respiratory infections, such as RAOM is a separate issue. In addition, recurrent respiratory infections often are treated, if not overtreated, with antibiotics and immunomodulators so that RAOM could be diminished.

Breastfeeding is well known as an important protective measure to promote the global wellbeing of the child. Male sex may be another protective factor, probably for hormonal balance.

On the other hand, the current study has some limitations, including the cross-sectional design, the lack of biomarkers measurement able to identify specific pathogenic mechanisms. However, the strength of the study is the high number of enrolled children and the real-life setting, so the outcomes may mirror what happens in daily clinical practice.

In conclusion, the current study showed that allergy was not a risk factor for RAOM. Moreover, this study demonstrated that, during an ORL visit, it was possible to define some factors involved in the recurrence of AOM, including female sex, artificial feeding, tonsillar and adenoid hypertrophy, whereas male sex and recurrent respiratory infections could protect from RAOM.

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