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Diagnosis and management of acute mastoiditis in a cohort of Italian children

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Expert Reviews

Diagnosis and management of acute mastoiditis in a cohort of Italian children

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Objective: The Italian Society for Pediatric Infectious Diseases created a registry to determine the management of pediatric acute mastoiditis (AM) in Italy. Methods: A cross-sectional survey of paediatricians was conducted to evaluate hospitalization due to AM in Italian pediatric wards between 1 January 2002, and 31 December 2013. Results: A total of 913 children (561 males, 61.4%) were included in this study. The annual number of AM cases significantly increased during the study period (30 in 2002 and 98 in 2013) but only among older children (≥4 years old; p = 0.02). AM complications occurred in 69 (7.6%) of the children and sequelae were observed in 13 (1.4%) patients. Conclusion: The annual number of pediatric AM cases admitted to Italian pediatric wards increased in the past few years; this increase was strictly age-related. The risk of severe AM complications appeared relatively low, and most AM cases could be treated conservatively.

Keywords: acute mastoiditis • acute otitis media • antibiotic treatment • ear • pediatric otolaryngology • pneumococcal vaccination

In the pre-antibiotic era, acute mastoiditis (AM) was a common complication of acute otitis media (AOM). Between 20% and 50% of AOM cases progressed to AM, which has a 100% mortality rate [1,2]. The introduction of antibiotics led to a sharp decline in AM incidence. By the end of the last century, less than 1% of children with AOM suffered from AM worldwide despite poor diagnostic and therapeutic approaches in developing countries [3–6]. However, in recent years, despite the global incidence of AM remaining stable [7] or continuing to decline [8] in some countries, in others a significant increase in the number of children suffering from this disease was evidenced [9]. The most common explanations include the emergence of antibiotic resistance among AOM-causing pathogens and restricted antibiotic use in AOM treatment to prevent antibiotic misuse in most of the recommendations for diagnosis and therapy of this disease prepared worldwide [10–13]. In addition, the inclusion of the heptavalent and 13-valent pneumococcal conjugate vaccines (PCV7 and PCV13, respectively) in pediatric immunization schedules are thought to contribute to this rise in AM cases due to the serotype replacement phenomenon [14–16]. In Italy, national AOM treatment guidelines were prepared in 2010 [17]. PCV7 was included free of charge in the national immunization schedule in 2002 but vaccination coverage was very low in many regions until 2007 and PCV13, licensed in 2010, has only recently reached >80% coverage in many of the most populated regions [18]. The Italian Society for Pediatric Infectious Diseases (SITIP) created a pediatric AM registry to determine the prevalence of pediatric AM in Italy and to describe the clinical findings, microbiology, treatment, and complications of AM. In this study, we analyzed and described all AM cases between 2002 and 2013 that were reported by pediatricians in the SITIP AM registry.

Material & methods

Study design & population

We conducted a cross-sectional survey of pediatricians who participated in the SITIP AM registry between 1 September 2013 and 31 December 2013. The SITIP AM registry includes all pediatric infectious disease (PID) specialists working in hospitals in Italy. Pediatricians were e-mailed between 1 January 2014 and 31 January 2014 and asked to respond to a brief

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survey. Pediatricians were asked about AM patients <18 years who had been admitted to their hospital between 1 January 2002 and 31 December 2013. Surveys could be returned by mail or completed online using the web link provided in the e-mail. Reminder e-mails were sent 1 month later, and reminder letters and replacement surveys were sent to non-respondents after an additional 8 weeks. This study was approved by the Ethics Committee of the University of Milan, Italy, and informed consent was obtained from all participants.

Survey

The survey was prepared by two senior PID specialists (P.M. and S.E.). A convenience sample of PID specialists were administered the survey as a pilot. The survey was comprised of four sections: (i) general characteristics of the AM patients; (ii) clinical manifestations of the AM patients considered suggestive of AM; (iii) radiological and laboratory tests used to support AM diagnosis; and (iv) treatment prescribed for AM (including the molecule, route of administration, dosage, and duration of therapy) and its clinical outcome. All the data had to be obtained from ambulatory or hospital medical records. Among the general characteristics data regarding vaccine administration were included. Particular attention was paid to the influenza and pneumococcal vaccine administration. Enrolled subjects were considered fully vaccinated against pneumococcal infections when they have received, according to the Italian vaccination schedule [18], two doses of PCV7 or PCV13 at 3 and 5 months of age and a booster dose at about 1 year or two doses in the second year or a single dose between 2 and 5 years of age.

Statistical analysis

Continuous variables are presented as mean values ± standard deviation or median with the interquartile range. Continuous variables were analyzed using a two-sided Student's test if they were normally distributed (based on Shapiro–Wilk's test) or a two-sided Wilcoxon rank-sum test if they were not normally distributed. Categorical variables are presented as numbers and percentages and were analyzed using contingency tables and the Chi-squared or Fisher's exact test, as appropriate. AM patients were stratified according to age (<2 years, between 2 and 4 years, and ≥4 years). Cochran-Armitage trend tests were used to analyze patient enrolment during the study period. All statistical analyses were two-tailed, and a p-value ≤0.05 was considered statistically significant.

Results

Twenty-five hospitals with PID wards participated in this study. Table 1 summarizes the demographic characteristics of AM cases included in the study. More than 80% of the cases were diagnosed in five geographical regions (Lombardy, Lazio, Emilia, Piedmont, Veneto); these regions had the highest number of participating PID wards (14/25, 56.0%). Data on 913 AM patients (561 males, 61.7%) with a mean admission age of 5.1 ± 3.8 years (median, 4.0 years; range: 0.1–17 years) were included. Among these patients, 246 (26.9%) were <2 years old, 204 (22.3%) were between 2 and 4 years old, and 463 (50.7%) were ≥4 years old. No differences in ethnicity and baseline clinical information were observed between these age groups.

Figure 1 shows the distribution of hospitalized AM cases according to age. The annual number of AM diagnoses significantly increased during the study period (p = 0.03). This increase was statistically significant for older (≥4 years old, p = 0.02) but not younger (<2 years old, p = 0.69; 2–4 years old, p = 0.22) patients.

The number of AM diagnoses sharply increased after 2010. We had data on PCV7 and PCV13 vaccination for 362 children; 202 (55.8%) of these children were not fully vaccinated. Only 18 of 108 (16.7%) children with AM were vaccinated with either PCV7 or PCV13 before 2010. After 2010, 142 of 254 (55.9%; p < 0.0001) children with AM were fully vaccinated.

Table 2 summarizes the clinical symptoms and manifestations of the children with AM. Before hospitalization, only 667 (72.3%) of the children had at least one symptom typical of AOM or a documented AOM diagnosis via otoscopy. This was significantly more common among children <2 years than in older patients (p < 0.001). Fever, othalgia, irritability, anorexia, and rhinitis were significantly more common among children <2 years than in the other age groups. Rhinorrea, retroauricolar erythema, and retroauricolar edema were also significantly more common among children <2 years than in the other age groups.

AM microbiology was evaluated in 177 subjects. Exudate was obtained from the ear canal for culturing primarily via tympanocentesis in 147 (83.0%) patients or puncturing of retro-auricular abscesses while under local anesthesia in 5 (2.8%) patients; in 25 (14.1%) patients, exudate was collected pre-operatively. In 78 (44.1%) of the cases, no pathogen was isolated. The most frequently isolated pathogen was *Pseudomonas aeruginosa* (29.4%), followed by *Staphylococcus aureus* (6.2%); in these cases, exudate was collected from the ear canal. *Streptococcus pneumoniae* was identified in 10 (5.7%) cases; in these cases, exudate was obtained pre-operatively.

Table 3 summarizes the radiographic examinations performed at diagnosis. AM was diagnosed or confirmed using radiographic examinations in 477 (51.7%) cases. In 415 (87.0%) cases, imaging was used to confirm the clinical suspicion of AM. However, in 62 (13.0%) cases, AM was diagnosed using CT scans, which were performed for neurological problems with no clinical evidence of AM. Typically, these diagnoses were made after observing mastoid changes consistent with AM and occurred primarily among older patients and in more recent years. CT scans of the mastoid were most common (272/913 children, 29.8%), followed by that of the brain (107/913 children, 11.7%). Brain MRI had a limited role in this cohort (67/913 children, 7.3%), and cranic x-rays were used in less than 5% of the cases (32/913 children, 3.5%).

During hospitalization, most patients (840/913, 92.0%) underwent intravenous antibiotic treatment. However, in 288 (34.3%) cases, patients were switched to oral antibiotics after 3–7 days. More than 80% of patients received monotherapy consisting of a third-generation cephalosporin (primarily

Table 1. Characteristics of the children with a diagnosis of acute mastoiditis who were included in the study.				
	n (%)	<2 years n (%)	2–4 years n (%)	≥4 years n (%)
Total patients	913	246	204	463
Geographic regions †				
Lombardy	217 (23.5)	68 (27.6)	37 (18.1)	112 (24.2)
Lazio	176 (19.1)	34 (13.8)	49 (24.0)	92 (19.9)
Emilia	148 (16.0)	45 (18.3)	38 (18.6)	63 (13.6)
Piedmont	118 (12.8)	36 (14.6)	30 (14.8)	52 (11.2)
Veneto	115 (12.5)	32 (13.1)	17 (8.3)	59 (12.7)
Other Italian regions	149 (16.1)	31 (12.6)	33 (16.2)	85 (18.4)
Gender				
Male	561 (61.4)	153 (62.2)	123 (60.3)	285 (61.6)
Female	352 (38.6)	93 (37.8)	81 (39.7)	178 (38.4)
Age (years)				
Mean ± SD	5.1 ± 3.8	1.1 ± 0.4	3.0 ± 0.5	8.0 ± 3.0
Median (IQR)	4.0 (5.6)	1.2 (0.6)	3.1 (0.9)	7.4 (4.9)
Ethnicity				
Caucasian	856 (93.8)	230 (93.5)	190 (93.1)	436 (94.2)
Other clinical information				
Born at term	703 (76.9)	196 (79.7)	155 (75.9)	352 (76.0)
Breastfeeding for at least 1 month	570 (62.4)	163 (66.2)	125 (61.3)	282 (60.9)
History of allergy	52 (5.7)	10 (4.1)	11 (5.4)	31 (6.7)

†The sum does not add up to the total due to a few missing values.
IQR: Interquartile range; SD: Standard deviation. No significant differences were observed.

ceftriaxone) at a proper dosage. The median duration of antibiotic therapy was 13 days (ranging from 7 to 28 days). After a positive AM diagnosis, 79 (8.5%) patients underwent surgery. Mastoidectomy was performed in 40 (50.6%) cases, the retroauricolar abscess was drained in 12 (15.2%), and explorative miringotomy was performed in 27 (34.1%).

Table 4 summarizes the evolution of AM after diagnosis. The median duration of hospitalization was 7.1 days (range: 0–43 days). Complications occurred in 69 (7.6%) cases, but there were no differences between age groups. Thrombosis of the ipsilateral sinus was the main complication observed (22/913, 2.4%), followed by facial palsy (16/913, 1.8%). In 900 (98.6%) cases, patients were considered cured after discharge: sequelae were observed in 13 (1.4%) patients. However, no patients died.

Discussion

This 12-year retrospective study of pediatric AM provides updated information on the frequency with which AM is diagnosed among Italian children and on how supposed or demonstrated AM is treated by PID specialists in Italian hospitals.

Between 2002 and 2013, the annual number of pediatric AM cases admitted to the Italian hospitals in different regions of Italy progressively increased. The increase was strictly

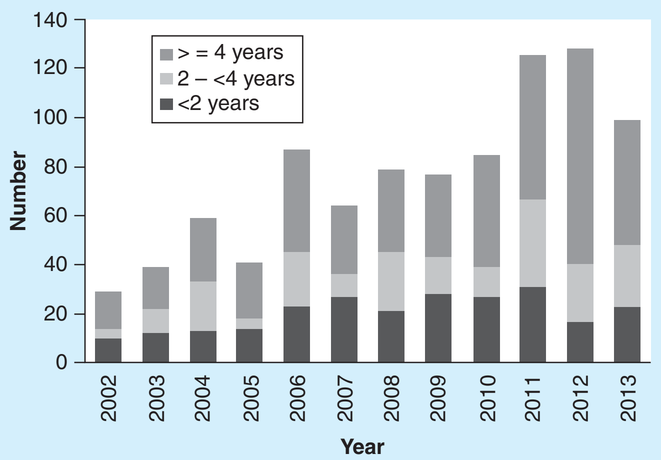

Figure 1. Age distribution of acute mastoiditis cases in the participating hospitals during 2002–2013.

Table 2. Acute mastoiditis symptoms diagnosis according to patient age.

	n (%)	<2 years n (%)	2–4 years n (%)	≥4 years n (%)	p-value
Total patients	913	246	204	463	
Symptoms					
Fever ≥38˚C	599 (65.3)	195 (79.3)	137 (67.2)	264 (57.0)	<0.001
Othalgy	665 (72.8)	142 (57.7)	148 (72.6)	375 (81.0)	<0.001
Irritability	139 (15.2)	52 (21.1)	38 (18.6)	49 (10.6)	<0.001
Anorexia	43 (4.7)	17 (6.9)	13 (6.4)	13 (2.8)	0.02
Vomit	45 (4.9)	11 (4.5)	5 (2.5)	29 (6.3)	0.10
Sleeping disturbance	74 (8.1)	21 (8.5)	16 (7.8)	37 (8.0)	0.96
Rhinitis	133 (14.6)	58 (23.6)	36 (17.7)	39 (8.4)	<0.001
Cough	62 (6.8)	23 (9.4)	16 (7.8)	23 (5.0)	0.07
Signs					
Rhinorrea	130 (14.2)	55 (22.3)	25 (12.3)	50 (10.8)	0.007
AOM	167 (18.3)	54 (21.9)	37 (18.1)	76 (16.4)	0.37
Othorrea	175 (19.2)	40 (16.3)	36 (17.6)	99 (21.4)	0.79
Otitis media with effusion	234 (25.6)	66 (26.8)	49 (24.0)	119 (25.7)	0.56
Retroauricolar erythema	619 (67.8)	190 (77.2)	133 (65.2)	296 (63.9)	0.006
Retroauricolar edema	637 (69.8)	199 (80.9)	139 (68.1)	299 (64.6)	<0.001
Retroauricolar pain	592 (64.8)	152 (61.8)	130 (63.7)	310 (66.9)	0.74

AOM: Acute otitis media.

age-related and significantly higher among children aged ≥4 years. We were unable to calculate the actual incidence and prevalence of AM in children in these geographic areas since not all AM cases in each region were evaluated. However, the increasing number of AM cases is consistent with reports published in the past 15 years [7]. Thus, the increase in pediatric AM may be due to several factors such as the increase in AOM-causing bacteria that have antibiotic resistance, serotype replacement following the administration of PCV, changes to health service access, and above all, the practice of 'watchful waiting' for AOM [19]. In this study, watchful waiting seems to have played a predominant role in the increase in AM incidence. The increase in AM diagnoses was particularly evident after 2010. In 2010, national guidelines for Italy were published that recommended watchful waiting for select AOM cases and restricted antibiotic use in older children [17].

The number of AM diagnoses increased despite the implementation of regional programs that improved the administration of PCV to infants and children. AM cases among children who were fully vaccinated with PCV7 or PCV13 increased over time, which could suggest that these vaccines offer poor protection against AM. Several studies have reported conflicting results on the impact of PCV7 or PCV13 on AM incidence. One study has reported a decrease in AM incidence after the introduction of PCV7 [16]; however, another study reported no change or even an increase in AM incidence [20]. Recently, one study observed a sudden initial decline in AM incidence in Colorado [15]. In that study, AM incidence eventually returned to pre-PCV7 levels, which may be explained by replacement phenomenon [15]. PCV13 has also appeared to reduce AM incidence [21]; however, not enough time has passed to determine whether possible serotype replacement may lead to an increase in incidence [21]. In our study, the low incidence of AM pneumococcal cases may explain why we did not observe an impact by either PCV7 or PCV13 vaccination. In addition, the number of patients for whom microbiological studies were performed was too small to draw firm conclusions about the effect of these vaccines on AM incidence.

However, it is possible that the increase in the annual number of AM cases diagnosed in the participating hospitals does not reflect the real pediatric AM incidence in Italy. This study was a non-population-based study. A recent evaluation has shown that non-population-based studies frequently lead to reports of increased AM incidence, while population-based studies do not [5]. Thus, the changes in AM incidence found in the literature could be attributed to changes in how studies are conducted rather than actual changes in disease incidence. In addition, the merging of health care facilities may also lead to the perception that AM incidence has increased [22].

Table 3. Radiographic examinations performed at diagnosis according to patient age.

	n (%)	<2 years n (%)	2–4 years n (%)	≥4 years n (%)	p-value
Total patients	913	246	204	463	
Cranic x-ray					
No	881 (96.5)	235 (95.5)	199 (97.5)	447 (96.5)	0.55
Yes	32 (3.5)	11 (4.5)	5 (2.5)	16 (3.5)	
Brain computed tomography					
No	806 (88.3)	231 (93.9)	177 (86.8)	398 (86.0)	0.001
Yes	107 (11.7)	15 (6.1)	27 (13.2)	65 (14.0)	
Mastoid computed tomography					
No	641 (70.2)	171 (69.5)	148 (72.5)	322 (69.5)	0.94
Yes	272 (29.8)	75 (30.5)	56 (27.5)	141 (30.5)	
Brain magnetic resonance					
No	846 (92.7)	234 (95.1)	187 (91.7)	425 (91.8)	0.19
Yes	67 (7.3)	12 (4.9)	17 (8.3)	38 (8.2)	

The criteria for diagnosing AM remain controversial and change over time, which could possibly result in false results and in overestimation of the incidence of AM. In this study, we found more than 25% of the children with AM diagnoses, a prevalence only slightly lower than that observed in a study of Swedish children who did not have symptoms of a previous AOM episode and, consequently, should have not been included among AM cases [23]. CT or MR imaging has been shown to contribute to AM diagnoses; however, these tests can lead to false acute AM diagnosis. When CT and MR scans are performed for clinical problems besides AM, mastoid images consistent with AM can be observed despite the lack of any

Table 4. Evolution of acute mastoiditis after diagnosis according to patient age.

	n (%)	<2 years n (%)	2–4 years n (%)	≥4 years n (%)	p-value
Total patients	913	246	204	463	
Duration of hospitalization					
Mean ± standard deviation, days	7.1 ± 5.1	7.2 ± 5.1	7.7 ± 5.7	6.7 ± 4.9	0.69
Patients with complications	69 (7.6)	13 (5.3)	19 (9.3)	37 (8.0)	0.14
Thrombosis of the ipsilateral sinus	22 (2.4)	5 (2.0)	5 (2.4)	12 (2.6)	0.76
Facial palsy	16 (1.8)	3 (2.8)	4 (1.9)	9 (1.9)	0.70
Subperiosteal abscess	12 (1.3)	2 (0.8)	3 (1.5)	7 (1.5)	0.43
Dizziness	10 (1.1)	2 (0.8)	2 (0.9)	6 (1.3)	1.00
Intracranial abscess	5 (0.5)	0 (0.0)	3 (1.5)	2 (0.4)	0.09
Meningitis	3 (0.3)	0 (0.0)	2 (0.9)	1 (0.2)	1.00
Fistulation	1 (0.1)	1 (0.4)	0 (0.0)	0 (0.0)	0.45
Patients with sequelae	13 (1.4)	3 (2.8)	4 (1.9)	6 (1.3)	0.70
Hearing loss	7 (0.8)	2 (0.8)	3 (1.5)	2 (0.4)	0.66
Facial palsy	4 (0.4)	1 (0.4)	1 (0.5)	2 (0.4)	1.00
Neurologic delay	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.4)	0.54
Patients who died	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–

clinical signs and symptoms [3,14]. Thus, if these cases are included in epidemiological evaluations of AM, AM incidence will be overestimated. This seems confirmed in this study where 13.0% of AM patients who had a radiological examination underwent a brain CT scan for neurological problems, which revealed a mastoid modification that led to AM diagnosis despite no previous clinical suspicion of this disease. Interestingly, the use of MR imaging in our study compared to CT scans was limited. However, MR imaging should be recommended instead of CT scans in children since it does not use radiation but still improves the efficiency of AM diagnosis [24].

We note that the microbiological evaluations conducted in this study primarily identified *P. aeruginosa* and *S. aureus,* which were mostly isolated from the tympanocentisis in the ear canal. This is surprising because both these pathogens are not frequently found in samples taken during surgery or via aspiration from retroauricular abscess which have the greatest probability to identify the true cause of AM [14]. *P. aeruginosa* is the most common pathogen for chronic suppurative OM and, together with *S. aureus,* the most common cause of external otitis. In contrast, in the population enrolled in this study, *S. pneumoniae,* usually considered the most common etiologic agent of AM [14], was identified in a small number of children, just when appropriate samples for culture were taken. This suggests that both the first pathogens represent contamination from or simultaneous infection of the ear canal. Despite similar findings and conclusions that have been previously reported [25,26], they suggest that in a not marginal number of cases AM cases included in this survey were not true AM. However, these misleading results did not influence the antibiotic therapy chosen. Most of the children received an intravenous treatment of ceftriaxone. Ceftriaxone is a third-generation cephalosporin that is active against most AOM-causing pathogens, including *S. pneumoniae* but has poor efficacy against *P. aeruginosa* and *S. aureus*. This suggests that pediatricians did not consider the microbiological findings and treated children according to the national guidelines mainly devoted to the eradication of *S. pneumoniae* and to cover potential intracranial spread of the infection [17].

Our findings on the evolution of AM, the need for surgery, and the incidence of AM complications were similar to those of other studies [23,25,26]. Together, these data seem to indicate that the risk of severe AM complications appears relatively low. Most AM cases can be treated conservatively according to the national guidelines for complicated AOM. However, comparisons between these studies remain difficult due to the different criteria used for AM diagnosis even if it is reasonable to think that the incidence of severe AM complications may be higher than that reported in the studies in which stringent criteria for AM diagnosis are followed.

In conclusion, this study highlights how difficult it is to quantify AM incidence in children when no population-based studies are performed. Moreover, the lack of consistent diagnostic criteria and therapeutic approaches for AM in the pediatric population makes comparing data from different studies nearly impossible. International guidelines for managing AM are needed to standardize approaches to AM and to identify risk factors for AM complications. On the contrary, several problems in the evaluation of data regarding incidence of AM as well as the role of vaccine prevention and AOM therapy in conditioning AM occurrence will continuously arise.

Financial & competing interests disclosure

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Key issues

- A slight but significant increase in acute mastoiditis (AM) incidence has been reported in several countries in the past few years.
- In Italy, the annual number of pediatric AM cases progressively increased between 2002 and 2013 in an age-dependent manner.
- The number of AM cases increased despite the implementation of regional programs to improve the administration of pneumococcal conjugate vaccines to infants and children.
- AM symptoms were observed more often among children <2 years old than among older children.
- AM diagnoses were made or confirmed by radiographic examinations in half of the cases.
- The risk of severe AM complications appeared relatively low, and most AM cases could be treated conservatively.
- International guidelines for managing AM are needed to standardize approaches to AM and to identify risk factors for AM complications.

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• **These results show that acute otitis media (AOM) prescriptions for antibiotics and adjunctive treatments are often inappropriate and highlight the need for educational strategies to improve their compliance with evidence-based guidelines for AOM treatment.**
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