

# A comparison of systemic inflammatory responses between immunocompetent and immunocompromised patients presenting with otorrhea due to chronic suppurative middle ear disease

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Accepted for publication 20 February 2015  
*Clin. Otolaryngol.* 2015, **40**, 468–473

**Objectives:** To study the occurrence of fever and the behaviours of inflammatory blood markers (C-reactive protein – CRP and procalcitonin – PCT) during episodes of otorrhea due to uncomplicated chronic otitis media in immunocompetent and immunocompromised patients.

**Design:** Prospective study of patients presenting with otorrhea over a 36-month period.

**Setting:** All patients were treated at Bonsucesso General Hospital, a tertiary referral hospital in Rio de Janeiro, Brazil.

**Participants:** A total of 84 participants, of which 50 were immunocompetent and 34 were immunocompromised.

Immunocompetent patients had a total of 106 episodes of otorrhea, and immunocompromised patients had 117 episodes of otorrhea.

**Main outcome measures:** Occurrence of fever (axillary temperature over 38°C) and elevation of C-reactive protein and procalcitonin levels above the normal ranges.

**Results:** In the immunocompetent group, the levels of procalcitonin were elevated in five of 106 episodes of otorrhea. The C-reactive protein levels were above the normal range in nine of 106 episodes, the same number of episodes in which fever was observed. In the immunocompromised group, procalcitonin was elevated in 38 of 117 episodes of otorrhea, C-reactive protein levels were abnormal in 40 episodes, and fever was detected in 37 episodes. Cases of otorrhea with systemic inflammatory response were significantly more common in immunocompromised patients with associated rhinosinusitis.

**Conclusions:** Otorrhea due to uncomplicated chronic otitis media rarely causes a systemic inflammatory response in immunocompetent patients. Its occurrence in immunocompromised patients seems to be more related to concurrent rhinosinusitis than to the chronic middle ear inflammation itself.

Chronic otitis media (cholesteatomatous or non-cholesteatomatous) is an indolent condition that may remain oligosymptomatic for years. Although both intra- and extratemporal complications may occur, very often, patients spend decades presenting only with recurrent middle ear discharge.<sup>1,2</sup>

It is well known by otolaryngologists that in uncomplicated chronic otitis media, episodes of otorrhea have little or no systemic repercussion. Fever and malaise are seldom reported, and topical, rather than systemic, treatment is the rule. Nevertheless, there is very little documented evidence of these facts in the literature.

Considering the long course of the disease, it is not uncommon that patients with chronic otitis media develop

other conditions in which episodes of fever and systemic inflammatory response need further thorough investigation, such as rheumatic disorders, immunodepressing diseases (AIDS, lymphoproliferative disorders), immunodepressing treatments (chemotherapy, post-organ transplantation) and admissions to intensive care units. The occurrence of otorrhea in these patients will alarm the primary physician, who will call upon the otolaryngologist to treat the middle ear inflammation as a possible source of the fever. Colleagues might even question the need for immediate surgical intervention given the serious consequences of a spreading infection in such patients.

The otolaryngologist is then faced with the dilemma of whether the otorrhea is really the origin of the fever and the systemic inflammatory response or whether the fever is caused by another site of infection or even from the primary disease. In the absence of signs of complication in physical and imaging exams, how often does chronic otitis media cause such systemic manifestations, and is there a difference

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between immunocompetent and immunocompromised patients in this regard?

In order to address this issue, we studied the occurrence of fever and the behaviours of inflammatory markers (C-reactive protein – CRP and procalcitonin – PCT) in immunocompetent and immunocompromised patients presenting with otorrhea due to uncomplicated chronic otitis media.

## Patients and methods

### Participants

We conducted a prospective observational study. From July 2005 to July 2008, patients presenting with middle ear discharge due to chronic middle ear disease were recruited from the Otolaryngology department of a tertiary teaching hospital setting in Brazil.

Patients, or rather ears, were followed for new episodes of otorrhea during this 3-year period or until they underwent surgery. Patients with bilateral disease who had an operation performed in one ear had only that ear excluded from further analysis, whereas episodes of otorrhea on the contralateral unoperated side were still considered. Ears that underwent previous surgeries were not included.

As the aim was to investigate the systemic inflammatory response during episodes of otorrhea in uncomplicated chronic otitis media, all episodes of otorrhea with clinical or imaging evidence of intra- or extratemporal complications were excluded (CT scans were performed in every episode if there was any clinical suspicion).

Patients with obvious concomitant infections in other sites, such as urinary or skin infections, were also excluded. All patients had a chest X-ray to exclude pulmonary infections. Patients with evidence of upper respiratory infection, suggesting viral or bacterial rhinosinusitis, had their symptoms duly recorded, but they

were not excluded because of the possible causal relationship between rhinosinusitis and otorrhea. Patients were considered to have rhinosinusitis if they presented with at least two of the following manifestations: acute mucous or purulent nasal discharge, acute nasal obstruction and facial pain. If only one of these symptoms was present, a sinus CT scan was performed to corroborate the diagnosis.

Patients were divided into two groups: immunocompetent and immunocompromised. As our department has long shown an interest in otolaryngological manifestations of immunosuppressed patients, many centres refer their cases to us, resulting in a large number of immunocompromised patients with suppurative chronic otitis media.

In the immunocompromised group, 132 episodes of otorrhea were initially enrolled, from 56 ears of 48 patients. Thirteen episodes were excluded because of a possible concurrent infection in a different organ (mainly pneumonia), and another two episodes were excluded because of suspicion of intracranial complications. Further analysis included 117 episodes of otorrhea in 42 ears of 34 patients. Age varied from 20 to 68 years old, with a mean age of 38 years old (patients under 18 years old were not included in the study). The underlying immunosuppressing conditions were AIDS (16), organ transplantation (6) and lymphoproliferative malignancies (12). Although some patients also had diabetes, no one was considered immunocompromised because of this isolated condition. On the other hand, patients with diabetes were not included in the immunocompetent group.

In the immunocompetent group, 116 episodes of otorrhea were enrolled, from 74 ears of 59 patients. Ten episodes were excluded due to the suspicion of concurrent infection in a different organ, leaving 106 episodes of otorrhea in 65 ears of 50 patients for further analysis. Age varied from 18 to 58 years old, with a mean age of 32.

**Table 1.** Characteristics of otorrhea episodes in immunocompetent and immunocompromised patients with and without rhinosinusitis

Group	Episodes of otorrhea	Number of patients*	Procalcitonin (ng/dL)				CRP (mg/dL)		Fever (Number of cases positive for fever)
			<0.5	≥0.5 and <2	≥2 and <10	≥10	Average	>6	
Immunocompetent	106	50	101	4	1	–	3.2	9	9
Without rhinosinusitis	78	42	75	3	–	–	3.2	4	3
With rhinosinusitis	28	19	26	1	1	–	3.3	5	6
Immunocompromised	117	34	79	26	9	3	9.0	40	37
Without rhinosinusitis	57	21	53	2	1	1	4.4	4	5
With rhinosinusitis	60	27	26	24	8	2	13.4	36	32

\*The sum of patients with and without rhinosinusitis in each group does not equal the total number of patients in each group because a same patient had different episodes of otorrhea with and without rhinosinusitis.

### Ethical considerations

All patients were treated according to the protocol approved by the hospital's medical ethical committee. Patients gave their written informed consent to participate in the study.

### Outcome measures

During each episode of otorrhea, patients had their axillary temperature checked four times a day for 5 days. If they had one or more measurements over 38°C, they were considered positive for fever. Analgesics and anti-inflammatories were only given after fever had been detected, if so.

Also, during each episode of otorrhea, blood was collected to determine the levels of procalcitonin and C-reactive protein. Procalcitonin was measured by a semiquantitative immunoassay method PCT-Q (BRAHMS) that allows four different readings: (i) <0.5 ng/mL, (ii) ≥0.5 and <2 ng/mL, (iii) ≥2 and <10 ng/mL and (iv) ≥10 ng/mL. C-reactive protein was measured by nephelometric method (Behring®, Inc., Deerfield, Illinois, USA). Normal reference values were between 0 and 6 mg/dL.

### Data analysis

The chi-square ( $\chi^2$ ) test was used for the comparison of categorical variables between groups. The Cochran–Mantel–Haenszel test was used to verify associations adjusting for a confounding factor (rhinosinusitis). The Mann–Whitney *U*-test (nonparametric test) was used for the comparison of the numerical variable of C-reactive protein values between groups as they showed a non-Gaussian distribution.

The significance criterion adopted was 5%. Data were processed by the SAS 6.04 software (SAS Institute, Inc., Cary, NC, USA).

### Results

Fifty immunocompetent patients had a total of 106 episodes of uncomplicated otorrhea in 65 affected ears (average of 2.12 episodes per patient and 1.63 episodes per ear). Thirty-four immunocompromised patients had 117 episodes of otorrhea in 42 affected ears (average of 3.44 per patient and 2.79 per ear). Age difference between groups was not statistically significant.

In the immunocompetent group, the levels of procalcitonin were elevated (>0.5 ng/dL) in only five of 106 episodes of otorrhea (4.7%). The C-reactive protein levels were above the normal range (>6 mg/dL) in nine of 106 episodes (8.5%), the same number of episodes in which fever was observed (see Table 1). In the immunocompromised group, on the other hand, procalcitonin was elevated in 38 of 117 episodes

**Table 2.** Comparison of inflammatory markers and occurrence of rhinosinusitis in episodes of otorrhea between immunocompetent and immunocompromised patients

Values	Immunocompetent		Immunocompromised		P-value*	P-value†
	n	%	n	%		
PCT (ng/dL)						
≥0.5	5	4.7	38	32.5	<0.0001	<0.0001
<0.5	101	95.3	79	67.5		
CRP (mg/dL)						
≥6	9	8.5	40	34.2	<0.0001	0.001
<6	97	91.5	77	65.8		
Fever						
Present	9	8.5	37	31.6	<0.0001	0.003
Absent	97	91.5	80	68.4		
Rhinosinusitis						
Present	28	26.4	60	51.3	<0.0001	
Absent	78	73.6	57	48.7		

\*Descriptive level for chi-square test.

†Descriptive level for Cochran–Mantel–Haenszel test adjusted for rhinosinusitis.

**Table 3.** Comparison between inflammatory markers during otorrhea between immunocompetent and immunocompromised patients stratified by the occurrence of rhinosinusitis

Subgroup	Values	Immunocompetent		Immunocompromised		P-value*
		n	%	n	%	
With rhinosinusitis (n = 88)						
PCT	≥0.5 ng/dL	2	7.1	34	56.7	<0.0001
	<0.5 ng/dL	26	92.9	26	43.3	
CRP	≥6 mg/dL	5	17.9	36	60.0	<0.0001
	<6 mg/dL	23	82.1	24	40.0	
Fever	Present	6	21.4	32	53.3	0.005
	Absent	22	78.6	28	46.7	
Without rhinosinusitis (n = 88)						
PCT	≥0.5 ng/dL	3	3.9	4	7.0	0.33
	<0.5 ng/dL	75	96.1	53	93.0	
CRP	≥6 mg/dL	4	5.1	4	7.0	0.45
	<6 mg/dL	74	94.9	53	93.0	
Fever	Present	3	3.9	5	8.8	0.20
	Absent	75	96.1	52	91.2	

\*Descriptive level for chi-square test.

of otorrhea (32.5%), C-reactive protein levels were over 6 mg/dL in 40 episodes (34.2%), and fever was detected in 37 episodes (31.6%). The difference between groups was statistically significant for all three outcome measures ( $P < 0.0001$  – see Table 2).

The concurrence of sinonasal symptoms was found in 28 of 106 episodes of otorrhea in the immunocompetent group (26.4%) and in 60 of 117 episodes in the immunocompromised group (51.3%). This difference has also reached statistical significance ( $P < 0.0001$ ).

Next, the results were stratified by the presence or absence of rhinosinusitis. If we only considered patients without rhinosinusitis, there were no statistical differences in the occurrence of fever or elevation in inflammatory markers between immunocompromised and immunocompetent patients. In the immunocompromised group without rhinosinusitis, episodes of otorrhea in which procalcitonin levels were abnormal dropped to four of 57 (7%). In this same subgroup, elevated C-reactive protein levels were also found in only four cases (7%), and fever in five (8.8% – see Table 3).

The cases of otorrhea with systemic inflammatory response were mainly concentrated in the subgroup of immunocompromised patients with rhinosinusitis, in which elevated procalcitonin and C-reactive protein levels were found, respectively, in 34 and 36 of 60 episodes (56.7% and 60%). Fever was detected in 32 cases (53.3%). All outcome measures in this subgroup showed statistically more abnormalities when compared to any other subgroup (Table 3).

Statistical analysis also showed a strong association between abnormal procalcitonin and C-reactive protein values. Procalcitonin levels were found to be abnormal in

85.7% of the episodes in which C-reactive protein levels were also elevated (above 6 mg/dL). Conversely, procalcitonin was within normal range in all but one episode in which C-reactive protein levels were normal.

## Discussion

Otorrhea is the most common clinical manifestation of suppurative chronic otitis media, and it is caused by inflammation of the middle ear mucosa. The degree to which such inflammation causes systemic manifestations is not clear in the literature.

Episodes of otorrhea associated with viral or bacterial rhinosinusitis in patients with chronic otitis media are quite common. The inflammation of the respiratory mucosa spreads to the middle ear through the Eustachian tube causing the discharge.<sup>3</sup> Nevertheless, there are other possible mechanisms that may lead to otorrhea in the absence of upper respiratory infection, such as mechanical, chemical and microbiological agents entering the middle ear from the external ear through the tympanic perforation.

Opposite to otorrhea in chronic middle ear disease, rhinosinusitis is very commonly associated with an exacerbated systemic response.

Fever and inflammatory blood markers are commonly used tools to assess systemic inflammatory response. The occurrence of fever is an extremely practical way of determining such response, and it is reported to be more valuable than total white blood cell count.<sup>4</sup>

C-reactive protein (CRP) is a member of the pentraxin family of proteins. It is an acute phase protein, produced

by the liver and by adipocytes, whose levels rise dramatically during inflammatory processes. This increment is due to a rise in the plasma concentration of interleukin-6 (IL-6), which is produced predominantly by macrophages, as well as by adipocytes.<sup>5</sup>

Procalcitonin (PCT), the precursor of the hormone calcitonin, is produced under normal conditions in the C cells of the thyroid gland.<sup>6</sup> In healthy subjects, procalcitonin levels are <0.10 ng/mL. There is increasing evidence that procalcitonin is a reliable marker of inflammatory processes, especially those whose sources are bacterial infections.<sup>7</sup>

### Synopsis of key findings

Our results corroborate with the notion that inflammation of the middle ear mucosa is not a common cause of systemic inflammatory response in immunocompetent patients. Only 8.5% of the episodes of otorrhea in this group lead to fever or elevated C-reactive protein levels. Considering procalcitonin as a reliable marker of systemic bacterial infections, one could infer that the occurrence of bacteremia was even lower (4.7%). In future studies, it might be of interest to isolate bacteria in both blood cultures and middle ear discharges in order to compare those results against these findings.

Although we found a much higher incidence of fever and elevated procalcitonin and C-reactive protein levels during episodes of otorrhea in the immunocompromised group, it became quite clear that it was the sinonasal infection and not the middle ear inflammation that was causing the systemic inflammatory response in most cases. The occurrence of elevated inflammatory markers was over eight times more common in immunocompromised patients with rhinosinusitis than in immunocompromised patients with otorrhea alone. Fever was also six times more common in the first subgroup when compared with the second.

The fact that the association between rhinosinusitis and otorrhea was higher in the immunocompromised group was actually expected, as rhinosinusitis is more common in immunocompromised patients than in the general population.<sup>8</sup> In patients with AIDS, the occurrence of rhinosinusitis is inversely proportional to CD4 levels.<sup>9</sup> The severity of such infections also increases with the degree of immunosuppression.<sup>10</sup>

It is very important to emphasise that these results concern uncomplicated chronic otitis media. The presence of temporal or extratemporal complications, such as petrositis, subperiosteal abscess, intracranial abscess or meningitis, should be carefully ruled out, especially in the immunocompromised group where they tend to occur more often.<sup>1,2</sup>

### Clinical applicability of the study

In face of these results, patients with uncomplicated suppurative chronic otitis media presenting with fever or other signs of exacerbated systemic inflammatory response should not have these manifestations primarily attributed to the inflammation of the middle ear mucosa, but rather undergo careful investigation. Particularly in the immunocompromised group, other sites of infection or primary disease activity should be considered.

When rhinosinusitis is present, aggressive treatment options – such as surgery – should focus on the sinus infection rather than on the middle ear because the former is more likely to be causing systemic response or deterioration.

### Conclusions

Otorrhea due to uncomplicated chronic otitis media rarely causes a systemic inflammatory response in immunocompetent patients. The occurrence of fever and elevated inflammatory blood markers in immunocompromised patients with otorrhea seems to be more related to concurrent rhinosinusitis than to the chronic middle ear inflammation itself.

### Keypoints

- Uncomplicated chronic otitis media is not a common cause of systemic inflammatory response.
- In immunocompetent patients, only 4.7% of episodes of otorrhea raised PCT levels.
- Although we found a much higher incidence of fever and elevated PCT and CRP levels during episodes of otorrhea in the immunocompromised group, this seems to be due to the concurrence of rhinosinusitis.
- Immunocompromised patients presenting with otorrhea and fever and/or elevation of PCT/CRP levels should undergo careful investigation for other sites of infection (such as rhinosinusitis) or primary disease activity.

### Conflict of interests

None to declare.

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