

Longitudinal Analysis of Inflammatory Biomarkers During Acute Rhinosinusitis

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Objective: To illuminate the pathophysiology of acute rhinosinusitis (ARS) with sequential monitoring of inflammatory biomarkers during an ARS episode and to clarify their diagnostic usability in bacterial ARS.

Study Design: Inception cohort study with 50 conscripts with ARS.

Methods: We collected peripheral blood high-sensitive C-reactive protein (hs-CRP), white blood cell (WBC), procalcitonin, and nasal nitric oxide (nNO) counts at 2 to 3 and 9 to 10 days of symptoms during an ARS episode. We simultaneously gathered various clinical parameters and microbiological samples. Bacterial ARS was confirmed with a positive culture of sinus aspirate.

Results: Reciprocal correlations and a significant change in biomarker levels between the two visits suggest that ARS involves a local and systemic inflammatory response that was strongest at 2 to 3 days. High-sensitive CRP and nNO reflected responses best (52% had increased CRP levels at 2–3 days; 66% had decreased nNO levels). White blood cell and procalcitonin counts rarely exceeded the reference range. Increased local and systemic inflammatory response were linked to multiple, adenoviral, or influenza A viral etiology or the detection of bacterial ARS. Local response correlated with imaging findings of wide paranasal sinus involvement and ostiomeatal complex occlusion. At 9 to 10 days, elevated (≥ 11 mg/L) and moderately elevated (≥ 49 mg/L) hs-CRP predicted bacterial ARS well (likelihood ratio [LR] $+$ 3.3 and LR $+$ 15.8, respectively), but the sensitivity for both findings remained low.

Conclusion: Acute rhinosinusitis (particularly bacterial ARS) involves a local and systemic inflammatory response that is strongest at the beginning of symptoms. Elevated hs-CRP supports the diagnosis of bacterial ARS.

Key Words: Acute rhinosinusitis, bacterial, C-reactive protein, CRP, high-sensitive CRP, procalcitonin, nasal nitric oxide, NO.

Level of Evidence: 4.

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INTRODUCTION

Acute rhinosinusitis (ARS) is a complex entity with an exact pathogenesis that still is partly obscure. In most cases, ARS involves both the nasal passages and the paranasal sinuses,^{1–3} and both viruses and bacteria are involved in the pathogenesis.^{4–6} First, viral infection and middle meatal pathogenic bacterial coinfection can modify the disease process, and the end result may be bacterial secondary infection of the sinuses.^{7–9} The key pathogenic process of ARS is the inflammatory reaction of the nasal and paranasal mucosa,^{10–13} which may

theoretically be linked to the microbiological etiology, the spread of the disease to the paranasal sinuses, and to symptoms.

In theory, biomarkers that parallel the local and systemic inflammatory reaction could shed light on the pathophysiology and development of bacterial ARS. Peripheral blood leucocytes (white blood cell count [WBC]) and C-reactive protein (CRP) as well as nasal nitric oxide (nNO) have been suggested as possible biomarkers of disease activity in ARS.¹⁴ In addition, a proinflammatory biomarker—procalcitonin (PCT)—has been proposed as a pertinent marker of bacterial infection.¹⁵ Longitudinal studies with wild and experimental colds have revealed that about half of infected subjects present a mild increase in CRP, but these studies have not examined whether the subjects developed bacterial ARS.^{16,17} Others have shown in cross-sectional studies that microbiologically confirmed bacterial ARS is associated with elevated CRP and WBC levels at the time of the diagnosis, but the studies have not followed up these biomarkers systematically from the beginning of the ARS episode.^{18,19} We hypothesized that systematic sequential monitoring of these biomarkers in the same patients during a single ARS episode with microbiological confirmation of bacterial ARS would provide a further view of the pathophysiology of ARS.

We conducted an inception cohort study among conscripts during a single episode of ARS and took sequential

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total WBC, high-sensitive CRP (hs-CRP), PCT, and nNO counts. Our aim was to 1) investigate the biomarker levels during the ARS episode and particularly in relation to the development of culture-proven bacterial ARS; 2) look at the relationship between the biomarker levels and microbiological and clinical findings; and 3) determine the diagnostic accuracy of these biomarkers in bacterial ARS.

MATERIALS AND METHODS

Study Population and Protocol

We conducted a prospective inception cohort study among conscripts completing their compulsory military service in the Kainuu Brigade in Northern Finland. All of the patients provided written informed consent, and the study protocol was approved by the ethics committee of the Northern Ostrobothnia Hospital District, Finland.

We have used this same study population to study the microbiology,⁹ clinical diagnostics,²⁰ and imaging findings²¹ of ARS. Briefly, the patients were recruited and examined at the health center of the Kajaani Garrison, Finland. The participants were enrolled between February 1, 2012, and April 15, 2012, from consecutive conscripts who sought medical care due to ARS symptoms. The participants had to have ARS determined by the following inclusion criteria: acute onset within 4 days, presence of nasal symptoms (blockage or discharge),¹⁰ and abnormal nasal findings (mucosal edema or secretion). Patients excluded had concomitant infection necessitating antimicrobial treatment, respiratory infection, or antimicrobial treatment within 3 weeks preceding the first visit; nasal allergy or asthma requiring medication; chronic nasal symptoms or polyps; or prior nasal or sinus surgery.

Clinical Data

At enrollment, we collected background information and examined the patients. A follow-up visit was scheduled for the workday closest to the 10th day of symptoms. The recorded symptoms, imaging examinations, and microbiologic specimen and analyses have been described earlier in detail.^{9,20,21} What follows is a brief description of these data.

Recording of Symptoms. The participants recorded in a symptom diary the presence and severity (0 = none to 10 = worst possible) of acute symptoms daily for 10 days.¹⁰ The following symptoms were recorded: nasal blockage, clear nasal discharge, purulent nasal discharge, postnasal discharge, reduction/loss of smell, and facial pain/pressure. The diary started from the onset of symptoms. We summed up the grades for each symptom to obtain a total symptom score (0–60) for each day.^{9,20}

Cone-Beam Computed Tomography of the Paranasal Sinuses. A paranasal cone-beam computed tomography (CBCT) scan was taken at enrollment and at the follow-up visit. Coronal, axial, and sagittal slices of the maxillary, ethmoid, and sphenoid sinuses and the ostiomeatal complex (OMC) were visualized. Both sides of the paranasal sinuses were graded separately as follows²²: grade 0 (normal), ≤ 3 mm mucosal thickening; grade 1 (minor abnormality), ≥ 4 mm mucosal thickening at any point in the sinus²³; and grade 2 (major abnormality), air–fluid level, gas bubbles, or total opacification. The ostiomeatal complex (OMC) was graded as 0 (open) or 2 (occluded). We determined the total CBCT score (0–16) by summing up the grades of each sinus and the OMC on both sides.

Microbiological Specimen and Analyses. We took samples for multiplex respiratory virus polymerase chain reaction from the nasopharynx at both visits and the sinus aspirates at the follow-up visit. Searches were conducted for 12 respiratory

viruses. We took the middle meatus bacterial samples at both visits. If the paranasal CBCT scan at the follow-up visit showed total opacification, air–liquid level, or gas bubbles of either maxillary sinus, the patient underwent maxillary sinus aspiration under topical anesthesia. The aspirate was cultured to identify culture-proven bacterial ARS.²⁰

Measurement of Inflammatory Biomarkers

At enrollment and the follow-up visit, we took blood samples to determine the WBC count and the concentrations of hs-CRP and PCT, which reflect systemic inflammation. In addition, we measured the level of nNO, which mirrors local inflammation.

We analyzed the WBC count using an automatic impedance and flow cytometry analyzer (Celltac MEK-6420, Nihon Kohden Ltd, Tokyo, Japan), hs-CRP with a photometric and immunochemical method (Roche/Hitachi Modular P800 chemistry analyzer, Hitachi High-Technologies Corporation, Tokyo, Japan), and PCT using a chemiluminescence immunoassay (Advia Centaur XP, Siemens Healthcare GmbH, Erlangen, Germany). The minimum detectable levels of CRP and PCT were 0.05 mg/L and 0.05 μ g/L, respectively. The levels of nNO were measured with an electrochemical device (Niox Mino Nasal, Aerocrine, Solna, Sweden) using a firm nasal olive and direct sampling from both nasal cavities with a 5-mL/minute airstream generated by the analyzer. Pursed-lip breathing was performed by the patient during the measurement to maintain velum closure and to prevent nNO leakage through the velopharyngeal space.^{24,25} The minimum concentration (parts per billion) of the right and left nasal counts was used for each subject.

Statistical Analysis

For descriptive data, we calculated the median and interquartile range. To test the change in biomarker levels over time, we used the paired Wilcoxon signed rank test. To make the results comparable, the hs-CRP, WBC, and PCT levels were categorized similarly to earlier research.^{18,19,26} We used a nonparametric Mann-Whitney U test and a Kruskal-Wallis test to compare continuous variables. Correlation coefficients were calculated using Spearman rank correlation coefficients (r_s). All of the viral and bacterial samples were analyzed per patient.

Associations between culture-proven bacterial ARS and raised hs-CRP and WBC counts were studied further by cross-tabulation and calculation of sensitivity, specificity, 95% confidence intervals, and positive and negative likelihood ratios (LR+ and LR–).

RESULTS

Study Population

The opportunity to participate was offered to 66 patients. Of those, 51 consented and were enrolled. One patient was excluded because of pneumonia. Details of the demographic characteristics and the ARS episode of the remaining 50 patients are shown in Table I. Those seven patients (14%) who did not return the symptom diary were excluded from the analyses of symptoms. Twenty patients (40%) underwent maxillary sinus aspiration. The culture of the aspirate was positive for non-typeable *Haemophilus influenzae* (NTHi) in eight (16%) cases, which thus had culture-proven bacterial ARS.

Inflammatory Biomarkers During ARS

On average, hs-CRP and PCT levels decreased and nNO levels increased between the two visits, indicating

TABLE I.

Details of Background Characteristics and Acute Rhinosinusitis Episode in a Cohort of 50 Military Conscripts.

Characteristic	
Background Characteristics	
Male sex, N (%)	48 (96)
Mean age (range), years	20 (18–23)
Mean (range) body mass index	24 (18–31)
Basic education, N (%) ^a	
Primary	8 (16)
Middle	20 (40)
High school	21 (42)
Current tobacco use, N (%)	22 (44)
History of recurrent sinusitis, N (%)	8 (16)
Details of ARS	
Duration of symptoms at enrollment, median (IQR), days	2 (2–3)
Duration of symptoms at follow-up visit, median (IQR), days	10 (9–10)
Respiratory virus nucleic acid found in nasopharynx at enrollment N (%)	39 (78)
Most prevalent viruses found, N (%)	
Influenza A	17 (34)
Adenovirus	17 (34)
Pikornavirus group	19 (38)

N = number of patients; IQR = interquartile range.

^aNumbers do not add up to 50 because of missing data in one patient.

both local and systematic inflammatory reaction (Table II). At 2 to 3 days, hs-CRP counts had a moderate correlation with WBC ($r_s = 0.46$, $P = .001$), PCT ($r_s = 0.48$, $P < .001$), and nNO counts ($r_s = -0.42$, $P = .002$). Age, sex, and smoking status were not associated with any of the inflammatory biomarkers (data not shown).

At 2 to 3 days, 36% of the subjects had mildly elevated hs-CRP levels and 16% had moderately elevated hs-CRP levels. At 9 to 10 days, these proportions had declined to 18% and 8%, respectively. In 66% of the subjects, the nNO increased between the two visits. At both visits, a significantly larger proportion of subjects who eventually developed bacterial ARS had elevated hs-CRP levels as compared to subjects who did not (Fig. 1A). However, even among subjects with bacterial ARS, the median hs-CRP level was markedly higher at 2 to 3 days than at 9 to 10 days. At both visits, subjects with bacterial ARS had significantly lower median levels of nNO than those without (Fig. 1B).

WBC counts showed similar results as hs-CRP, but a substantially lower proportion of subjects had elevated WBC counts (Table II). In the overwhelming majority of subjects, procalcitonin levels did not increase over the reference range during ARS.

Associations Between Inflammatory Biomarkers and Clinical Data

At 2 to 3 days, the finding of multiple viruses, adenovirus or influenza A virus in the nasopharynx was

associated significantly with raised hs-CRP values or decreased nNO levels (Table III). The spreading of the disease and ostiomeatal occlusion shown in CBCT scans associated with lower nNO levels but not with higher hs-CRP levels. At 9 to 10 days, the presence of NTHi in the sinus aspirate associated both with raised hs-CRP values and decreased nNO values.

At 2 days, among all subjects the main symptom score correlated with neither hs-CRP nor nNO levels ($r_s = -0.04$, $P = .79$ and $r_s = 0.04$, $P = .79$, respectively). However, among subjects with bacterial ARS, a strong correlation was found between the hs-CRP level and the main symptom score ($r_s = 0.74$, $P = .04$).

Diagnostic Accuracy of Inflammatory Biomarkers in Bacterial ARS

At 9 to 10 days, elevated hs-CRP (≥ 11 mg/L) predicted bacterial ARS fairly well (LR+ 3.3) and moderately elevated hs-CRP (≥ 49 mg/L) very well (LR+ 15.8) (Table IV). The sensitivity figures for both of these findings, however, were low.

DISCUSSION

We conducted a prospective inception cohort study among 50 conscripts with ARS and measured various inflammatory biomarkers at 2 to 3 days of symptoms and again after 9 to 10 days. Our aim was to evaluate the pathophysiology and development of bacterial ARS and to clarify the diagnostic usability of the biomarkers. We found a significant change in hs-CRP, PCT, and nNO levels between the two visits, indicating the presence of a local and systemic inflammatory response during ARS. The significant reciprocal correlations between the biomarkers further support this finding. High-sensitive CRP and nNO levels reflected these inflammatory responses best. About half of the subjects had mildly or moderately increased hs-CRP levels at 2 to 3 days. White blood cell and PCT counts exceeded the reference range only rarely.

According to the hs-CRP and nNO values, the local and systemic inflammatory response were clearly greatest at the beginning of symptoms. Compared with nonbacterial ARS, bacterial ARS encompassed a more powerful local and systemic inflammatory reaction that was strongest at 2 to 3 days. Overall, we found the increased local and systemic inflammatory response to be linked to multiple, adenoviral, or influenza A viral etiology. Local response but not the systemic response correlated strongly with the spread of the disease to the paranasal sinuses or to occlusion of the ostiomeatal complex in a CBCT scan. In bacterial ARS, we found that the systemic inflammatory response correlated powerfully with the symptom score at the beginning of the ARS, which may indicate that the stronger symptoms in bacterial ARS could partly be the result of the enhanced inflammatory response.

The facts that the local and systemic inflammatory responses were stronger in bacterial ARS than in nonbacterial ARS, and that these reactions were strongest at the beginning of respiratory symptoms, indicates that bacterial ARS starts to develop during an early phase of

TABLE II.
Inflammatory Biomarkers During Acute Rhinosinusitis Episode in Cohort of 50 Military Conscripts.

Biomarker	2-3 Days of Symptoms			9-10 Days of Symptoms			P Value*
	All Subjects (n = 50)	BARS		All Subjects (n = 50)	BARS		
		Yes (n = 8)	No (n = 42)		Yes (n = 8)	No (n = 42)	
CRP (mg/l)							
< 11	24 (48)	2 (25)	22 (52)	37 (74)	3 (37)	34 (81)	
11-49	18 (36)	2 (25)	16 (38)	9 (18)	2 (25)	7 (17)	
≥ 49	8 (16)	4 (50)	4 (10)	4 (8)	3 (37)	1 (2)	
Median (IQR)	11.8 (3.9-26)			3.1 (1.2-12)			.001
WBC (x10 ⁹ /l)							
≤ 10	45 (90)	6 (75)	39 (93)	48 (96)	8 (100)	40 (95)	
> 10	5 (10)	2 (25)	3 (7)	2 (4)	0	2 (5)	
Median (IQR)	7.3 (5.5-8.1)			6.9 (5.3-8.2)			.16
PCT (μg/l)							
≤ 0.25	48 (96)	7 (88)	41 (98)	50 (100)	-	-	
> 0.25	2 (4)	1 (12)	1 (2)	0			
Median (IQR)	0.08 (0.05-0.11)			0.06 (0.05-0.09)			.02
nNO (ppb)							
Median (IQR)	75 (35-163)	40 (19-57)	107 (41-175)	152 (66-262)	26 (15-126)	161 (105-270)	.007

Data are No. (%) unless otherwise specified.

*Paired Wilcoxon signed rank test.

BARS = bacterial acute rhinosinusitis; CRP = high-sensitive C-reactive protein; IQR = interquartile range; nNO = nasal nitric oxide; PCT = procalcitonin; WBC = white blood cell;

symptoms. This is in agreement with our earlier finding that there is a gradually increasing discrepancy in CBCT and symptom scores between bacterial and nonbacterial ARS that begins at the start of the symptoms.²¹ Furthermore, we have shown earlier that the presence of pathogenic bacteria in the nasal middle meatus (coinfection) at the beginning of viral ARS modifies the symptoms and is one factor that may lead to the finding of the same bacteria in the maxillary sinus.⁹ However, here the middle meatal NTHi was not associated with raised CRP or decreased nNO. This raises the question of whether the pathogenic bacteria were already present in the maxillary sinus at the beginning of symptoms. We do not know this because we performed

the maxillary sinus aspirations and bacterial cultures at the follow-up visit. This would also argue against the generally presented hypothesis that bacterial ARS follows an antecedent viral ARS.¹¹

At 9 to 10 days, elevated hs-CRP (≥ 11 mg/L) predicted bacterial ARS relatively well (LR+ 3.3) and predicted moderately elevated hs-CRP (≥ 49 mg/L) very well (LR+ 15.8), but the sensitivity figures for these findings were low. We have earlier examined the respective figures for various symptoms and clinical findings in this same material.²⁰ Compared to these diagnostic measures, the finding of elevated CRP (≥ 11 mg/L) proved to be better at predicting bacterial ARS than symptoms; it paralleled the findings of moderate or profuse amount of nasal secretion

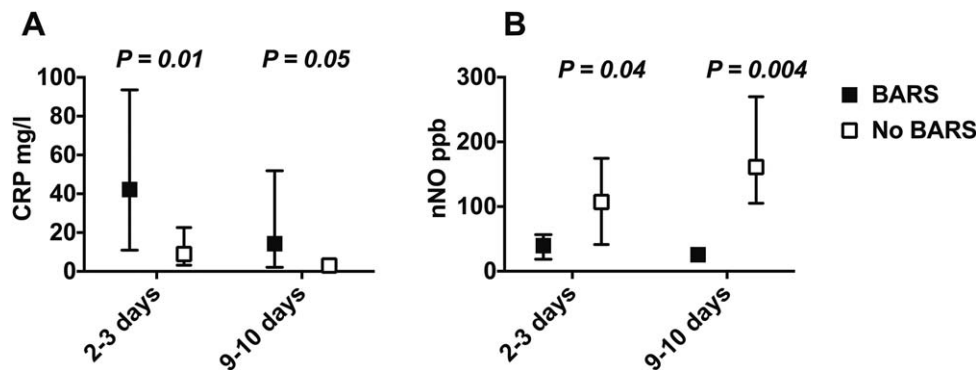


Fig. 1. (A) Systemic (high-sensitive C-reactive protein) and (B) local (nasal nitric oxide) inflammatory biomarker levels during bacterial (BARS) and nonbacterial (No BARS) acute rhinosinusitis episodes in a cohort of 50 conscripts.

Symbols represent the median; bars represent the interquartile range.

BARS = bacterial acute rhinosinusitis; CRP = C-reactive protein; No BARS = no bacterial acute rhinosinusitis; ppb = parts per billion.

TABLE III.
Systemic (high-sensitive C-reactive protein) and Local (nasal nitric oxide) Inflammatory Biomarker Levels According to Microbiological and Clinical Findings in a Cohort of 50 Military Conscripts With Acute Rhinosinusitis.

	Median (IQR) C-reactive Protein Level			Median (IQR) nNO (ppb) Level		
	At 2–3 days	At 9–10 Days	<i>P</i> Value*	At 2–3 days	At 9–10 Days	<i>P</i> Value*
Findings at 2–3 Days						
Viral Findings (NP)						
No virus	4.5 (1.6–16.0)		.01	114 (82–285)		.03
One virus	7.0 (3.8–19.1)			125 (43–175)		
Multiple viruses	24.2 (11.0–56.7)			42 (27–85)		
No adenovirus	7.2 (3.5–16.1)		.01	114 (40–175)		.29
Adenovirus	25.4 (8.4–72.0)			54 (31–116)		
No influenza A virus	7.4 (2.4–24.8)		.14	108 (43–211)		.02
Influenza A virus	14.7 (7.6–27.7)			36 (29–126)		
No picornavirus (entero or rhino)	8.6 (3.4–16.4)		.08	106 (36–159)		.46
Picornavirus	24.2 (6.1–55.7)			54 (32–174)		
No coronavirus	12.1 (4.0–28.8)		.32	81 (34–176)		.74
Coronavirus	9.4 (3.6–12.3)			47 (36–148)		
Bacterial Culture Findings (MM)						
No NTHi	10.7 (3.5–22.6)		.80	76 (34–152)		.96
NTHi	11.9 (4.0–31.8)			68 (38–176)		
Spread of Disease (CBCT)						
Nasal cavities only	5.5 (1.8–19.7)		.26	184 (79–356)		.01
One sinus group	8.1 (3.4–16.4)			114 (34–285)		
Two sinus groups	13.8 (4.0–32.8)			61 (36–148)		
Three sinus groups	20.0 (5.7–55.5)			43 (23–45)		
No ostiomeatal obstruction	6.7 (2.0–24.5)		.34	162 (61–333)		.009
Ostiomeatal obstruction	12.3 (4.1–27.1)			50 (34–129)		
Findings at 9–10 Days						
Viral Findings (NP)						
No virus		4.3 (0.8–7.6)	.34		198 (92–260)	.26
One virus		2.1 (1.1–5.6)			137 (42–184)	
Multiple viruses		4.8 (1.6–16.6)			152 (37–313)	
No adenovirus		2.6 (1.1–6.4)	.05		150 (69–224)	.44
Adenovirus		9.2 (1.6–38.7)			178 (40–312)	
No influenza A virus		3.1 (1.2–7.6)	.54		160 (97–265)	.07
Influenza A virus		3.9 (1.7–15.2)			71 (19–200)	
No picornavirus (entero or rhino)		3.7 (1.6–14.7)	.30		161 (69–262)	.51
Picornavirus		2.0 (1.1–10.0)			124 (52–254)	
No coronavirus		3.2 (1.2–13.8)	.76		152 (61–253)	.15
Coronavirus		3.1 (1.4–∞)			312 (144–∞)	
Bacterial Culture Findings (MM)						
No NTHi (middle meatus)		2.7 (1.0–5.8)	.13		149 (71–262)	.83
NTHi		5.4 (1.8–14.4)			156 (34–274)	
Viral Findings (SINUS)						
No virus		4.4 (1.3–7.6)	.43		67 (44–190)	.62
Any virus		8.1 (1.3–45.6)			69 (20–152)	
Bacterial Culture Findings (SINUS)						
No pathogenic bacteria		3.0 (1.2–7.0)	.05		161 (105–270)	.004
NTHi		14.3 (2.1–51.9)			26 (15–126)	

*Mann-Whitney U test and Kruskal-Wallis test.

CBCT = cone-beam computed tomography; IQR = interquartile range; MM = nasal middle meatus; nNO = nasal nitric oxide; NP = nasopharynx; NTHi = nontypeable *H influenzae*; SINUS = sinus maxillaris.

TABLE IV.

Diagnostic Accuracy of Inflammatory Biomarker Findings 9 to 10 Days After Onset of Symptoms in Identifying Culture-Proven Bacterial ARS in Cohort of 50 Conscripts With ARS.

Biomarker Findings at 9–10 Days of Symptoms	N (%)	Sensitivity (95% CI)	Specificity (95% CI)	LR+	LR-
CRP (mg/l)					
≥ 11	13 (26)	63 (25–91)	81 (66–91)	3.3	0.5
≥ 49	4 (8)	38 (9–76)	98 (87–100)	15.8	0.6
WBC (x 10 ⁹ /L)					
> 10	2 (4)	0	95 (84–99)	0	1.1

ARS = acute rhinosinusitis; CRP = high-sensitive C-reactive protein; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; N = number; WBC = white blood cell count.

and cervical adenopathy but was poorer than the finding of nasal secretion in the posterior pharynx (supplementary material). Moderately elevated CRP (≥ 49 mg/L) accurately predicted bacterial ARS but only was present in four patients. Because of the relatively high negative likelihood ratios, the absence of elevated CRP could not be used to rule out bacterial ARS. Thus, CRP cannot be recommended for routine screening of bacterial ARS. Because the WBC and PCT counts rarely exceeded the reference values, their diagnostic value was low.

Our findings that about half of the cases had raised hs-CRP values at the beginning of ARS agree with those of Whicher et al. and Melbye et al.^{16,17} We do not know which proportions of patients suffered from bacterial ARS in these two studies because the researchers did not look for the presence of bacterial ARS. Here, the nasopharyngeal findings of multiple viruses, adenovirus, or influenza A virus was associated with the inflammatory response. Earlier, Ruuskanen et al. found elevated CRP in influenza and adenovirus infections, and Melbye in influenza infections.^{17,27} Savolainen et al. and Hansen et al. have shown that clearly pathological values of CRP associate with bacterial ARS but have not calculated their sensitivity, specificity, or predictive values for this finding.^{18,19} Patients with radiologic sinusitis have been found to have lower maxillary sinus NO levels than control subjects.²⁸ One proposed mechanism for this is blockage of the sinus ostia, which reduces NO levels in nasally exhaled air.²⁹ In support of this, we found that bacterial ARS involved lower nNO levels than non-bacterial ARS and that ostiomeatal occlusion confirmed by imaging associated with low nNO levels.

To minimize selection bias, we recruited consecutive patients. We were not able to verify viral etiology in all the subjects, similar to prior research on natural colds.³⁰ We did not perform maxillary sinus aspiration to every patient, but only to those with CBCT findings that supported bacterial ARS. This might have caused information bias. However, CT is considered to be the best imaging modality for evaluating paranasal sinus disease.¹⁰ We defined bacterial ARS to include only the maxillary sinuses for which sinus aspirate is possible. Due to available resources, the study group was relatively small. Despite this, we found significant associations

between hs-CRP and nNO levels and various clinical parameters. We wanted to increase the possibility of encountering frequent bacterial ARS; therefore, conscripts were recruited. The amount of patients who get bacterial sinusitis during ARS in primary care usually is estimated to be 2%^{10,11} We would have needed 400 such patients to get the eight cases of bacterial ARS that we had in this study.

Concerning the generalizability of our results, several issues require recognition. Due to the military environment, most of the conscripts were men. Smoking was common but did not correlate with the biomarker levels. The only bacteria that we found from the maxillary sinuses were NTHi. This is probably explained by the fact that NTHi earlier had been reported to be a major nasal and paranasal pathogen among Finnish conscripts.^{31,32} Overall, the present finding of ARS involving an inflammatory response warrants reconfirmation among other patients and bacteria.

CONCLUSION

Acute rhinosinusitis (particularly bacterial ARS) involves a local and systemic inflammatory response that is strongest at the beginning of symptoms. Elevated hs-CRP supports the diagnosis of bacterial ARS.

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