



Inflammatory Biomarkers During Bacterial Acute Rhinosinusitis

Timo J. Autio^{1,2,3} · Timo Koskenkorva^{1,2,3} · Petri Koivunen^{1,2,3} · Olli-Pekka Alho^{1,2,3}

© Springer Science+Business Media, LLC, part of Springer Nature 2018

Abstract

Purpose of Review Diagnosis of bacterial acute rhinosinusitis is difficult. Several attempts have been made to clarify the diagnostic criteria. Inflammatory biomarkers are easily obtainable variables that could shed light on both the pathophysiology and diagnosis of bacterial acute rhinosinusitis. The purpose of this review article is to assess literature concerning the course of inflammatory biomarkers during acute rhinosinusitis and the use of inflammatory biomarkers in diagnosing bacterial acute rhinosinusitis.

Recent Findings We included C-reactive protein, erythrocyte sedimentation rate, white blood cell counts, procalcitonin, and nasal nitric oxide in this review and found that especially elevated C-reactive protein and erythrocyte sedimentation rate are related to a higher probability of a bacterial cause of acute rhinosinusitis. Still, normal levels of these two biomarkers are quite common as well, or the levels can be heightened even during viral respiratory infection without suspicion of bacterial involvement.

Summary Elevated levels of C-reactive protein or erythrocyte sedimentation rate support diagnosis of bacterial acute rhinosinusitis, but due to a lack of sensitivity, they should not be used to screen patients for bacterial acute rhinosinusitis.

Keywords Acute rhinosinusitis · Bacterial · C-reactive protein (CRP) · Erythrocyte sedimentation rate (ESR) · High-sensitive CRP · Procalcitonin · Nasal nitric oxide (nNO) · White blood cell count (WBC)

Introduction

Acute rhinosinusitis (ARS) is defined as a sudden onset of symptomatic, reversible inflammation involving both the nasal and paranasal mucosa and lasting up to 12 weeks [1–4]. ARS is one of the most common reasons for health care appointments, leading to as many as millions of visits around the world [5–7]. Typical symptoms are nasal discharge and obstruction, facial pain or pressure, and loss or reduction of smell [1–4]. Both viruses and bacteria are often related to the pathophysiology of ARS [2, 4]. In the beginning of ARS,

respiratory viral infection and middle meatal bacterial co-infection influence the course of ARS and, in some cases, may also lead to secondary bacterial infection and prolonged and more severe symptoms [1, 8, 9]. Recent guidelines suggest that we should diagnose and treat bacterial ARS, but due to their similar clinical impressions, viral and bacterial ARS are difficult to differentiate and thus antibiotics are often used for no reason in viral ARS, also [1–4].

Inflammatory biomarkers are used to diagnose bacterial disease, measure the severity or course of a disease or to follow the patient's healing [1]. The markers are usually part of a human inflammatory response and, therefore, reflect the inflammatory processes of a disease. Inflammatory biomarkers are usually easily obtained from a blood sample and may offer a diagnostic tool in diseases that are hard to diagnose clinically, such as bacterial ARS [1]. Several inflammatory biomarkers such as C-reactive protein (CRP), white blood cell count (WBC), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), and nasal nitric oxide (nNO) have been suggested to reflect the degree of inflammation and, thus, shed light on the pathophysiology of bacterial ARS [1, 10]. Elevated CRP and ESR have also been suggested to be used as possible diagnostic criteria for bacterial ARS to guide

This article is part of the Topical Collection on *Rhinosinusitis*

✉ Timo J. Autio
timo.autio@ppshp.fi

¹ Department of Otorhinolaryngology and Head and Neck Surgery, Oulu University Hospital, P.O. Box 21, FI-90029, OYS Oulu, Finland

² PEDEGO Research Unit, University of Oulu, Oulu, Finland

³ Medical Research Center Oulu, Oulu, Finland

antibiotic treatment. The use of inflammatory biomarkers, CRP especially, in diagnostics has been reported to reduce the amount of antibiotics prescribed in patients with respiratory infections [1, 11]. However, the behaviour of inflammatory biomarkers during an ARS episode and the possible use of these markers in diagnosing bacterial ARS remain unclear. There are a limited amount of studies describing the use of inflammatory biomarkers in diagnosing bacterial ARS in patients whose diagnoses have been confirmed by sinus aspiration and bacterial culture (culture-proven bacterial ARS). In addition, the behaviour of inflammatory biomarkers in different phases of an ARS episode is also seldom reported.

The purpose of this article is to review the available literature concerning the possible use of inflammatory biomarkers in diagnosing bacterial ARS. Because bacterial ARS is often preceded by a viral infection, the review also addresses inflammatory biomarker findings during viral ARS as far as it helps in understanding the pathophysiology of bacterial ARS.

Inflammatory Biomarkers in ARS

C-Reactive Protein

CRP is an acute-phase protein produced by the liver in response to infection or inflammation. In a healthy person, the level of CRP is low (< 10 mg/l), but the level can rise quickly within hours and reach peak values (350–400 mg/l) after 48 h [12]. The level of CRP also decreases rapidly due to a short half-life, 6–8 h [1]. Single measurements of CRP are considered to have limited value, but elevated levels have generally been connected to bacterial infections and sequential measurements usually reflect the course of the infection [1, 12, 13].

Elevated CRP findings peaking after 2–3 days of symptoms of acute respiratory infection have been reported by Whicher et al. and Melbye et al. [14, 15]. They found that approximately half of the cases of natural and inoculated rhinovirus and influenza A viral infections without bacterial suspicion have elevated CRP levels. The elevated CRP levels were reported to decline rapidly and abnormal results were scarce after 7 days of symptoms [15]. Comparable results have also been found by Ruuskanen et al. and Autio et al. in patients with adenovirus infection [16, 17•]. Autio et al. [17•] also found that the inflammatory reaction during ARS measured by CRP was stronger at the beginning, after 2–3 days of symptoms, than later, after 9–10 days of symptoms. In patients with symptom duration of less than 3 weeks, elevated CRP levels have been reported to be more common in culture-proven bacterial ARS than in non-bacterial ARS [17•, 18•, 19•]. Still, normal CRP levels have also been reported to be common [17•, 18•, 19•]. Hansen et al. [18•]

reported that a CRP level of 11–49 mg/l and a CRP level > 49 mg/l are both associated with culture-proven bacterial maxillary sinusitis (odds ratios 8.9 and 10.5, respectively). Still, as much as half of patients with ARS and no suspicion of bacterial involvement have also been reported to have elevated CRP levels [14, 15]. In a previous study by Autio et al. [17•], sensitivity, specificity, and predictive values were calculated for elevated CRP values to find patients with culture-proven bacterial ARS (Table 1). In that study, elevated CRP (≥ 11 mg/l) after 9–10 days of symptoms predicted bacterial ARS relatively well (positive likelihood ratio, LR+, 3.3) and moderately elevated CRP (≥ 49 mg/l), very well (LR+ 15.8). Nevertheless, the sensitivity values of these two CRP thresholds remained low (63 and 38%, respectively) and the negative likelihood ratios, LR–, were relatively high (LR– 0.5 and 0.6, respectively). Therefore, the authors stated that elevated CRP values should not be used to screen for bacterial ARS even though, after 9–10 days of symptoms, they did support the diagnosis of bacterial ARS. Still, when compared with the earlier study by Autio et al. [24], findings of elevated CRP (≥ 11 mg/l) were better at predicting culture-proven bacterial ARS than any symptom and as good as a physical finding of a moderate or profuse amount of secretion in the nasal cavity at 9–10 days. We found only one controlled study that monitored CRP during treatment of ARS. In a randomised controlled study evaluating the effect of penicillin in clinically diagnosed ARS, Hansen et al. [25] reported that the levels of CRP had returned to normal after 7 days in 88% of the penicillin group and in 75% of the control group. The difference was statistically significant.

Erythrocyte Sedimentation Rate

ESR is based on sedimentation of red cells in plasma, which reflects the level of acute-phase proteins and therefore inflammation. The test is not specific for any disease, but still is a tool that is used to evaluate the severity or activity of inflammation in various inflammatory conditions [26]. The level of ESR in a healthy person tends to be higher in women and the elderly. Usually, a value < 15 mm/h in males and < 20 mm/h in females under 50 years old is considered normal [27].

Melbye et al. [15] found ESR to peak after 4–5 days of ARS symptoms and reported that influenza A virus was most often related to higher ESR levels. Lindbaek et al. [22] reported that high ESR levels were related to mucosal abnormalities seen in paranasal computed tomography scans of patients with ARS. Hansen et al. [18•] and Savolainen et al. [19] both reported elevated ESR in patients with culture-proven bacterial ARS but also concluded that normal levels are common in

Table 1 Studies addressing the use of inflammatory biomarkers in diagnosing bacterial acute rhinosinusitis

Study	Reference standard	Main findings
Autio et al. 2017 [17•]	Maxillary sinus aspirate + bacterial culture	CRP ≥ 11 mg/l $\rightarrow$ LR+ 3.3, LR- 0.5 CRP ≥ 49 mg/l $\rightarrow$ LR+ 15.8, LR- 0.6
Hansen et al. 2009 [18•]	Maxillary sinus aspirate + bacterial culture	CRP 11–49 mg/l $\rightarrow$ OR 8.9 CRP > 49 mg/ml $\rightarrow$ OR 10.5 Moderate ESR ¹ $\rightarrow$ OR 4.3 High ESR ¹ $\rightarrow$ OR 4.9
Young et al. 2003 [23]	Clinical criteria	Radiography is better than CRP in diagnosing ARS
Savolainen et al. 1997 [19•]	Maxillary sinus aspirate + bacterial culture	Normal CRP, ESR, and WBC counts are common in culture-proven bacterial ARS
Hansen et al. 1995 [20]	Appearance of maxillary sinus aspirate	CRP 11–24 mg/l $\rightarrow$ OR 2.7 CRP 25–49 mg/l $\rightarrow$ OR 3.5 CRP > 49 mg/l $\rightarrow$ OR 7.4
Van Buchem et al. 1995 [21]	Appearance of sinus aspirate	ESR > 10 mm/h $\rightarrow$ 72% of patients had fluid in the maxillary sinus
Lindbaek et al. 1996 [22]	Computed tomography of the paranasal sinuses	ESR > 10 mm/h was related to radiologic acute sinusitis

CRP C-reactive protein, ESR erythrocyte sedimentation rate, LR+ positive likelihood ratio, LR- negative likelihood ratio, mm/h millimetres per hour, mg/l milligrammes per litre, OR odds ratio, WBC white blood cell count

¹ Moderate ESR: 11–30 mm/h in males, 21–30 in females; high ESR: > 30 mm/h

bacterial ARS. Additionally, in a study by Puhakka et al. [28], elevated levels of ESR were found in patients with a spontaneously recovering common cold. We found no original studies where the sensitivity or specificity of elevated ESR in diagnosing bacterial ARS was reported or where ESR had been monitored during an ARS episode with sequential measurements of ESR. However, increased ESR levels have been associated with a positive bacterial culture from the sinus aspiration. A study by Hansen et al. [18•] reported that the probability of a positive bacterial culture rose in patients with higher ESR levels. They reported that a moderate level of ESR (21–30 mm/h in females and 11–30 mm/h in males) was associated with a positive bacterial culture from the sinus aspiration (odds ratio 4.3). The association between a high level of ESR (> 30 mm/h) and bacterial ARS was similarly high (odds ratio 4.9). However, 42% of the patients with culture-proven bacterial ARS had a low ESR level (< 10 mm/h). In a randomised controlled study evaluating the effect of penicillin in clinically diagnosed ARS, the authors found no difference in the ESR levels or any change in ESR between treatment and placebo groups during a 7-day follow-up [25]. Even though high ESR levels have been related to bacterial ARS even in a culture-proven setup, the frequency of normal ESR levels even in culture-proven bacterial ARS and elevated levels in viral infection without suspicion of bacterial involvement suggest that ESR should not be used to screen for bacterial ARS.

White Blood Cell Count

Only a small proportion of human white blood cells circulate freely. Some of them are attached to blood vessel walls and most of them are stored in bone marrow. White blood cells are primarily involved in response to local inflammation caused by a variety of viruses or bacteria [29]. WBC count measures only freely circulating cells. The upper limit of WBC in a healthy person is usually considered to be $8 \times 10^9/l$. WBC count is reported to be elevated more often in bacterial disease [30] and only minor changes have been reported in confirmed viral upper respiratory tract infections [28, 31]. WBC counts have been examined in patients with culture-proven bacterial ARS by Autio et al. and Savolainen et al. [17•, 19•]. Both authors concluded that WBC rarely exceeded the reference range during bacterial ARS. Autio et al. also concluded that WBC had no value in diagnosing bacterial ARS. We found no studies addressing a possible change in WBC count during treatment of ARS.

Procalcitonin

In a healthy person, procalcitonin (PCT) is synthesised in the thyroid gland. The levels of PCT in a healthy person are low (< 0.05 $\mu\text{g/l}$). Bacterial endotoxins and inflammatory mediators in bacterial infection rapidly activate PCT production in other parenchymal tissues as well. During acute infection, PCT levels peak after 6–24 h and changes are detectable as

fast as after 2–4 h [32, 33]. PCT levels do not rise significantly in viral infections [33], and PCT has been reported to be an accurate variable in distinguishing bacterial and non-bacterial infections [34].

We found only one study that reported PCT values during an ARS episode and examined their diagnostic ability to detect bacterial ARS [17•]. In that study, the level of PCT was rarely significantly elevated after 2–3 or 9–10 days of symptoms and had no value in diagnosing bacterial ARS.

Nasal Nitric Oxide

Nasal nitric oxide (nNO) is a gaseous agent that is believed to have a role in the regulation of blood flow and ciliary movement of nasal and paranasal mucosa and also to have antibacterial, antiviral, and pro-inflammatory effects. nNO is suggested to have a role in the local immune system [35, 36]. High levels of nNO have been reported earlier in patients with allergic rhinitis, asthma, or acute respiratory infection [36]. On the other hand, both adult and child patients with clinically diagnosed ARS with suspicion of bacterial aetiology have been reported to have low nNO levels that rise after treatment with antibiotics [37, 38]. The range of nNO in a healthy person is reported to be 450–900 parts per billion (ppb) [36].

In a report by Autio et al. [17•], the levels of nNO were lower in patients with culture-proven bacterial ARS both at the beginning of symptoms at 2–3 days and at the time of diagnosis at 9–10 days of symptoms. The authors were unfortunately unable to determine a threshold of nNO for diagnosing bacterial ARS. The authors also found that the level of nNO correlated with the level of CRP, a wider spread of the disease to the paranasal sinuses and occlusion of the ostiomeatal complex. Even though nNO seems to be lower in bacterial ARS than in non-bacterial ARS, the use of nNO in diagnosing bacterial ARS is limited due to multiple sources of error [39, 40]. There still are problems in obtaining reproducible results using nNO measurements, and a reliable threshold of nNO for diagnosing bacterial ARS has not yet been reported.

Discussion

The literature concerning the behaviour of inflammatory biomarkers during an ARS episode and the use of inflammatory biomarkers in diagnosing bacterial ARS are still limited. In addition, the research on rhinosinusitis has been concentrated more on CRS than ARS during the past few years. Also, many of the studies reviewed in this article were published more than 20 years ago and comparison of these studies is difficult due to the fact that the studies have used different reference standards for diagnosing bacterial ARS. Many studies use

clinical criteria, paranasal computed tomography findings, or appearance of sinus puncture material as a reference standard for bacterial ARS. Only a few studies (Table 1) have used the positive bacterial culture obtained from a paranasal sinus, most often the maxillary sinus, as a reference standard, as suggested by Chow et al. [2].

The levels of CRP and ESR usually peak after a few days of ARS symptoms and the elevated levels decrease rapidly during the episode. Clearly elevated levels in several inflammatory biomarkers reveal an obvious systemic inflammation reaction, which is the strongest at the beginning of the episode. Both normal and elevated levels of CRP, ESR, and WBC have been reported in patients with culture-proven bacterial ARS. Especially elevated CRP and ESR have been related to a higher probability of bacterial disease, but elevated levels have also been reported in viral ARS without suspicion of bacterial involvement [14, 15, 17•, 18•, 19•, 28]. The sensitivity, specificity, and predictive values of elevated inflammatory biomarker levels have not been reported often. We found one study [17•] that reported the LR+ of elevated CRP to be relatively high, but the low sensitivity of this finding makes it unreliable in screening patients with bacterial ARS. There is no data supporting the use of inflammatory biomarkers in the follow-up of ARS patients.

As in CRS, cytokines have also been studied in ARS. High levels of cytokines, especially interleukins, tumour necrosis factor alpha, and interferons have been found in nasal secretions or nasal washings in patients with ARS symptoms or a verified upper respiratory tract virus infection, but we were not able to find studies where these cytokines or their levels would have been studied in diagnosing bacterial ARS [1, 41–43]. We still need further investigation of inflammatory biomarkers, especially compared with culture-proven bacterial ARS.

Conclusion

Changes in inflammatory biomarkers are common in both viral and bacterial ARS. Elevated CRP or ESR levels may support diagnosis of bacterial ARS, but due to the frequency of normal levels in patients with confirmed culture-proven bacterial ARS and elevated levels in patients with no suspicion of bacterial involvement, the use of CRP nor ESR should not be used to screen for bacterial ARS.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

- Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European position paper on rhinosinusitis and nasal polyps 2012. *Rhinol Suppl.* 2012;23(23):1–298.
- Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJ, Hicks LA, et al. Infectious Diseases Society of America. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *Clin Infect Dis.* 2012;54(8):e72–e112. <https://doi.org/10.1093/cid/cis370>.
- Desrosiers M, Evans GA, Keith PK, Wright ED, Kaplan A, Bouchard J, et al. Canadian clinical practice guidelines for acute and chronic rhinosinusitis. *J Otolaryngol Head Neck Surg.* 2011;40(Suppl 2):S99–193.
- Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, Brook I, Ashok Kumar K, Kramper M, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg.* 2015;152(2 Suppl):S1–S39. <https://doi.org/10.1177/0194599815572097>.
- Anon JB, Jacobs MR, Poole MD, Ambrose PG, Benninger MS, Hadley JA, et al. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol Head Neck Surg.* 2004;130(1 Suppl):1–45.
- Bachert C, Hörmann K, Mosges R, Rasp G, Riechelmann H, Müller R, et al. An update on the diagnosis and treatment of sinusitis and nasal polyposis. *Allergy.* 2003;58(3):176–91. <https://doi.org/10.1034/j.1398-9995.2003.02172.x>.
- Hsiao CJ, Cherry DK, Beatty PC, Rechtsteiner EA. National Ambulatory Medical Care Survey: 2007 summary. *Natl Health Stat Rep.* 2010;27(27):1–32.
- Berg O, Carenfelt C, Rystedt G, Änggård A. Occurrence of asymptomatic sinusitis in common cold and other acute ENT-infections. *Rhinology.* 1986;24(3):223–5.
- Autio TJ, Tapiainen T, Koskenkorva T, Narkio M, Lappalainen M, Nikkari S, et al. The role of microbes in the pathogenesis of acute rhinosinusitis in young adults. *Laryngoscope.* 2015;125(1):E1–7. <https://doi.org/10.1002/lary.24862>.
- Meltzer EO, Hamilos DL, Hadley JA, Lanza DC, Marple BF, Nicklas RA, et al. Rhinosinusitis: developing guidance for clinical trials. *J Allergy Clin Immunol.* 2006;118(5 Suppl):S17–61. <https://doi.org/10.1016/j.jaci.2006.09.005>.
- Aabenhus R, Jensen JU, Jorgensen KJ, Hrobjartsson A, Bjerrum L. Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care. *Cochrane Database Syst Rev.* 2014;11:CD010130.
- Clyne B, Olshaker JS. The C-reactive protein. *J Emerg Med.* 1999;17(6):1019–25. [https://doi.org/10.1016/S0736-4679\(99\)00135-3](https://doi.org/10.1016/S0736-4679(99)00135-3).
- van der Meer V, Neven AK, van den Broek PJ, Assendelft WJ. Diagnostic value of C reactive protein in infections of the lower respiratory tract: systematic review. *BMJ.* 2005;331(7507):26–0. <https://doi.org/10.1136/bmj.38483.478183.EB>.
- Whicher JT, Chambers RE, Higginson J, Nashef L, Higgins PG. Acute phase response of serum amyloid A protein and C reactive protein to the common cold and influenza. *J Clin Pathol.* 1985;38(3):312–6. <https://doi.org/10.1136/jcp.38.3.312>.
- Melbye H, Hvidsten D, Holm A, Nordbø SA, Brox J. The course of C-reactive protein response in untreated upper respiratory tract infection. *Br J Gen Pract.* 2004;54(506):653–8.
- Ruuskanen O, Putto A, Sarkkinen H, Meurman O, Irjala K. C-reactive protein in respiratory virus infections. *J Pediatr.* 1985;107(1):97–100. [https://doi.org/10.1016/S0022-3476\(85\)80624-7](https://doi.org/10.1016/S0022-3476(85)80624-7).
- Autio TJ, Koskenkorva T, Leino TK, Koivunen P, Alho OP. Longitudinal analysis of inflammatory biomarkers during acute rhinosinusitis. *Laryngoscope.* 2017;127(2):E55–61. **Reference 17 is important because the reference standard used in this study for bacterial acute rhinosinusitis was positive bacterial culture from a maxillary sinus aspiration. Therefore, the diagnosis of bacterial acute rhinosinusitis in this study was culture-proven.**
- Hansen JG, Højbjerg T, Rosborg J. Symptoms and signs in culture-proven acute maxillary sinusitis in a general practice population. *APMIS.* 2009;117(10):724–9. **Reference 18 is important because the reference standard used in this study for bacterial acute rhinosinusitis was positive bacterial culture from a maxillary sinus aspiration. Therefore, the diagnosis of bacterial acute rhinosinusitis in this study was culture-proven.**
- Savolainen S, Jousimies-Somer H, Karjalainen J, Ylikoski J. Do simple laboratory tests help in etiologic diagnosis in acute maxillary sinusitis? *Acta Otolaryngol Suppl.* 1997;529:144–7. **Reference 18 is important because the reference standard used in this study for bacterial acute rhinosinusitis was positive bacterial culture from a maxillary sinus aspiration. Therefore, the diagnosis of bacterial acute rhinosinusitis in this study was culture-proven.**
- Hansen JG, Schmidt H, Rosborg J, Lund E. Predicting acute maxillary sinusitis in a general practice population. *BMJ.* 1995;311(6999):233–6. <https://doi.org/10.1136/bmj.311.6999.233>.
- Van Buchem L, Peeters M, Beaumont J, Knottnerus A. Acute maxillary sinusitis in general practice: the relation between clinical picture and objective findings. *Eur J Gen Pract.* 1995;1(4):155–60. <https://doi.org/10.3109/13814789509161629>.
- Lindbaek M, Hjortdahl P, Johnsen UL. Use of symptoms, signs, and blood tests to diagnose acute sinus infections in primary care: comparison with computed tomography. *Fam Med.* 1996;28(3):183–8.
- Young J, Bucher H, Tschudi P, Periat P, Hugenschmidt C, Welge-Lüssen A. The clinical diagnosis of acute bacterial rhinosinusitis in general practice and its therapeutic consequences. *J Clin Epidemiol.* 2003;56(4):377–84. [https://doi.org/10.1016/S0895-4356\(02\)00590-5](https://doi.org/10.1016/S0895-4356(02)00590-5).
- Autio TJ, Koskenkorva T, Narkio M, Leino TK, Koivunen P, Alho OP. Diagnostic accuracy of history and physical examination in bacterial acute rhinosinusitis. *Laryngoscope.* 2015;125(7):1541–6. <https://doi.org/10.1002/lary.25247>.
- Hansen JG, Schmidt H, Grinsted P. Randomised, double blind, placebo controlled trial of penicillin V in the treatment of acute maxillary sinusitis in adults in general practice. *Scand J Prim Health Care.* 2000;18(1):44–7.
- Kratz A, Plebani M, Peng M, Lee YK, McCafferty R, Machin SJ, et al. ICSH recommendations for modified and alternate methods measuring the erythrocyte sedimentation rate. *Int J Lab Hematol.* 2017;39(5):448–57.
- Brigden ML. Clinical utility of the erythrocyte sedimentation rate. *Am Fam Physician.* 1999;60(5):1443–50.
- Puhakka T, Mäkelä MJ, Alanen A, Kallio T, Korsoff L, Arstila P, et al. Sinusitis in the common cold. *J Allergy Clin Immunol.* 1998;102(3):403–8. [https://doi.org/10.1016/S0091-6749\(98\)70127-7](https://doi.org/10.1016/S0091-6749(98)70127-7).
- Werman HA, Brown CG. White blood cell count and differential count. *Emerg Med Clin North Am.* 1986;4(1):41–58.
- Stock W, Hoffman R. White blood cells 1: non-malignant disorders. *Lancet.* 2000;355(9212):1351–7. [https://doi.org/10.1016/S0140-6736\(00\)02125-5](https://doi.org/10.1016/S0140-6736(00)02125-5).
- McClain MT, Park LP, Nicholson B, Veldman T, Zaas AK, Turner R, et al. Longitudinal analysis of leukocyte differentials in peripheral blood of patients with acute respiratory viral infections. *J Clin Virol.* 2013;58(4):689–95. <https://doi.org/10.1016/j.jcv.2013.09.015>.

32. Davies J. Procalcitonin. *J Clin Pathol*. 2015;68(9):675–9. <https://doi.org/10.1136/jclinpath-2014-202807>.
33. Gilbert DN. Procalcitonin as a biomarker in respiratory tract infection. *Clin Infect Dis*. 2011;52(Suppl 4):S346–50. <https://doi.org/10.1093/cid/cir050>.
34. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. *Clin Infect Dis*. 2004;39(2):206–17. <https://doi.org/10.1086/421997>.
35. Djupesland PG, Chatkin JM, Qian W, Haight JS. Nitric oxide in the nasal airway: a new dimension in otorhinolaryngology. *Am J Otolaryngol*. 2001;22(1):19–32. <https://doi.org/10.1053/ajot.2001.20700>.
36. Scadding G, Scadding GK. Update on the use of nitric oxide as a noninvasive measure of airways inflammation. *Rhinology*. 2009;47(2):115–20.
37. Lanz MJ, Prendes S, Peyrou N, Toledo G, Ferrer CM. Nasal nitric oxide as a noninvasive marker in the antibiotic treatment of acute bacterial sinusitis. *J Allergy Clin Immunol*. 2008;121(2):530–1. <https://doi.org/10.1016/j.jaci.2007.09.034>.
38. Baraldi E, Azzolin NM, Biban P, Zacchello F. Effect of antibiotic therapy on nasal nitric oxide concentration in children with acute sinusitis. *Am J Respir Crit Care Med*. 1997;155(5):1680–3. <https://doi.org/10.1164/ajrccm.155.5.9154876>.
39. de Winter-de Groot KM, van der Ent CK. Measurement of nasal nitric oxide: evaluation of six different sampling methods. *Eur J Clin Investig*. 2009;39(1):72–7. <https://doi.org/10.1111/j.1365-2362.2008.02064.x>.
40. American Thoracic Society & European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med*. 2005;171(8):912–30.
41. Repka-Ramirez S, Naranch K, Park YJ, Clauw D, Baraniuk JN. Cytokines in nasal lavage fluids from acute sinusitis, allergic rhinitis, and chronic fatigue syndrome subjects. *Allergy Asthma Proc*. 2002;23(3):185–90.
42. Rudack C, Stoll W, Bachert C. Cytokines in nasal polyposis, acute and chronic sinusitis. *Am J Rhinol*. 1998;12(6):383–8. <https://doi.org/10.2500/105065898780708008>.
43. Riechelmann H, Deutschle T, Rozsasi A, Keck T, Polzehl D, Burner H. Nasal biomarker profiles in acute and chronic rhinosinusitis. *Clin Exp Allergy*. 2005;35(9):1186–91. <https://doi.org/10.1111/j.1365-2222.2005.02316.x>.