



Research Article

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The C-Reactive Protein Response in Beta-Hemolytic Streptococcal Infections

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Abstract

Background: C-reactive protein (CRP) is an acute-phase serum protein that activates the complement. It is secreted by the liver in response to inflammatory cytokines. CRP levels increase rapidly after tissue damage in response to inflammation and infection and decrease with the resolution of the condition.

Material and method: We analyzed 230 patients that had positive cultures of the pharyngeal exudate for group A, C or G β -hemolytic streptococci, admitted to the Clinical Hospital of Infectious Diseases "Sf. Parascheva" Iasi between 1.07.2018-31.12.2018, which we have corroborated with inflammation markers (CRP, leucocyte count, fibrinogen) and with clinical diagnosis.

Results: Only 155 (67.4%) patients were confirmed with streptococcal angina or scarlet fever. 72.2% of the patients have been diagnosed with group A streptococci (GAS) infection, 14.2% with group C streptococci (GCS) and 13.5% with group G streptococci (GGS) infection. 75 patients were healthy carriers of β -hemolytic streptococci: GAS was isolated from 23.8%, GCS from 60.7% and GGS from 22.2% patients. In 90.9% of GCS infections CRP values were above 50mg/L, while 38.4% and, respectively, 23.8% of those infected with GAS or GGS have such values. In only 52.3% GGS patients CRP level was above 5mg/L.

Conclusion: 1. The most common streptococcal pharynx infections were GAS ones, followed by GCS and GGS. 2. CRP values in patients with GCS infection are more often above 50mg/L than in those with GAS or GGS infections. 3. Pharyngeal GCS carriage is the most common of all pathogenic β -hemolytic streptococci. 4. The inflammatory response to GGS is low.

Keywords: C-reactive protein; Beta hemolytic streptococci; Infection

Abbreviations: CRP: C-reactive Protein, GAS: Group A Streptococcus, GCS: Group C Streptococcus, GGS: Group G Streptococcus

Introduction

C-reactive protein (CRP) was introduced into medical practice in the 1990s as a rapid orientation test [1]. Some factors that may influence CRP levels are age, sex, weight, cholesterol level, blood pressure, smoking status [1]. The native CRP is composed of 5 identical subunits bound by non-covalent bonds, placed around a central pore, in the characteristic form of "lectin fold", as a beta-folded sheet [2]. It irreversibly dissociates in inflammation into 5 monomers, the monomeric CRP. The native CRP activates the classical complement pathway and it induces apoptosis and phagocytosis. The monomeric CRP plays an important role in chemotaxis and in directing leukocytes to the inflammatory area, delaying apoptosis. The human CRP gene can be found at 1q23.2 on the long arm of chromosome 1, and, to date, there have been

no allelic variations or genetic deficiencies discovered for this gene although some polymorphisms have been identified [1]. CRP synthesis starts in response to pro-inflammatory cytokines, particularly IL6, IL1 and TNF alpha [3].

Kingsley and Jones [4] state that in the case of infections, CRP increases in response to the cytokines IL6 and IL1 and has a stable rate of decomposition. It is mainly synthesized by hepatocytes but can also be synthesized by smooth muscle tissue [5], macrophages [6], endothelial cells [7], lymphocytes and adipocytes [8]. It will bind to microbial polysaccharides and damaged cell ligands by activating the complement. CRP levels increase rapidly, up to 1000-fold after tissue injury as a systemic response to inflammation or infection and decrease exponentially with condition resolution [9].

CRP provides information about the inflammatory reaction and it helps to manage the antibiotic therapy [10]. Black, et al. [11] specify that CRP is not only a marker of inflammation and infection, but also plays a protective role against infectious agents by activating the complement system. Kingsley and Jones [4] state that CRP can be used in the differentiation between colonization and infection, but it cannot help to distinguish between types of infection. Huang, et al. [12] assert that the determination of CRP values decreased the rate of antibiotic therapy in lower respiratory tract infections.

Cals and Weert [13] highlighted an association between high CRP values and bacterial infections. Acute pharyngitis is one of the most common complaints that a physician encounters in the ambulatory care setting. Typically, the incidence peaks during childhood and in adolescents. Although there are a large number of visits each year for pharyngitis, the majority of these cases are viral and are self-limiting. However, group A streptococcus (GAS) is the most common bacterial etiology for acute pharyngitis. The prevalence of streptococcal pharyngeal infections in non-A group streptococcus is constantly increasing. The rapid antigen detection test limits doctors to the determination of GAS [14]. As the rapid diagnosis of infectious diseases is an important practical problem for the case and the doctor, with an epidemiological, social, family, biological and economic impact, we attempted to establish the CRP response in different type beta-hemolytic streptococcal infections.

Material and Methods

The main purpose consists in conducting a retrospective study of microbiologically confirmed cases with pharyngeal β -hemolytic streptococci, by assessing the rate and the mean values of CRP according to the pathogen agent and establishing the status of infectious or colonizing agent. We analyzed 230 consecutive patients admitted to the Clinical Hospital of Infectious Diseases "Sf. Parascheva" Iasi between 1.07.2018-31.12.2018, which follow the inclusion criteria. Inclusion criteria: positive culture of the pharyngeal exudate for group A, C or G β -hemolytic streptococci; CRP level determined for the patient. Exclusion criteria: culture negative for β -hemolytic streptococci; incomplete laboratory data for the patient. The examination protocol included CRP values,

which we have corroborated with inflammation markers such as white blood cell count and differential, fibrinogen and with clinical diagnosis.

One pharyngeal swab per patient was inoculated on Columbia Blood Agar (Bio maxima, Poland) and incubated at 37°C in an 5% carbon dioxide atmosphere for 48 hours. A culture was considered positive for beta-hemolytic streptococcus with a growth of any number of large beta-hemolytic colonies, gram-positive staining with streptococcal morphology, and a negative catalase test. Serogrouping of beta-hemolytic streptococci was performed with the Streptococcal Grouping Kit (Oxoid, UK). The culture was considered negative when beta-hemolytic colonies of group A, C, G streptococci were absent after 48 hours of incubation. CRP was quantified using RX Imola Chemistry Analyzer (Furuno, Japan).

Result

A total of 230 patients were enrolled. Only 155 (67.4%) patients were confirmed with streptococcal angina or scarlet fever, based on clinical presentation and inflammatory syndrome. The rest of 75 patients, without inflammatory signs were considered healthy carriers of β -hemolytic streptococci: GAS was isolated from 35 patients (23.8% of GAS positive pharyngeal exudate), respectively, group C streptococci (GCS) from 34 patients (60.7% of GCS positive pharyngeal exudate) and group G streptococci (GGS) from 6 patients (22.2% of GGS positive pharyngeal exudate). GAS was identified in 61 males (41.5%) and in 86 females (58.5%), GCS in 20 males (35.7%) and 36 females (64.3%), GGS in 16 males (59.3%) and 11 females (40.7%). GAS and GCS were more frequent in females, but GGS was most common in males.

55 of the patients (23.9% of the total number of patients) were diagnosed with scarlet fever; 52 of them (94.6%) was confirmed with GAS, 1 (1.8%) with GCS and 2 (3.6%) with GGS. 100 patients (43.5%) had the diagnosis of angina; 60 of them (60%) was confirmed with GAS, 21 (21%) with GCS and 19 (19%) with GGS. The rest of them (32.6%) were colonized with beta-hemolytic streptococcus. The age of the patients ranged from 1 to 86 years. No significant differences were found in age between patients (Table 1).

Table 1: Number of patients per investigated parameter and clinical diagnosis.

Strep Group	Total Patients (no)	CRP (mg/dL)					Diagnosis	
		<5	5-50	50-100	100-150	>150	Scarlet fever	Angina
A	112	15	54	29	6	8	52	60
C	22	2	0	7	6	7	1	21
G	21	10	6	3	1	1	2	19

Discussion

Only 67% of the patients from whom we isolated beta-hemolytic streptococci were infected. The most frequent carrier state was for GCS (Figure 1). The most frequent infection was produced by GAS, present in 112 cases (72.2% of infected patients), followed by GCS with 14.2% (22 patients) and GGS with 13.5% (21 patients)

(Figure 2). Infection with groups GCS was associated with higher CRP concentrations (mean 134 mg/L) compared with those with GAS infection (mean 55 mg/L) and GGS infection (mean 32 mg/L). In 90.9% of GCS infections CRP values were above 50 mg/L, while 38.4% and, 23.8%, respectively, of those infected with GAS or GGS had such values (Figures 3,4,5). The highest CRP concentration

was observed among patients with group C streptococcus infection (Figure 4). We found that in GGS infected patients' inflammatory

syndrome was not important; in only 52.3% GGS patients CRP level was above 5 mg/L (Figure 5).

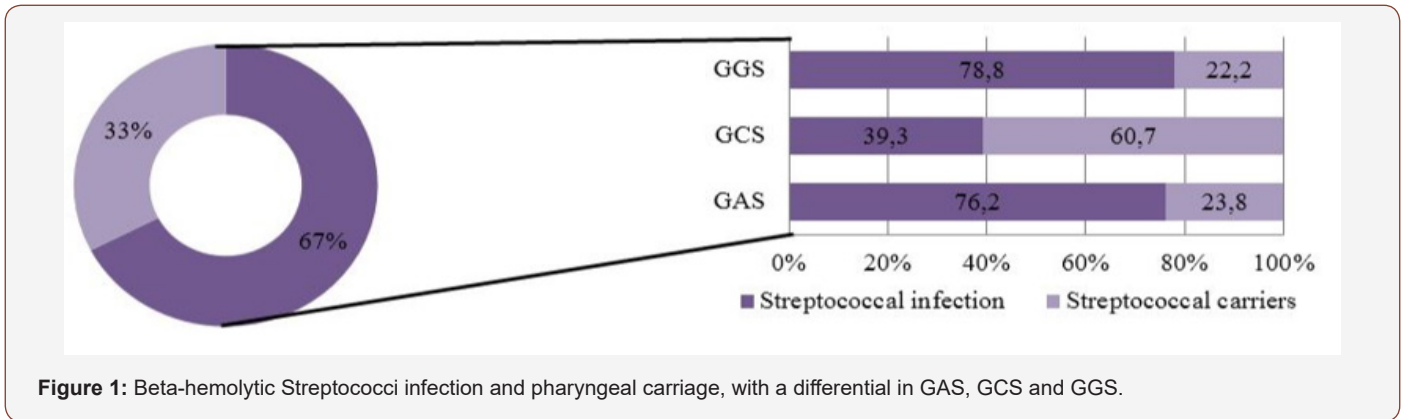


Figure 1: Beta-hemolytic Streptococci infection and pharyngeal carriage, with a differential in GAS, GCS and GGS.

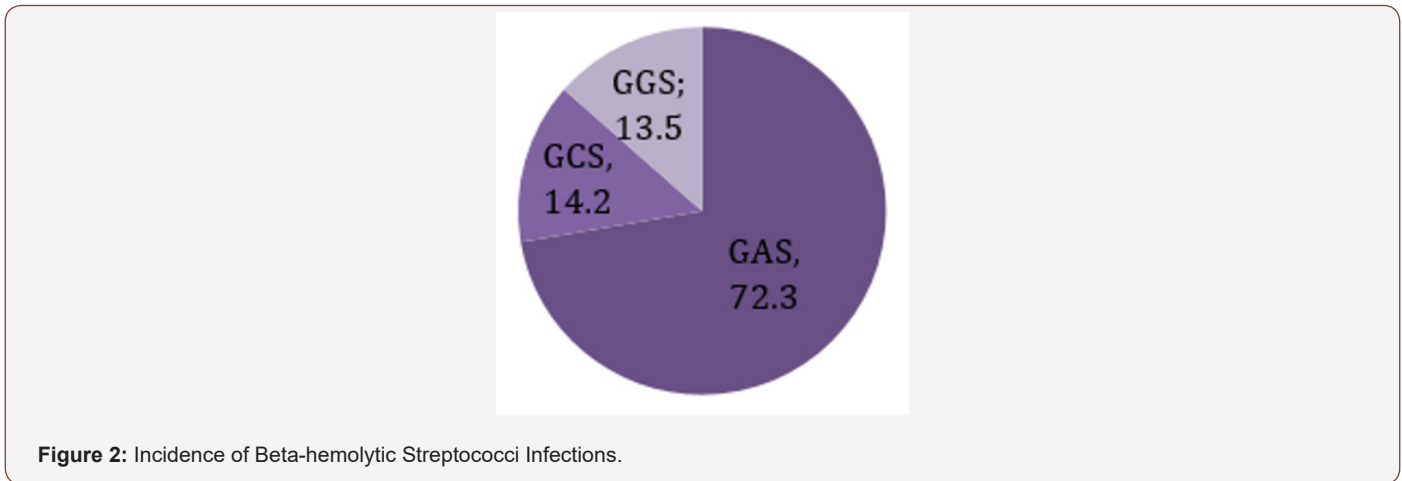


Figure 2: Incidence of Beta-hemolytic Streptococci Infections.

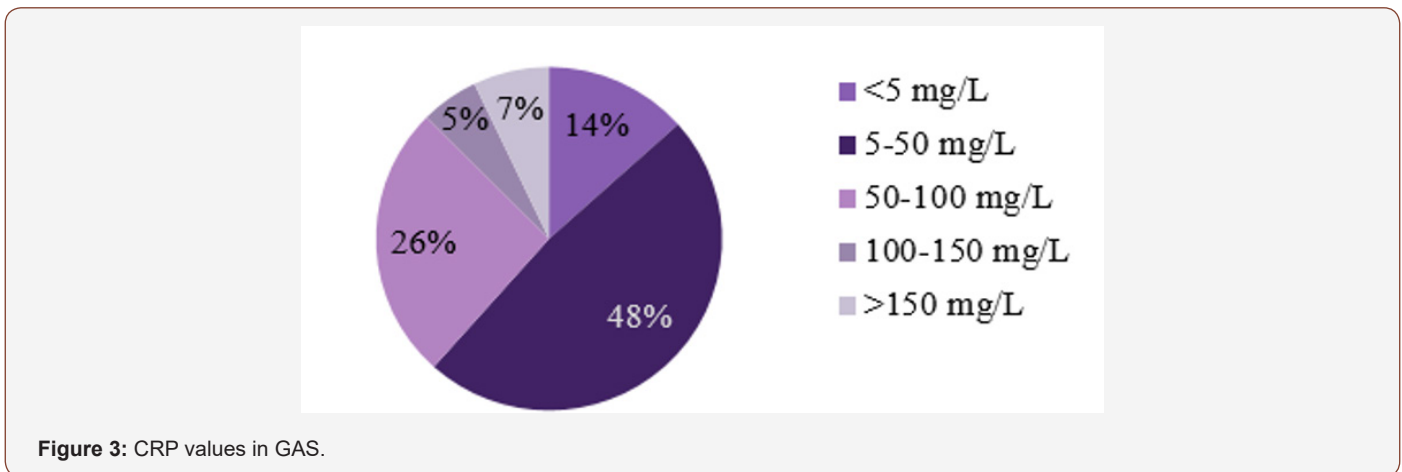


Figure 3: CRP values in GAS.

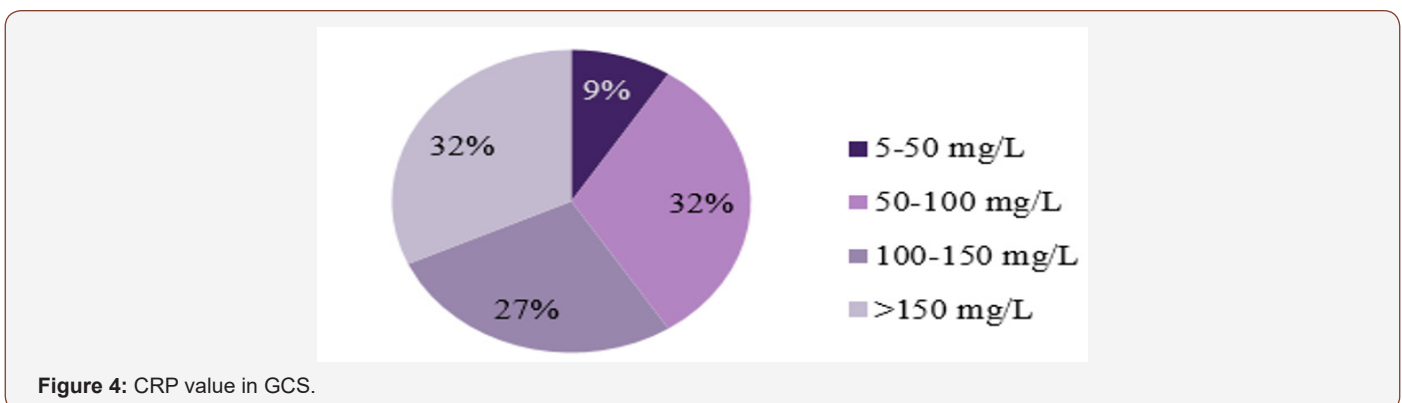


Figure 4: CRP value in GCS.

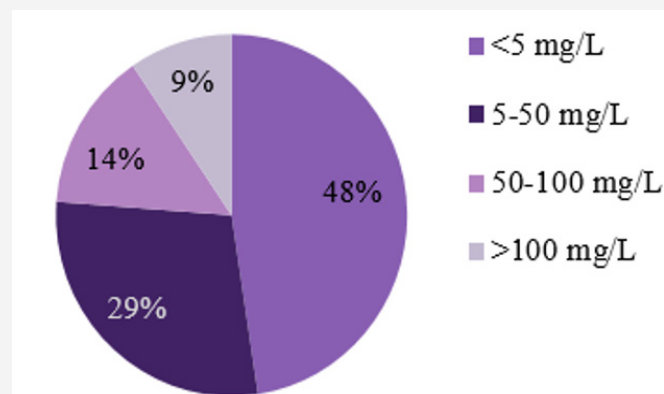


Figure 5: CRP value in GGS.

This is one of the few studies that emphasized the role of CRP as a rapid orientation test in the diagnosis of A, C or G streptococcal infection. CRP provides information about the inflammatory response and can be used as a guidance in managing the antibiotic therapy. CRP can make the difference between a streptococcal infection and a streptococcus healthy carrier with angina caused by a viral infection, by highlighting the presence of the inflammatory reaction. Our analysis awares that group C and G streptococci should be considered as throat pathogens along with GAS. The frequency of patients with GCS and GGS infection is about one fifth of the patients with GAS, as it has also been shown in other studies [15-17], we may consider that GCS and GGS are frequent causes of streptococcal infections. Few previous studies have analysed the variation of CRP in group A, C and G streptococcal infections. Our findings are in agreement with Calviño, et al. [18] from the Institute of Primary Care and Public Health, Cardiff University School of Medicine, that analysed the association between CRP rapid test and GAS infection. They observed an increased frequency of GAS infections compared to GCS and GGS, but a higher median CRP value (49.9mg/L) in patients with GCS and GGS infections, with the peak value recorded in GCS patients.

Furthermore, our results are similar with the results obtained by Lindbæk, et al. [17]. They have looked into the clinical symptoms and signs in sore throat patients with large colony variant β -haemolytic streptococci groups C or G versus group A. They concluded that CRP levels above 25 mg/L were significantly associated with presence of streptococci group C or G. They also stated that group C and G streptococci should be considered as throat pathogens in line with GAS. Hjortdahl and Melbye [19] examined if on-site testing enhances the diagnosis of streptococcal pharyngitis in adults. They obtained a mean CRP value of 50.4 mg/L in their GAS patients. Our mean CRP value in GAS infected patients of 55mg/L was similar to their findings.

Melbye, et al. [20] observed the daily reduction in C-reactive protein values in group-A streptococcal pharyngitis treated with antibiotics. They examined daily eleven adult patients with sore throat and confirmed GAS infection. Their average CRP value was of 100.3 mg/L, higher than our result (55mg/L). This difference may

be caused by our significantly bigger number of GAS patients (147 patients compared with 11 patients).

There are some authors that suggest that CRP testing is overused [21,22]. Our results reveal that CRP is useful for differentiating GAS infection from GCS and GGS ones and from other etiologies that do not require antibiotic therapy. Nowadays, the diagnosis of sore throat is based on microbiological identification. The culture of the pharyngeal exudates is the gold standard used when evaluating the etiology of the infection. Rapid detection of increased CRP values in sore throat patients can differentiate the bacterial from the viral angina, thus being able to increase the number of correctly treated patients. One strength of this study is that we have considered a statistically significant number of patients.

Conclusion

1. The most common streptococcal pharyngeal infections were produced by GAS, followed by GCS and GGS.
2. CRP values in patients with GCS infection are more often above 50mg/L than in those with GAS or GGS infections.
3. Pharyngeal GCS carriage is the most common of all pathogenic β -hemolytic streptococci.
4. The inflammatory response to GGS is low.

Acknowledgement

None.

Conflict of Interest

No conflict of interest.

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