# IMMUNOGLOBULIN SERUM CONCENTRATIONS DO NOT CORRELATE WITH ACUTE APPENDICITIS

## AS CONCENTRAÇÕES SÉRICAS DE IMUNOGLOBULINA NÃO SE CORRELACIONAM COM A APENDICITE

NUNO CARVALHO[1,2], ELISABETE CAROLINO[3], ISABEL CARVALHO[4], VANESSA LISBOA[4], HÉLDER COELHO[5], MADALENA TRINDADE[1], JOÃO VAZ[1], LUIS MOITA[6,7], PAULO COSTA[1,2]

1 Serviço Cirurgia Geral, Hospital Garcia de Orta, Almada, Portugal
2 Faculdade Medicina, Universidade Lisboa, Portugal
3 H&TRC- Health & Technology Research Center, ESTeSL- Escola Superior de Tecnologia da Saúde, Instituto Politécnico de Lisboa, Lisboa, Portugal
4 Serviço de Patologia Clínica, Hospital Garcia de Orta, Almada, Portugal
5 Serviço de Anatomia Patológica, Hospital Garcia de Orta, Almada, Portugal
6 Innate Immunity and Inflammation Lab – Instituto Gulbenkian de Ciência, Oeiras, Portugal
7 Instituto de Histologia e Biologia do Desenvolvimento, Faculdade Medicina, Universidade Lisboa, Portugal

**ABSTRACT**

Immunoglobulins are a central component of humoral immunity and their serum concentrations are routinely determined in clinical practice because they provide key information on the humoral immune status. In a single centre prospective design study, we evaluated IgA, IgE, IgG, and IgM serum concentrations in patients with histologically confirmed acute appendicitis (study group, N=54) and compared it to the control group (N=69), patients submitted to appendectomy, but with normal histological findings, patients submitted to day case surgery and healthy volunteers. The serum concentrations of immunoglobulins were normal in all cases, except for IgE, that were elevated in both the study (20%) and control (21 %) groups (p= 0.609). These values are in good agreement with the prevalence of allergies in the general population. Our study is the first to address specifically the acute appendicitis Immunoglobulins humoral immune response in the English literature. We showed that acute appendicitis does not elicit a specific humoral immune response.

***Key words:*** *acute appendicitis, Humoral immune response, IgA, IgE, IgG, IgM.*

**RESUMO**

As imunoglobulinas são um componente central da imunidade humoral e as suas concentrações séricas são determinadas por rotina na prática clínica, pois fornecem informações importantes sobre o estado imunológico humoral. Num estudo prospetivo de centro único, avaliámos as concentrações séricas de IgA, IgE, IgG e IgM em doentes com apendicite aguda confirmada histologicamente (grupo de estudo, N=54) e comparámos com o grupo controle (N=69), doentes submetidos a apendicectomia, mas com achados histológicos normais, doentes submetidos a cirurgia de ambulatório e voluntários saudáveis. As concentrações séricas de imunoglobulinas foram normais em todos os casos, exceto para IgE, que estava elevada tanto no grupo estudo (20%)

quanto no grupo controle (21%) (p= 0,609). Esses valores estão em boa concordância com a prevalência de alergias na população geral. O nosso estudo é o primeiro a abordar especificamente a resposta imune humoral de imunoglobulinas na apendicite aguda na literatura inglesa. Demonstrámos que a apendicite aguda não provoca uma resposta imune humoral específica.

***Palavras chave:*** *apendicite aguda, Resposta imune humoral, IgA, IgE, IgG, IgM.*

## 1. INTRODUCTION

While appendectomy for acute appendicitis (AA) is a common surgical procedure, the pathophysiology and natural history of this condition remain unclear[1]. The underlying pathogenesis is controversial: luminal obstruction, followed by bacterial invasion that triggers acute inflammation, primary infection, genetic factors, hypersensitivity type I reaction, are all possible causes of AA[2]. Whatever the inciting cause, all these possibilities are thought to lead to bacterial overgrowth and acute inflammation, which is responsible for the clinical manifestations [3].

Surprisingly, little is known about the humoral immune response in AA. In this study, we evaluate the humoral immune response, determining serum Immunoglobulins (Igs) in patients with AA and compare it with a control group. We hope that knowledge on humoral immune response could give new insights into its aetiology and pathogeny by reflecting its potential underlying cause.

## 2. OBJECTIVE

This study aimed to investigate the Igs humoral immune response in acute appendicitis.

## 3. MATERIALS AND METHODS

### 3.1. Study population

This was a pilot study, as the current literature did not provide sufficient information for sample size determination[4]. It was a single-center prospective observational study, conducted between April 2016 and June 2017 at Hospital Garcia de Orta (a 600-bed tertiary public hospital that provides medical care to 280 000 habitants of an urban area). The study group consisted of patients with AA confirmed by histology. The control group was composed by patients admitted with a clinical diagnosis of AA, submitted to appendectomy, but with normal histological findings and patients with *appendix in situ* (AIS) submitted to day case surgery, mainly abdominal wall surgery, and healthy volunteers. Patients with a history of previous appendectomy were excluded, as appendectomy can change Igs serum level profile[5]. Patients aged less than 18 years were also excluded as they are taken care by the Pediatrics department. Also, pregnant women were excluded as pregnancy can induces alterations in Igs serum levels[6].

### 3.2. Pathologic analysis

Appendix specimens obtained from surgery were formalin fixed, divided into three segments from tip to base, and paraffin embedded. Histological criteria were used for AA definition: presence of neutrophil infiltration in the *muscular propria*. AA was classified as acute phlegmonous appendicitis (APA), when neutrophil infiltration was limited to the *muscular propria*, or acute gangrenous appendicitis (AGA), when there was a background of transmural inflammation associated with necrosis of the wall of the appendix[7]. No clinical significance was attributed to the presence of

neutrophils in the mucosa that were considered as a normal variant[8]. The specimens were classified as non-pathologic appendix (NPA), also known as negative appendectomy, when no neutrophil infiltrate was shown in the *muscular propria*[7]. All histological examinations were carried out by the same dedicated gastrointestinal pathologist, one of the co-authors, blinded to serum Igs profile (CH).

### 3.3. Laboratory Proceeding

In patients with the clinical diagnosis of AA, a 5 ml blood sample was collected by venipuncture in vacutainers before anesthesia induction. In the control group, blood samples were collected at the time of intravenous access for day-case surgery or by schedule in healthy volunteers. The samples were centrifuged at a speed of 2500 rpm for 5 min and the serum stored at –20°C until it was processed. The quantitative determination of Igs A, G, and M is based on the principle of immunological agglutination, an immunoturbidimetric assay performed on Roche® automated clinical chemistry analyzer, Modular EVO P800. The quantitative determination of total IgE is based on a solid-phase, two-step chemiluminescent immunoassay performed on the Siemens® analyzer, Immulite®2000XPi. The reference intervals indicated by the manufacturer for healthy adults adopted at Hospital Garcia de Orta Pathology department were 70–400 mg/dL for IgA, < 120 U/mL for IgE, 700–1600 mg/dL for IgG and 40–230 mg/dL for IgM.

### 3.4. Statistical analysis

Data were analyzed using SPSS statistical software, V26.0, for Windows. The results were considered significant at the 5% significance level. To test the normality of the data, the Shapiro-Wilk test was used. To characterize the sample, frequency analysis (n, %) was used for qualitative data and for quantitative data, the mean and standard deviation were used. To compare the quantitative data between the histology groups, the one-way ANOVA was used (when the assumptions of normality were verified) or the Kruskal-Wallis test (when the assumptions of normality were not verified). To compare Igs serum levels between AA and controls, Mann-Whitney test was used, since the normality assumption was not verified. To study the association between qualitative data, the Chi-Square test (when the applicability assumptions were verified) or the Fisher's exact test or the Chi-Square test by Monte Carlo Simulation (when the applicability assumptions were not verified) were used.

### 3.5. Other Data

Personal information including age, sex, BMI, symptom onset and their duration, absence of peritonitis, localized or generalized peritonitis, surgical details, open or laparoscopic appendectomy, complications, length of hospital stay and other particular features of histology were evaluated (some data not showed). Individuals were also enquired about any symptoms pertaining to allergic disorders, episodes of infections and regular medication. This study is part of a more extensive research project, and many data are not presented here.

### 3.6. Ethical considerations

Patients gave written informed consent for participating in the study, which conformed to the principles of the Helsinki's declaration. The study was reviewed and approved by the Ethics Committee of the Hospital Garcia de Orta (Reference number 05/2016). All data were anonymized and the results were presented in such ways that make it impossible to identify single patients.

The datasets generated during the current study are available from the corresponding author on reasonable request.

## 4. RESULTS

### 4.1. Patients' characteristics

There were 54 patients with a histological diagnosis of AA, 39 with APA and 15 with AGA. The control group was composed of 69 individuals: 10 patients with a clinical diagnosis of AA, submitted to appendectomy, but with negative histology (NPA), 59 with AIS, of which 29 were patients submitted to day case surgery, mainly abdominal wall surgery, and 30 healthy volunteers. Patients' demographics characteristics are depicted in Table 1.

Statistically significant differences were detected only in relation to BMI (p=0.005), confirming that the groups with lower BMI are AIS and NHF.

### 4.2. Serum IgA, IgE, IgG and IgM levels

Concentrations of Igs IgA, IgE, IgG, and IgM in serum are shown in Tables 2 and 3. No differences were found between AA (APA and AGA) and the control group (NPA, day case surgery, healthy volunteers) for all the studied Igs (Table 2).

We evaluated APA and AGA individually, as these different histologic types of AA can have potentially different pathogenies[9,10] and again no differences were found (Table 3).

For most of the Igs, the values were within the normal range, except for IgE, which was elevated in 20 % of AA patients and in 21 % of the patients in the control group (Table 4).

No significant difference was found for IgE between groups (p= 0.609).

Table 1 – **Patients' demographics characteristics**

| AIS | | Histology | | | | |
|---|---|---|---|---|---|---|
| | | NHF | APA | AGA | p | |
| Age (Mean ± SD) | | 37.63±17.05 | 32.20±8.94 | 39.85±15.58 | 36.93±14.53 | 0.753[a] |
| Gender (N. %) | Female | 21 (35.6%) | 7 (70%) | 22 (56.4%) | 6 (40.0%) | 0.054[b] |
| | Male | 38 (64.4%) | 3 (30%) | 17 (43.6%) | 9 (60.0%) | |
| Allergy (n. %) | No | 40 (76.9%) | 7 (70%) | 30 (83.3%) | 12 (85.7%) | 0.777 (C.I.95%=(0.769;0.785))[c] |
| | Yes | 12 (23.1%) | 3 (30%) | 6 (16.7%) | 2 (14.3%) | |
| BMI (Mean ± SD) | | 24.04±4.23 | 22.78±3.87 | 26.69±5.29 | 28.25±4.27 | 0.005*[a] |

AIS – *Appendix in situ* NHF – Normal Histologic Findings

APA – Acute Phlegmonous Appendicitis AGA – Acute Gangrenous Appendicitis

a. One Way ANOVA. b. Qui-Square test. c. Qui-Square test by Monte Carlo Simulation

C.I. – Confidence Interval

* Statistically significant differences at a 5% significance level

Table 2 – **Immunoglobulin Serum Levels in Acute Appendicitis and Controls**

| Immunoglobulin | Histology | N | Ranks | | Test Statistics[a.b] | |
|---|---|---|---|---|---|---|
| | | | Mean Rank | Sum of Ranks | Mann-Whitney U | p |
| IgA | Control | 69 | 63.11 | 4354.50 | 1786.500 | 0.697 |
| | Acute Appendicitis | 54 | 60.58 | 3271.50 | | |
| | Total | 123 | | | | |
| IgG | Control | 69 | 65.33 | 4508.00 | 1633.000 | 0.241 |
| | Acute Appendicitis | 54 | 57.74 | 3118.00 | | |
| | Total | 123 | | | | |
| IgM | Control | 69 | 65.65 | 4530.00 | 1611.000 | 0.199 |
| | Acute Appendicitis | 54 | 57.33 | 3096.00 | | |
| | Total | 123 | | | | |
| IgE | Control | 67 | 61.62 | 4128.50 | 1700.500 | 0.692 |
| | Acute Appendicitis | 53 | 59.08 | 3131.50 | | |
| | Total | 120 | | | | |

a. Grouping Variable: Histology

b. Mann-Whitney test

Table 3 – **Immunoglobulin Serum Levels in APA, AGA and Controls**

| Immunoglobulin | Histology | Ranks | | Test Statistics[a.b] | | |
|---|---|---|---|---|---|---|
| | | N | Mean Rank | Kruskal-Wallis H | df | p |
| IgA | Control | 69 | 63.11 | 1.011 | 2 | 0.603 |
| | APA | 39 | 63.37 | | | |
| | AGA | 15 | 53.33 | | | |
| | Total | 123 | | | | |
| IgG | Control | 69 | 65.33 | 1.421 | 2 | 0.491 |
| | APA | 39 | 57.09 | | | |
| | AGA | 15 | 59.43 | | | |
| | Total | 123 | | | | |
| IgM | Control | 69 | 65.65 | 2.016 | 2 | 0.365 |
| | APA | 39 | 59.15 | | | |
| | AGA | 15 | 52.60 | | | |
| | Total | 123 | | | | |
| IgE | Control | 67 | 61.62 | 0.211 | 2 | 0.900 |
| | APA | 39 | 58.42 | | | |
| | AGA | 14 | 60.93 | | | |
| | Total | 120 | | | | |

APA – Acute Phlegmonous Appendicitis AGA – Acute Gangrenous Appendicitis

a. Kruskal Wallis Test

b. Grouping Variable: Histology

df. Degrees of freedom

Table 4 – **Immunoglobulin abnormal blood levels**

| | Control Group n (%) | Acute Appendicitis n (%) | *p* value |
|---|---|---|---|
| **IgA** | ↑ 2 (2.8) | ↑ 1 (2.2) | 0.999[a] |
| **IgE** | ↑ 14 (21) | ↑ 9 (20) | 0.609[b] |
| **IgG** | ↔ | ↑ 1 (2.2) | 0.439[a] |
| **IgM** | ↑ 1 (1.4) | ↑ 1 (2.2) | 0.999[a] |

a. Fisher Exact Test

b. Chi Squared Test

## 5. DISCUSSION

Igs are a central component of humoral immunity, measured routinely in clinical practice, as they provide key information regarding the humoral immune status[11].

The etiology of AA remains controversial[2]. Current knowledge is still limited in both appendicitis pathophysiology and causative mechanism[2,12]. Recent theories have focused on genetic factors, environmental influences, allergies, and infections[2,13,14].

Humoral immune response has been studied in different clinical situations, including chronic liver disease, trauma, or acute myocardial infarction, all with significant alterations that are clinically relevant[15,16,17,18]. Alcohol consumption and tobacco smoke also interfere with Igs levels (16). Our comprehensive study in a general adult population showed that serum concentrations of Igs in AA do not significantly differ from patients without appendicitis. Recent studies showed that APA and AGA can have different etiologies[9,10] and so, we evaluated APA and AGA individually, but again no differences were founded. Albeit not significant, it is interesting to note that Igs concentrations, whether IgA, IgE, IgG, or IgM are higher in the control group than in the AA group (Tables 2 and 3). It is possible that the small appendix size prevents local changes to have statistically significant repercussions at a systemic level.

Infection has been proposed as a cause of AA, whether it is primary or following luminal obstruction, with a wide range of infectious entities having been identified[19]. A humoral immune response is a key factor to fight an infection[20].

The diagnosis of an acute infectious disease most commonly involves the detection of the pathogen by culture, immunoassay, or molecular methods[15].

For many infections, a more convenient and less expensive alternative is the detection of the IgM antibody, while IgG testing can help determine whether or not an infection was recent[15].

We evaluated the general concentrations of Igs, because no specific agent was uniformly identified in association with AA and so no specific Ig could be evaluated, because it would be impractical to tests for all specific infectious agents. Therefore, the generic humoral immune response was our target, which can be a relevant limitation.

No significant differences were found between IgM and IgG concentrations in the AA and control groups. These results can be an argument against an infectious origin of AA, because if this were the case, higher values would be expected in the AA group. However, when a patient is at an early stage of this disease, IgM and IgG antibodies may not yet be detectable in peripheral blood[15]. In the present series, the mean time to presentation was 37,33±23,89 hours, ranging between 6 and 124 hours. Furthermore, we measured total and not specific Igs concentrations.

Serum IgA has effector functions that allow for the destruction of microorganisms and mammalian cells[21]. IgA deficiency is the most common primary immunoglobulin deficiency and is associated with infections, namely in gastrointestinal tract[22]. IgA concentrations were normal, with no deficiency detected in any case of AA.

Studies had showed an IgA reduction after appendectomy[5]. In our case, IgA determination was performed before appendectomy. It would be interesting to know the current levels of IgA in these patients.

Though statistically not significant, IgA, IgG and IgM levels were increased in patients with histologic proven AA.

The immune system can react to otherwise harmless environmental agents, causing hypersensitivity reactions. Type I hypersensitivity reactions are mediated by allergen-specific IgE[23]. AA has histological features of an allergic reaction[24]. Allergic patients are characterized by the increased production of IgE antibodies to antigens from different sources[25].

If AA is an allergic reaction, it is expected that IgE levels are elevated. In our study, 9 cases of histological confirmed AA (20 %) and12 cases from the control group (21 %) had elevated levels of IgE. These values are in accordance with the prevalence of allergic diseases in the general population[23].

Serum IgE can be normal in allergy, as most of IgE is located at the target organ, where it binds to mast cells, and is therefore not present in the serum. In a previous study, we showed IgE increased deposition in APA compared with incidental appendectomy[26]. The non-specificity of IgE was the reason we evaluated total IgE[27]. Furthermore, experimental allergy can be induced in animals in the absence of IgE[28].

A recent retrospective cohort study showed that children with IgE-mediated allergy had a lower risk of complicated appendicitis[29].

In a recent paper, Das *et al.* demonstrated that serum IgE concentrations were significantly higher in recurrent appendicitis[30]. The authors hypothesized that persistently high serum IgE levels may lead to recurrent appendicitis, as seen in bronchial asthma[30]. A prospective pediatric study showed no differences in IgE serum levels in complicated and uncomplicated AA[31]. In our study, no peculiar IgE response was founded in association with AA.

### *Strengths*

This is the first study in the English literature reporting on the Igs humoral immune response in acute appendicitis, namely IgA, IgE, IgG and IgM. Previous studies had focus only on IgE blood levels. The prospective nature of the study, which involved precise AA histologic definitions and the enrollment of a heterogeneous control group are notorious strengths.

### *Limitations*

The main limitation was the absence of specific Igs determination, the lack of immunological profiles prior to acute appendicitis and the small sample size from a single institution. The results should be reproduced by others, preferentially with specific Igs determinations. It is strongly recommended that others studies should evaluate different components of the humoral immune response, and correlate with Igs response in acute appendicitis.

## CONCLUSIONS

The present study showed no specific Igs humoral immune response in acute appendicitis, as the Igs serum profile was identical to the control group. Thus, acute appendicitis does not elicit a humoral immune response, at least detectable with routine laboratorial evaluation.


## Acknowledgements

We specially thank patients, surgical residents, surgeons, anesthesiologists, pathologists, nurses, medical students, and many others, as without their generous co-operation and hard work, this study would not have been possible.

We thank José Maria Covas Lima for reviewing the manuscript.


## Conflicts of interest

No conflicts of interest were declared regarding this work.

## REFERENCES


1. Neufeld MY, Bauerle W, Eriksson E, Azar FK, Evans HL, Johnson M, Lawless RA, Lottenberg L, Sanchez SE, Simianu VV, Thomas CS, Drake FT. Where did the patients go? Changes in acute appendicitis presentation and severity of illness during the coronavirus disease 2019 pandemic: A retrospective cohort study. Surgery. 2021 Apr; 169(4):808-815. doi: 10.1016/j.surg.2020.10.035. Epub 2020 Dec 4. PMID: 33288212; PMCID: PMC7717883.
2. Carvalho N, Borges F, Costa B, Costa P. A etiologia da apendicite aguda. Será a alergia o elo perdido? Uma revisão narrativa. The aetiology of acute appendicitis. Is allergy the missing link? A narrative review. Revista Portuguesa de Cirurgia, [S.l.], n. 52, p. 1-10, mar. 2022. ISSN 2183-1165
3. Watson Ng WS, Hampartzoumian T, Lloyd AR, Grimm MC. A murine model of appendicitis and the impact of inflammation on appendiceal lymphocyte constituents. Clin Exp Immunol. 2007 Oct; 150(1):169-78. doi: 10.1111/j.1365-2249.2007.03463.x. Epub 2007 Aug 3. PMID: 17680826; PMCID: PMC2219294.
4. Van den Boom AL, de Wijkerslooth EML, Mauff KAL, Dawson I, van Rossem CC, Toorenvliet BR, Wijnhoven BPL. Interobserver variability in the classification of appendicitis during laparoscopy. Br J Surg. 2018 Jul; 105(8):1014-1019. doi: 10.1002/bjs.10837. Epub 2018 Apr 16. PMID: 29663311; PMCID: PMC6033013.
5. Andreu-Ballester JC, Pérez-Griera J, Ballester F, Colomer-Rubio E, Ortiz-Tarín I, Peñarroja Otero C. Secretory immunoglobulin A (sIgA) deficiency in serum of patients with GALTectomy (appendectomy and tonsillectomy). Clin Immunol. 2007 Jun;123(3):289-97. doi: 10.1016/j.clim.2007.02.004. Epub 2007 Apr 20. PMID: 17449327
6. Abu-Raya B, Michalski C, Sadarangani M, Lavoie PM. Maternal Immunological Adaptation During Normal Pregnancy. Front Immunol. 2020 Oct 7;11:575197. doi: 10.3389/fimmu.2020.575197. PMID: 33133091; PMCID: PMC7579415.
7. Rolf Pieper, Lars Kager, Per Nasman, Lamps LW. Beyond acute inflammation a review of appendicitis and infections of the appendix. Diagnostic Histopathology 14:2, 2008.
8. Cooley Butler, Surgical Pathology of Acute Appendicitis. Human Pathology – Vol 12, Nº 10 October 1981. 870-878
9. Rubér M, Berg A, Ekerfelt C, Olaison G, Andersson RE. Different cytokine profiles in patients with a history of gangrenous or phlegmonous appendicitis. Clin Exp Immunol. 2006 Jan;143(1):117-24. doi: 10.1111/j.1365-2249.2005.02957.x. PMID: 16367942; PMCID: PMC1809572.
10. Rubér M, Andersson M, Petersson BF, Olaison G, Andersson RE, Ekerfelt C. Systemic Th17-like cytokine pattern in gangrenous appendicitis but not in phlegmonous appendicitis. Surgery. 2010 Mar;147(3):366-72. doi: 10.1016/j.surg.2009.09.039. Epub 2009 Nov 5. PMID: 19892382.
11. Guo X, Meng G, Liu F, Zhang Q, Liu L, Wu H, Du H, Shi H, Xia Y, Liu X, Li C, Bao X, Su Q, Gu Y, Fang L, Yu F, Yang H, Yu B, Sun S, Wang X, Zhou M, Jia Q, Chen X, Huang G, Song K, Niu K. Serum levels of immunoglobulins in an adult population and their relationship with type 2 diabetes. Diabetes Res Clin Pract. 2016 May; 115:76-82. doi: 10.1016/j.diabres.2016.03.007. Epub 2016 Mar 12. PMID: 27242126.
12. Salminen P. Acute Appendicitis Incidence-Predisposing Factors, From Microbiota to Socioeconomic Status? JAMA Surg. 2020 Apr 1;155(4):338-339. doi: 10.1001/jamasurg.2019.6031. PMID: 32129802.
13. Bhangu A, Søreide K, Di Saverio S, Assarsson JH, Drake FT. Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. Lancet. 2015 Sep 26; 386(10000):1278-1287. doi: 10.1016/S0140-6736(15)00275-5. Erratum in: Lancet. 2017 Oct 14; 390(10104):1736. PMID: 26460662
14. Carvalho N, Barros A, Coelho HO, Moita CF, Neves-Costa A, Pedroso D, Borges FC, Moita LF, Costa PM. A Th2 Cytokine Profile in Appendicular Lavage Fluid Suggests Allergy as a Possible Etiology for Acute Appendicitis. Mediators Inflamm. 2019 Oct 28; 2019:8146257. doi: 10.1155/2019/8146257. PMID: 31772507; PMCID: PMC6854935.
15. Landry ML. Immunoglobulin M for Acute Infection: True or False? Clin Vaccine Immunol. 2016 Jul 5;23(7):540-5. doi: 10.1128/CVI.00211-16. PMID: 27193039; PMCID: PMC4933779.
16. Kumar Y, Lakshmi PVM, Minz RW, Chhabra S, Saikia B (2015) Evaluation of Serum Immunoglobulins IgG, IgA, IgM and Total IgE in Chronic Alcoholics: A Community-based Study. Immunochem Immunopathol 1: 102. doi: 10.4172/2469- 9756.1000102
17. Fuller JM, Keyser JW. Serum immunoglobulins after surgical operation. Clin Chem. 1975 May; 21(6):667-71. PMID: 1122610.
18. Khamis RY, Hughes AD, Caga-Anan M, Chang CL, Boyle JJ, Kojima C, Welsh P, Sattar N, Johns M, Sever P, Mayet J, Haskard DO. High Serum Immunoglobulin G and M Levels Predict Freedom From Adverse Cardiovascular Events in Hypertension: A Nested Case-Control Substudy of the Anglo-Scandinavian Cardiac Outcomes Trial. EBioMedicine. 2016 Jul; 9:372-380. doi: 10.1016/j.ebiom.2016.06.012. Epub 2016 Jun 20. PMID: 27333022; PMCID: PMC4972545.
19. Lamps LW. Infectious Causes of Appendicitis. *Infect Dis Clin North Am*. 2010;24(4):995-1018. doi:10.1016/j.idc.2010.07.012
20. Aspasia Katragkou, Emmanuel Roilides, and Thomas J. Walsh. Role of Immunoglobulin Therapy to Prevent and Treat Infections. Management of Infections in the Immunocompromised Host, 2018. Jun 19: 339-358

21. Latiff AH, Kerr MA. The clinical significance of immunoglobulin A deficiency. Ann Clin Biochem. 2007 Mar;44(Pt 2):131-9. doi: 10.1258/000456307780117993. PMID: 17362578.
22. Woof JM, Kerr MA. The function of immunoglobulin A in immunity. J Pathol. 2006 Jan;208(2):270-82. doi: 10.1002/path.1877. PMID: 16362985
23. Vernersson, M., 2002. The rise and fall of IgE. Acta Universitatis Upsaliensis. *Comprehensive Summaries of Uppsala Dissertations from the Faculty of Science and Technology*. 742. 61 pp. Uppsala. ISBN 91-554-5388-0.
24. Aravindan KP. Eosinophils in acute appendicitis: possible significance. Indian J Pathol Microbiol. 1997 Oct;40(4):491-8. PMID: 9444860.
25. Pate MB, Smith JK, Chi DS, Krishnaswamy G. Regulation and dysregulation of immunoglobulin E: a molecular and clinical perspective. Clin Mol Allergy. 2010 Feb 23;8:3. doi: 10.1186/1476-7961-8-3. PMID: 20178634; PMCID: PMC2837605.
26. Carvalho N, Barros A, Coelho H, Cóias A, Botelho P, Cismasiu B, Moita L, Costa P. Increased IgE Deposition in Appendicular Tissue Specimens Is Compatible with a Type I Hypersensitivity Reaction in Acute Appendicitis. Mediators Inflamm. 2021 Oct 18;2021:4194859. doi: 10.1155/2021/4194859. PMID: 34707461; PMCID: PMC8545569.
27. Camilla Janefjord. Th1, Th2 and Treg associated factors in relation to allergy. Linköping University Medical Dissertations No. 947. ISBN: 91-85497-83-5
28. Dullaers M, De Bruyne R, Ramadani F, Gould HJ, Gevaert P, Lambrecht BN. The who, where, and when of IgE in allergic airway disease. J Allergy Clin Immunol. 2012 Mar;129(3):635-45. doi: 10.1016/j.jaci.2011.10.029. Epub 2011 Dec 9. PMID: 22168998.
29. Salö M, Gudjonsdottir J, Omling E, Hagander L, Stenström P. Association of IgE-Mediated Allergy With Risk of Complicated Appendicitis in a Pediatric Population. JAMA Pediatr. 2018 Oct 1;172(10):943-948. doi: 10.1001/jamapediatrics.2018.1634. PMID: 30083704; PMCID: PMC6233766.
30. Das NM, Thomas S, Aravindan KP. Morphology and serum IgE levels in recurrent acute appendicitis. Int. J. Adv. Res. 2016, 4(10), 855-859. **DOI:** 10.21474/IJAR01/1869
31. Gudjonsdottir J, Roth B, Lovén G, Ohlsson B, Hagander L and Salö M (2022) An Evaluation of Serum IgE and Th2-Associated Interleukins in Children With Uncomplicated and Complicated Appendicitis. Front. Pediatr. 10:884138. doi: 10.3389/fped.2022.884138

***Correspondência:***
NUNO CARVALHO
*e*-mail: nunomdc@sapo.pt

***Data de recepção do artigo:***
20/06/2022

***Data de aceitação do artigo:***
05/11/2022