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## Composition of the cellular infiltrate in patients with simple and complex appendicitis

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### ABSTRACT

**Background:** It is now well established that there are two types of appendicitis: simple (nonperforating) and complex (perforating). This study evaluates differences in the composition of the immune cellular infiltrate in children with simple and complex appendicitis.

**Materials and methods:** A total of 47 consecutive children undergoing appendectomy for acute appendicitis between January 2011 and December 2012 were included. Intraoperative criteria were used to identify patients with either simple or complex appendicitis and were confirmed histopathologically. Immune histochemical techniques were used to identify immune cell markers in the appendiceal specimens. Digital imaging analysis was performed using Image J.

**Results:** In the specimens of patients with complex appendicitis, significantly more myeloperoxidase positive cells (neutrophils) (8.7% versus 1.2%,  $P < 0.001$ ) were detected compared to patients with a simple appendicitis. In contrast, fewer CD8+ T cells (0.4% versus 1.3%,  $P = 0.016$ ), CD20+ cells (2.9% versus 9.0%,  $P = 0.027$ ), and CD21+ cells (0.2% versus 0.6%,  $P = 0.028$ ) were present in tissue from patients with complex compared to simple appendicitis.

**Conclusions:** The increase in proinflammatory innate cells and decrease of adaptive cells in patients with complex appendicitis suggest potential aggravating processes in complex appendicitis. Further research into the underlying mechanisms may identify novel biomarkers to be able to differentiate simple and complex appendicitis.

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## Introduction

Recent studies indicate that acute appendicitis is not an irreversibly progressive disease but that two distinct types of appendicitis can be identified: simple (uncomplicated or nonperforating appendicitis) and complex (complicated or perforating) appendicitis. Simple appendicitis can be treated with antibiotics only, whereas the second requires an appendectomy in most cases.<sup>1,2</sup> Initial nonoperative treatment has been investigated for acute simple appendicitis both in the adult and pediatric population with good results.<sup>3-8</sup> Approximately, in 60%-85% of the adult population and 62%-81% of the pediatric population, an appendectomy was avoided at 1-y follow-up after treatment with antibiotics only.<sup>3-8</sup> Selection of patients in these studies was based on clinical and radiological variables and did not include biochemical markers. Accurate identification of patients with simple or complex appendicitis will prevent unnecessary surgical interventions in patients with simple appendicitis, while making sure patients with complex appendicitis receive the surgical treatment that they require.

To identify biomarkers, which help to distinguish simple and complex appendicitis, it is essential to better understand the individual underlying pathogenesis of both types. These are predisposing factors for appendicitis in general, such as appendicular obstruction, infection, diet, and ischemia.<sup>9</sup> All the previously mentioned factors eventually lead to invasion of the appendiceal wall by intraluminal bacteria and activate innate immune cells such as macrophages, whereas danger signals due to ischemia-induced cell death can further augment immune responses.<sup>9-11</sup> For example, increase of extracellular ATP due to cell death in ischemic tissue is a strong inducer for innate cells such as macrophages and dendritic cells (DCs), which together with Toll like receptors (TLRs) triggering results in interleukin (IL)-1b production.<sup>12,13</sup> T cells activated by DC are subsequently recruited to the site of inflammation and can further contribute to inflammation or by means of T regulatory cells decrease inflammation. However, it is unknown why in one person this inflammation is impeded while in others leads to complex appendicitis.

Studies focusing on the composition of the cellular infiltrate in patients with appendicitis are scarce.<sup>14,15</sup> It has been noted that in all patients with appendicitis, there is an influx of neutrophils in the lamina propria.<sup>14</sup> Only one study compared the composition of the cellular infiltrate in patients with perforated appendicitis and nonperforated appendicitis and detected increased numbers of cluster of differentiation (CD)-8+ T cells in the specimens of the appendix of patients with perforated appendicitis.<sup>15</sup> Subsequent studies mainly focused on the systemic immune response and investigated the cytokine profiles in blood samples showing elevated levels of IL-6, IL-17, and interferon  $\alpha$  (INF- $\alpha$ ) in patients with complex appendicitis compared to simple appendicitis.<sup>16,17</sup>

The aim of this study is to evaluate differences in the composition of the infiltrate of mononuclear immune cells in the appendix between patients with simple and complex appendicitis. The results will help identify critical cell types distinguishing between these phenotypes and can be used to design further studies to identify new biomarkers.

## Materials and methods

### Study population

All children aged 0-17 y who underwent an appendectomy for suspected acute appendicitis in the Academic Medical Center, Amsterdam between January 2011 and December 2012 were included. Patients with a noninflamed appendix, a parasitic infection, those who underwent an appendectomy as a routine procedure (for instance in case of malrotation), or as an interval appendectomy after initial nonoperative treatment of appendicitis were excluded. The medical charts from the included patients were reviewed, and the specimens from the original histopathological examination of the appendix were collected, and additional staining procedures, as described in the following, were performed. Patients without histopathological specimens, missing data, or those unsuitable for staining were also excluded. Study approval was obtained from the medical ethics review board before the start of this study.

Patients were allocated into either the simple or complex appendicitis group according to the following definitions for simple and complex appendicitis.<sup>18,19</sup>

Simple appendicitis is diagnosed on the basis of (1) intraoperative findings: inflamed appendix without signs of gangrene, perforation, purulent fluid, contained phlegmone, or intra-abdominal abscess and (2) histopathological examination confirming the diagnosis of appendicitis without necrosis or perforation. Complex appendicitis is diagnosed on the basis of (1) intraoperative findings: signs of a gangrenous appendix with or without perforation, intra-abdominal abscess, appendicular contained phlegmone, or purulent free fluid and (2) histopathology confirming the diagnosis based on extensive necrotic tissue in the muscular layer of the appendix or signs of perforation. In case of discrepancies between clinical and pathological findings, discussion was held by the pathologist (J.R.) and one member of the surgical team (R.G.). In case of disagreement, a third reviewer was approached.

### Medical chart review

A standardized data extraction form was used to review the medical charts ([Appendix 1](#)).

### Staining and scanning

The original specimens of appendices were handled using a standardized protocol developed by the Department of Pathology, Academic Medical Center of Amsterdam. The hematoxylin and eosin-stained sections and tissue blocks were retrieved from the archive and re-evaluated to identify the most severely affected appendiceal segment based on microscopic examination by three of the authors (E.W., R.G., and J.R.), which was then selected for additional staining. Based on the literature, we decided to use the immune histochemical stains with antibodies specific for immune cells from the innate and adaptive immune response, and these are listed in [Table 1](#).

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