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Letter to the Editor

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Response to "The importance of an early gastroenteritis diagnosis to discard MIS-C during SARS-CoV-2 pandemic"

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Sir,

We read the interesting paper by Fernández-Miaja et al. where they report four cases of *Campylobacter jejuni* infection in patients with an initial diagnostic suspicion of multiinflammatory syndrome in children (MIS-C) and highlight the importance of ruling out other potential diagnosis in order to avoid unnecessary diagnostic tests and treatment [1]. Interestingly, two of their cases showed marked lymphopenia (<1000/mm^3), one of them with associated elevated C-reactive protein values. American College of Rheumatology guidelines recommend a complete diagnostic evaluation to rule out MIS-C in children with unremitting fever, suggestive clinical features, elevated acute phase reactants and at least one among several laboratory features, including an absolute lymphocyte count below 1000/mm^3 in the absence of other causes that could explain the clinical picture [2]. One study in search of red flags that might help discriminate between MIS-C and other common febrile conditions in children, found that absolute lymphopenia and an elevated C-reactive protein serum concentration were associated with a higher risk of MIS-C [3].

Does *Campylobacter* infection alone explain the association of fever, elevated C-reactive protein values and absolute lymphopenia? Can a child with these findings be safely sent home if a *Campylobacter* PCR test is positive or might a short period of observation in the hospital still be advisable?

We reviewed the clinical files of 110 children younger than 14 years of age with a diagnosis of *Campylobacter* infection seen in our hospital from January 1st2017 to June 1st2022 and compared the frequency of cases showing both elevated C-reactive protein and lymphopenia before (up to January 2020) and after the start of SARS-CoV-2 pandemia (from January 2020 onwards).

Results are shown in Table 1. As expected, more cases of *Campylobacter* infection were diagnosed in the first period while more laboratory studies were performed in the second period (47.2% vs 14.9%), probably as a reflection of the fear of missing a possible diagnosis of MIS-C in the pandemic era. No cases showing both elevated C-reactive protein and profound lymphopenia were observed among the 74 children seen in the prepandemic period, while four (11.1% of the total cases and 30.6% of those in whom laboratory tests were performed) were found in the pandemic era. Evidence of SARS-CoV-2 exposure in the previous weeks was confirmed in three of these cases and infection was documented in one child, who was initially diagnosed as possible MIS-C and treated with intravenous gammaglobulin and corticosteroids for one day; treatment was suspended when the diagnosis of *Campylobacter* infection was confirmed. Clinical characteristics and laboratory findings of these four patients are shown in table 2.

Our results raise the question of whether *Campylobacter* infection alone can be accountable for these laboratory findings and if a positive stool test can safely rule out a diagnosis of MIS-C or a short observation period in the hospital would be prudent, as children with MIS-C may develop additional organ system involvement over the course of admission [4]. Lymphopenia has been previously described in up to 11% of patients with *Campylobacter* infection returning from the tropics,

Table 1 **Comparison between the two periods.**

Time interval	*Campylobacter* infection cases	Positive study*	Negative study	No studies performed
2017-2019	74	0	11	63
2020-2022	36	4	13	19

*Positive study: C-reactive protein >30 mg/L AND absolute lymphocye count <1000/mm^3

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Table 2 **Patient characteristics and laboratory findings of the four patients with fever, lymphopenia and elevated acute phase reactants associated with *Campylobacter* infection.**

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
Demographic				
Sex	Female	Female	Male	Female
Patient age (years)	8	9	12	11
SARS-CoV-2				
Exposure	No	Yes (1 month earlier)	Yes (3 weeks earlier)	Yes (3 months earlier)
Infection	No	No	Yes (2 weeks earlier)	No
Presenting symptoms				
Days of fever at presentation	2	1	1	3
Abdominal pain	Yes	Yes	Yes	Yes
Vomiting	Yes	Yes	No	No
Diarrhea	Yes	No	Yes	Yes
Generalized myalgia	No	No	Yes	Yes
Laboratory values				
WBC/ml	6360	7780	11800	8960
Neutrophils/ml	5400	5930	9959	7350
Lymphocytes/ml	680	920	800	970
Hemoglobin (g/dl)	13,5	13,4	13,2	12,6
Platelets/ml	281000	108000	191000	228000
C-Reactive Protein (mg/L)	97	208	116	36
Procalcitonin (ng/ml)	ND	1,27	1,24	ND
SARS-CoV-2 RT PCR	Negative	Negative	Negative	Negative
Stool culture	*Campylobacter jejuni*	*Campbylobacter jejuni*	*Campylobacter jejuni and Yersinia enterocolitica*	*Campylobacter jejuni*
Disposal and Treatment				
Disposal	Admission (Surgery)	Admission Pediatric Intensive Care Unit	Admission Pediatric Ward	Discharged Home
Treatment	Appendicectomy Azithromycin	Azithromycin	Corticosteroids and intravenous gammaglobulin (1 day); azithromycin	None

RT-PCR: Reverse transcription polymerase chain reaction. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2. WBC: White blood cells.

but higher cut-off points to define lymphopenia were used in that study [5]. In a previous series of five cases of bacterial enteritis (4 *Salmonella* species, one *Campylobacter* species) mimicking MIS-C [4], although four patients had mild lymphopenia, none had an absolute count less than 1000 lymphocytes/mm^3.

Our study has several limitations, including the small number of cases, its retrospective nature, the low frequency of laboratory tests in the prepandemic period, the lack of data on SARS-CoV-2 infection in most of our patients, and the lack of serologic studies regarding their SARS-CoV-2 status, and larger prospective studies may shed light upon this subject.

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CONFLICT OF INTEREST

Authors declare have no conflict of interest

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