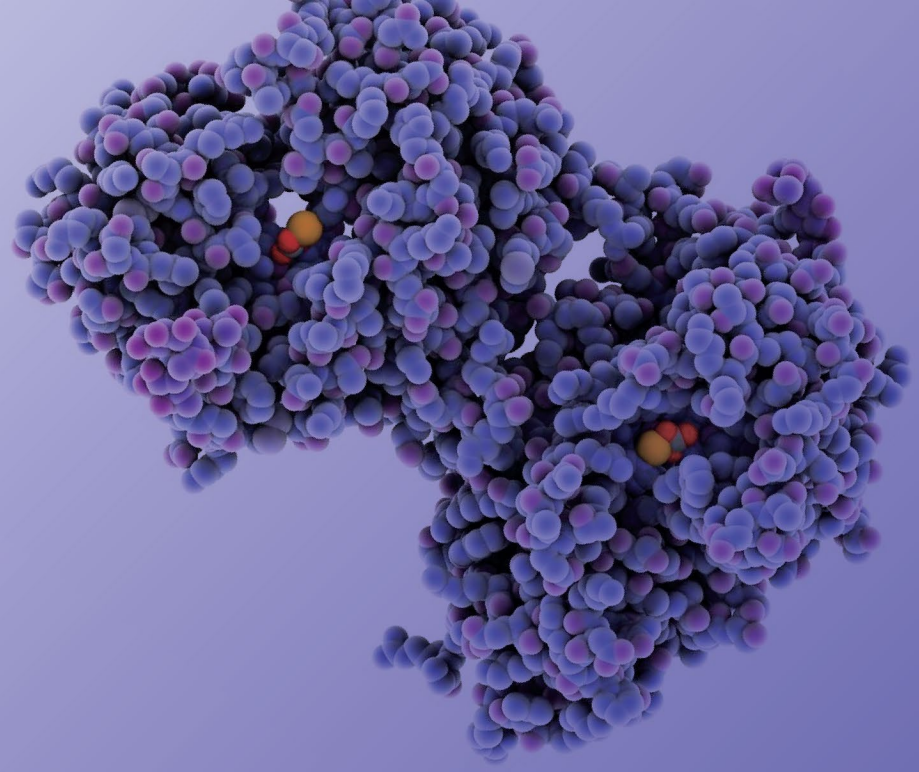


Is there a role for lactoferrin in the prevention or treatment management of COVID-19 in infants?

Epidemiological and Clinical Characteristics of COVID-19 Pediatric Cases in Italy: the ITALIAN PEDIATRIC REGISTRY of COVID-19 (n=168)

Characteristic	Value
Age	
Median age, years (IQR)	2.3 (0.3–9.6)
Age groups	**n (%)**
< 1 yr	66 (39.3)
1–5 yrs	38 (22.6)
6–10 yrs	24 (14.3)
11–17 yrs	40 (23.8)
Gender	**n (%)**
Males	94 (55.9)
Females	74 (44.1)
Signs and symptoms	**n (%)**
Fever	138 (82.1)
Cough	82 (48.8)
Rhinitis	45 (26.8)
Diarrhea	**22 (13.1)**

Characteristic	Value
Signs and symptoms *(continued)*	**n (%)**
Dyspnea	16 (9,5)
Pharyngitis	9 (5,4)
Vomiting	**9 (5.4)**
Conjunctivitis	6 (3.6)
Chest pain	4 (2.4)
Fatigue	3 (1.8)
Non-febrile seizures	3 (1.8)
Febrile seizures	2 (1.2)
Hospital admission	**110 (65.1)**
Age groups	**n (%)**
< 1 yr	52 (47.3)
1–5 yrs	24 (21.8)
6–10 yrs	13 (11.8)
11–17 yrs	21 (19.1)

EURO SURVEILLANCE 2020
Italian Pediatric Registry, the Italian SITIP-SIP SARS-Cov-2 pediatric infection study group (reported as of April 11, 2020) (Badolato R., Meini A., Plebani A. (Brescia), Garazzino S., Denina M. (Torino), Venturini E., Montagnani C., Galli L. (Firenze), Giaquinto C., Donà D. (Padova), Pierantoni L., Lanari M. (Bologna), Manno EC, Santilli V., Lancella L., Cursi L., Bernardi S., Campana A., Bozzola E., Krzysztofiak A., Villani A. (Roma), Felici E. (Alessandria), Vergine G. (Rimini), Giacchero R. (Lodi), Lo Vecchio A., Pecoraro C (Napoli), Rabbone I. (Novara), Marchisio P., Bosis S. (Milano), Nicolini G. (Belluno), Banderali G. (Milano S. Paolo), Abbagnato L. (Como), Nicastro E., Ghitti C., Lippi P. (Bergamo), Salvini F. (Milano Niguarda), Del Barba P. (Milano S. Raffaele), Agostiniani R. Pistoia), Cherubini S. (Busto Arsizio), Gianino P. (Asti), Vaccaro A. (Lucca), Manzoni P (Biella), Verna P. (Casale), Comberiati P. (Pisa), Di Filippo P (Pescara), Gallia (Milano PLS), Battezzati G. (S. Croce), Fiore L (Moncalieri), Tappi E. (Cuneo), Valentini P. (Roma) Esposito S., Dodi I. (Parma), Lazzerini M. (Trieste), Zuccotti GV (Milano), Castagnola E. (Genova), Corsello G. (Palermo), Cardinale F. (Bari), Tocco AM (Pescara), Ballardini G. (Verbania), Zavarise G. (Verona).

COVID-19 Frequently Involves the Gastrointestinal Tract in Children

Background:

- Most respiratory viruses (such as Entero, Adeno, Echo, etc) usually involve the gastrointestinal tract, with a variety of digestive symptoms.
- Angiotensin converting enzyme-2 (ACE-2) receptor and transmembrane serine protease 2 (TMPRSS2), which facilitates viral entry into the tissue, are co-expressed in the small intestinal epithelia of the gastrointestinal tract, not only in the respiratory mucosa. Moreover, ACE2 is expressed in the upper esophagus, liver, and colon.

Major facts:

- Combined evidence from USA, China, and Italy show that **gastrointestinal symptoms occur in 15% to 29% of COVID-19–positive children** admitted to the hospital
- Most of them develop **diarrhea and vomiting**
- Elevated transaminases are common
- Several reports indicate **viral RNA shedding in stool** detectable longer time period than in nasopharyngeal swabs; prolonged RT PCR positivity in the stool has raised the possibility of **oro-fecal transmission**

Possible Presentation of COVID-19 as Severe Gastrointestinal Disorders Ultimately Leading to Acute Ischemic Gastrointestinal Disease

Uncommon presentation in a 7-year-old child with no underlying comorbidities, hospitalized for persistent diarrhea and increasingly severe abdominal pain, but no history of cough or fever

- A complete workup was performed, including nasopharyngeal swab that disclosed positivity for COVID-19.
- Chest X-rays showed typical viral pneumonia patterns.
- She was referred to surgery and underwent exploratory laparoscopy revealing phlegmonous appendicitis with Peritonitis.
- No pathogens grew from any cultures.
- The child was treated empirically and recovered well.
- She became negative to COVID-19 after 17 days.
- Vomiting, diarrhea, and gastrointestinal symptoms are frequently described in Italian COVID-19 patients, including children.

Manzoni P, et al. *Pediatr Infect Dis J.* 2020

Possible Role(s) of Lactoferrin in Contrasting COVID-19: Nonspecific, Symptomatic Activities vs Specific, Anti SARS-CoV Actions

DOI: 10.1111/apa.15417

BRIEF REPORT

ACTA PÆDIATRICA
NURTURING THE CHILD
WILEY

Lactoferrin is an important factor when breastfeeding and COVID-19 are considered

International Journal of
Molecular Sciences

MDPI

Review

Lactoferrin as Protective Natural Barrier of Respiratory and Intestinal Mucosa against Coronavirus Infection and Inflammation

Elena Campione [1,*], Terenzio Cosio [1], Luigi Rosa [2], Caterina Lanna [1], Stefano Di Girolamo [3], Roberta Gaziano [4], Piera Valenti [2,†] and Luca Bianchi [1,†]

Peroni DG, et al. *Acta Paediatr.* 2020;10.1111/apa.15417; Campione E, et al. *Int J Mol Sci.* 2020;21:4903.

Possible Role(s) of Lactoferrin in Contrasting COVID-19 (1)

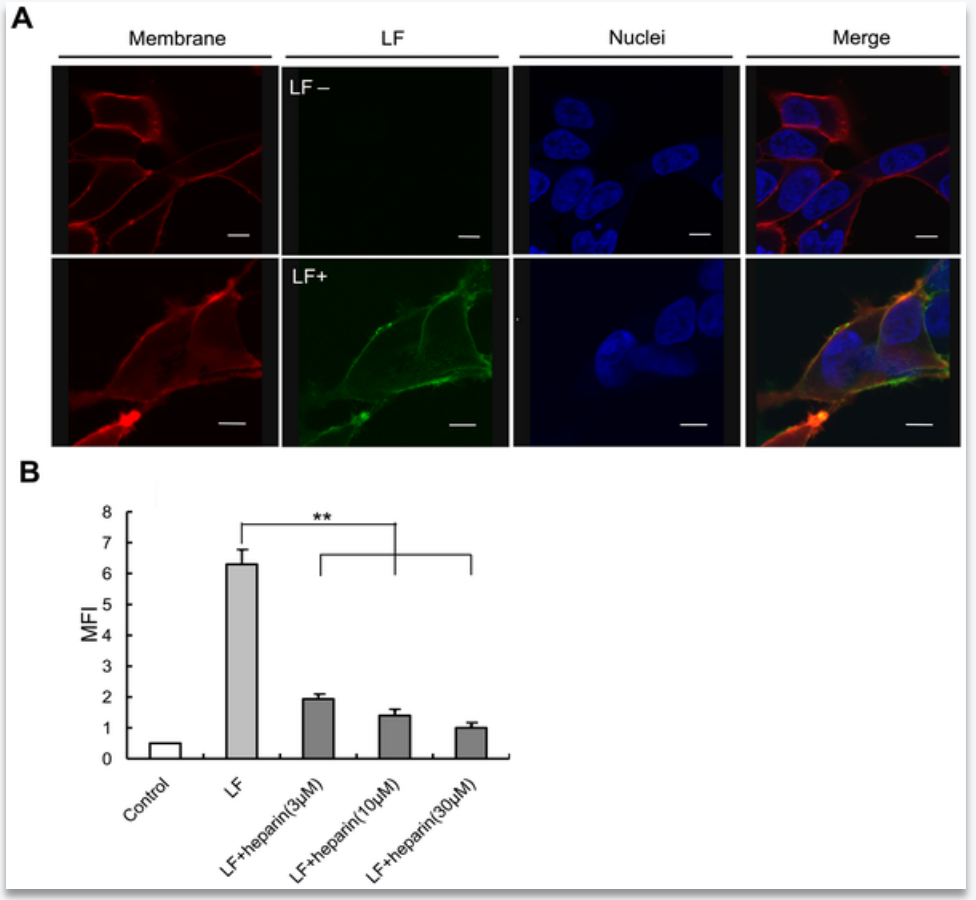
1. **NOT SPECIFIC—**During viral infections, LF is hyper-expressed (greater than 150-fold) in patients with proven viral infection compared with controls
2. **NOT SPECIFIC—**LF has antiviral activity against several naked and enveloped viruses of more than 30 families, mainly by preventing viral entry through binding the Heparan Sulfate sites
3. **NOT SPECIFIC—**LF has known and strong anti-inflammatory activities, reducing the ROS, modulation of the IL cascade, ultimately being putatively efficacious on reducing the burden of the COVID-19-associated «inflammatory storm»
4. **NOT SPECIFIC—**LF has iron-chelating activities, thus reducing inflammation during infection
5. **NOT SPECIFIC—**SARS-CoV-2 can invade enterocytes, causing symptoms and acting as a reservoir. Gastrointestinal symptoms can be the first clinical manifestation in infants. Lactoferrin has strong trophic actions on the gut, and can promote a local gut environment, namely favorable gut microbiota plus tight junctions, that reinforces the innate defenses of neonates, providing direct anti-inflammatory and immunomodulatory actions at intestinal level

Campione T, et al. *Int J Mol Sci.* 2020; Reghunathan R, et al. *Immunol BMC.* 2005;6:2; Raghuveer TS, et al. *Pediatr Res.* 2002.

Possible Role(s) of LACTOFERRIN in Contrasting COVID-19 (2)

SPECIFIC – Lactoferrin *in vitro* localizes to the cell membrane by targeting and inhibiting Heparan Sulfate Proteoglycans (HSPGs), a cell-entry protein that is critical for cell entry by the SARS pseudovirus as the first, low-affinity anchoring site.

- After anchoring, the viruses accumulate on the cell surface and recognise more virus-specific receptors. These include the angiotensin-converting enzyme 2 (ACE2) receptor, a metallopeptidase that has high affinity for the virus, can hook the virus terminals and facilitate entry into the cell.
- These mechanisms were seen in the 2002 SARS-CoV epidemic and are almost the same for SARS-CoV-2.
- Lactoferrin is able to block the interaction between spike viral protein and HSPGs in an ACE2-independent fashion.



Lang J, et al. *PLOS One.* 2011;6(8): e23710.
Peroni D, et al. *Acta Paed.* 2020;10.1111/apa.15417.