



COVID-19 in Infants and Children: Lessons From Italy

Overview

The COVID-19 pandemic is an unprecedented challenge for all health care systems worldwide. The experience of NICU and pediatric clinicians in Italy, one of the countries hardest hit by the pandemic, can provide valuable insight for hospitals and clinicians.

Paolo Manzoni, MD, PhD, shares his perspectives and research for COVID-19 in infants and children, comparing latest data and studies in China, Italy, and the United States. For newborns, data show there is no vertical transmission to date. Neonates, however, can experience mild-to-moderate forms of the disease. Dr. Manzoni further discusses the peculiar presentations in children, including gastrointestinal and peripheral vasculitis. While current data suggest children may be less severely affected and may experience different symptoms than adults, it is vital to understand the epidemiological and clinical characteristics of COVID-19 pediatric cases, because less seriously ill and asymptomatic children may be carriers of the virus.

Target Audience

This activity was developed for neonatologists, nurses, nurse practitioners, dietitians, hospital pharmacists, and other health care providers who have an interest in newborns, infants and toddlers.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Recognize symptoms of COVID-19 in pediatric and neonatal patients
- Review practical approaches for perinatal care, as well as delivery room and NICU procedures suggested during the COVID-19 pandemic.

Faculty

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Paolo Manzoni, MD, PhD

Speakers Bureau Sodilac—clinical area:
Lactoferrin use in infants

Mead Johnson Nutrition—clinical area: infant nutrition

The faculty for this activity has disclosed that there will be discussion about the use of products for non-FDA approved applications.

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This educational material was developed with the best available evidence when recorded on April 24, 2020 and includes some first-hand anecdotal observations. Recommendations may be subject to change as knowledge concerning neonatal, infants and children SARS-CoV-2 infection cases evolves.

This activity is supported by an independent educational grant from **Mead Johnson Nutrition**.

This activity is an online enduring material. It has been edited to meet requirements for online learning. Successful completion is achieved by reading and/or viewing the materials, reflecting on its implications in

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your practice, and completing the assessment component.

The estimated time to complete the activity is 1.0 hour.

This activity was released on May 07, 2020 and is eligible for credit through May 07, 2022.

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Editor's Note: This is a transcript of an audio webcast presented on April 24, 2020. It has been edited and condensed for clarity.

MODULE 1



Paolo Manzoni, MD, PhD: A very warm welcome to all of you for being here today. It is a pleasure for me to guide you through today's update on this dramatic epidemic. In Italy we have been, and we are currently severely affected, as you know. So, unfortunately, we have a lot of experience recognizing the disorder and trying to understand this very severe disease.

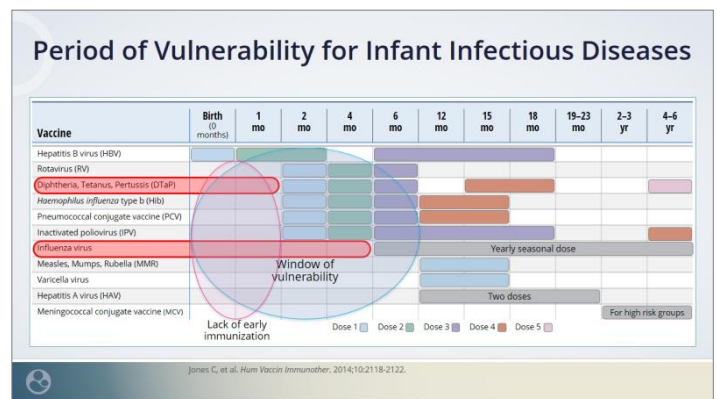
The flow of the talk today will be based on 3 modules that we'll review together. In the first module, I will update you on neonatal immunity in the first months of life, because this is by far the most important period for neonatologists and pediatricians.

In the second module, I will review what COVID-19, so far, [looks like] in children, infants, and neonates, while also describing what COVID-19 looks like in adults, in order to get inspired and better understand the burden of the disease.

In the final module, I will discuss pregnancy delivery and the NICU organization in the COVID-19 era in order to prompt you to the best possible practices during this moment.

Let's take a look at what is neonatal immunity. The first slide [Slide 1] very clearly shows you that in the flow of the ages of every child, the first months are really critical to get a good defense against acquired infections.¹ Both because in the first couple of

months, there's a lack of immunizations, and also because the opportunity to be able to defend, thanks to the vaccines, is not yet realized until the first 5 or 6 months of life.



Slide 1 – Period of Vulnerability for Infant Infectious Diseases

As a matter of fact, we have at least the first 3 months in which the child is not yet immunocompetent and needs to be defended with maternal antibodies, passed either through placenta—in a natural way, if the mother is already immunocompetent for that disease—or, thanks to a boost due to a maternal vaccination during pregnancy.

Also, it is very important what the baby receives through breastfeeding. Only very limited situations allow us to provide passive immunization. Let's think about hepatitis B, as an example, or let's think about palivizumab for respiratory syncytial virus (RSV), but only in very selective premature infants.

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In the following 3 months, and roughly up to 6 months, the child is getting step by step, a little more immunocompetent—but nonetheless it is still necessary to acquire defense—thanks to the antibodies acquired through breastfeeding, because the initial response to vaccines is, of course, still initial, and not yet full.

Neonates and Infants Immunity

Period of life	Is the child immune competent?	How can he/she be defended? (1)	How can he/she be defended? (2)
0-3 months	No	Maternal antibodies passed through placenta (natural + boosted by maternal vaccine in pregnancy)	Breastfeeding + passive immunization
3-6 months	No/Yes	Breastfeeding	Initial response to vaccines
6-24 months	Yes	Complete response to vaccines	Breastfeeding + infection experience
24 months—late childhood	Yes	Vaccine-derived immunity	Infection experience

Slide 2 – Neonates and Infants Immunity

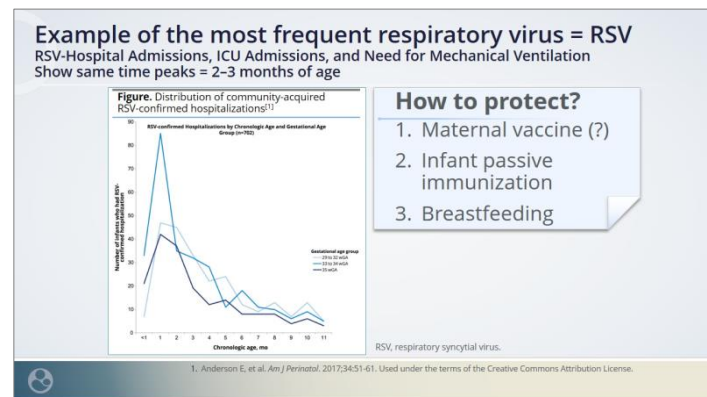
After 6 months, we presume the babies are developing full immunocompetency, or at the very least, they are competent in that they have already completed the first courses of vaccination. Again, breastfeeding remains a mainstay to deliver additional protection also in the second semester of life.

Infection Experiences

The baby, going to day care or simply living in society and no longer cocooned with the mother, little by little acquires infections, develops an infection experience. Together with immunity derived by vaccinations, this ultimately makes the child immunocompetent when he's in his second year of life.

With this in mind, it is clear that in the first 2–3 months, we are at the peak of our troubles, as pediatricians and neonatologists, facing infection disorders in children. This is a clear example of covering for RSV, the number 1 virus in the first month of life. RSV always produces the peak of

hospitalization, and the highest severity around 2–3 months of age in infants.²



Slide 3 – Example of the most frequent respiratory virus = RSV

Just because in these moments, the troubles are at their peak, and the protection of the infant—as we were reviewing earlier—can be provided by the same immunization of palivizumab, but only in limited situations, but basically by breastfeeding, and relying on antibodies provided by the mother, if the mother is able to pass through the placenta those kinds of antibodies. The first 3, 4, months of life are critical, and in this view, we see that COVID-19 makes no exception to that.

The neonate and young infant are protected only through antibodies from the mother. And we need to make sure the baby is getting, either way, those antibodies, either through the placenta during the pregnancy, or through the placenta thanks to a maternal booster provided by a vaccine, or through the transfer from fresh breast milk. I underline fresh breast milk, because donor pasteurized, or stored, or refrigerated breast milk has a decrease in the amount of viable antibodies.

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Importance of Maternal Transfer of Antibodies to the Fetus

- The first 3–4 months are the MOST CRITICAL
- The neonate and young infant are protected ONLY through ANTIBODIES FROM THE MOTHER:
 1. Transfer through placenta during pregnancy from immune mothers
 2. Transfer through placenta during pregnancy after boosting with a maternal vaccine
 3. Transfer through fresh breast milk

Serum concentrations of specific anti-RSV antibodies in the newborn: A serum concentration of specific antibodies 2 to 4 times lower in infants who have RSV disease is observed, compared with those who do not get sick from RSV

RSV Antibody Titer		Assay Method	Article
No RSV disease	RSV disease		
652.6	198.1	Membrane Fluorescent Antibody Test	Ogilvie. Maternal Ab & RSV. <i>J Med Virol.</i> 1981;7:263-71.
92	9.5	Neutralizing Ab	Glezen. <i>J Pediatr.</i> 1981;98:708-15.
40.00	11.08	MFAT	Roca. IgG Mozambique. <i>J Med Virol.</i> 2002;67:616.
44.16	11.37	Neutralizing Ab	
238.9	68.6	Neutralizing Ab	Piedra. Correlates of immunity. <i>Vaccine.</i> 2003;21:3479.
538.0	392.1	Neutralizing Ab	Eick. Native American Infants. <i>Pediatr Infect Dis J.</i> 2008 27:207.
1047	646	ELISA	Ochola. Infants in Kenya. <i>PLOS One.</i> 2009;4:e8088.

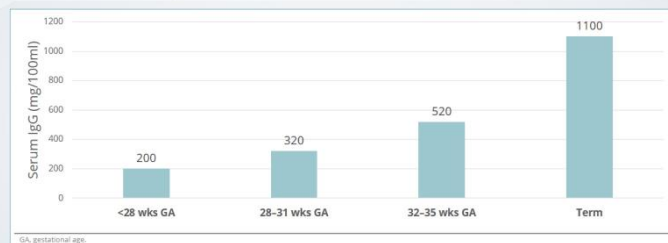
Slide 4 – Importance of Maternal Transfer of Antibodies to the Fetus

Let's skip now to this very important finding. When [a baby] is premature, a decrease in the transfer of antibodies is clearly understandable. The optimal transfer occurs at term, so only term infants complete the transfer of antibodies from the mother to the offspring. But take a look at how wide the gap is between 35 weeks and a term infant³ [Slide 5].

Slide 6

The number of antibodies makes a big difference, and it's making a big difference to the fact that after a few weeks those antibodies terminate, and their action, and their viability ends. It has been calculated in a precise way that antibodies transferred from the mother may have a life of 17 weeks, so they are able to protect the infant for the first 3 or 4 months. Probably a little less if those antibodies are transferred after maternal vaccination during pregnancy. But, as a matter of fact, these data explain very well, why in the first 3–4 months of life, babies need to get protection in this way.^{4,5}

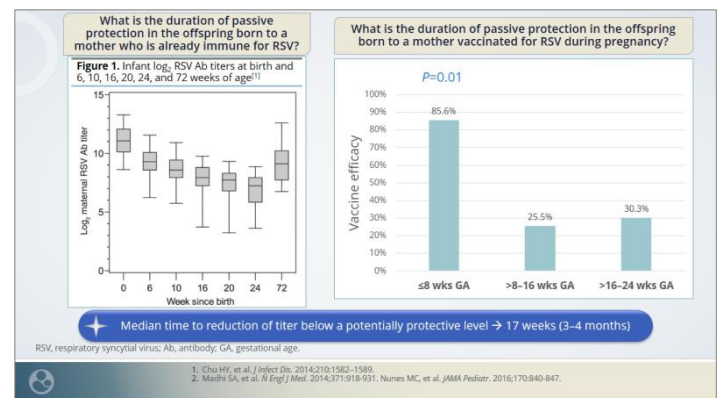
Prematurity Interrupts Optimal Transfer of Maternal IgG



Adapted from data and formulas as published by Yeung CY, Hobbs JR, Lencort. 1968;7553:1167-70.

Slide 5 – Prematurity Interrupts Optimal Transfer of Maternal IgG

There is a 60%–70% decrease in the amount of antibodies delivered, and this makes a big difference. There is no surprise when we review cases of infants having acquired RSV disease in the first months of life compared with those who were protected from RSV disease, we always see that those with RSV disease show levels of maternal antibodies 2- or 3-fold lower than those who were ultimately protected.



Slide 7

In summary, from this first module we know very well maternal antibodies are critical. We know very well that prematurity effects heavily the optimal design of the transfer of antibodies through the placenta. We know very well that the more

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antibodies you receive, the more protected you get, and we know very well that the duration of protection can be calculated, and it is not longer than 17 weeks, according to the evidence.

In Summary...

- The first 3–4 months are the most critical.
- Maternal antibodies → need to be fully provided through a TERM delivery!
- Duration of protection can be precisely calculated → 17 weeks.
- The more antibodies received, the more you are protected.
- Infants who get infected have fewer maternal antibodies.
- Maternal vaccination in pregnancy might be a good option for some preventable diseases that may be very severe in the first weeks of life (eg, pertussis, influenza, RSV, etc).
- Breastfeeding is currently the best possible option after birth.

Slide 8 – Module 1 Summary

We also know maternal vaccination in pregnancy could be a good option for some preventable diseases that may be very severe in the first weeks of life, when the transfer of antibodies through a natural course of pregnancy may not be able to fully prevent the disease we are trying to target.

And the final consideration, which is a usual refrain for all pediatricians and neonatologist, that **breastfeeding is currently the best possible option after birth to protect your baby.**

MODULE 2

Let's go to the second module where I will review the story of COVID-19 in children, infants, and neonates, and what we are learning daily in Italy from this devastating epidemic.

First, I think all of you know that COVID-19 may produce severe symptoms, including fatalities, or may result in mild or even asymptomatic disease. The ACE2 cellular receptor is emerging as critical, because this virus adheres to this receptor to enter the cell. Kids may have less severe disease because, in the case series reported so far, only 1% to 2% of the patients described are actually less than 18 years old. Even more, when you think of the case

fatality rate, because it's almost anecdotal in children so far, luckily. Whereas, in adults, the mortality rate spans between 2% and 8%, or even 10%, 12%, in some Italian regions.

What about COVID-19 Infections? Risk Factors and Severity

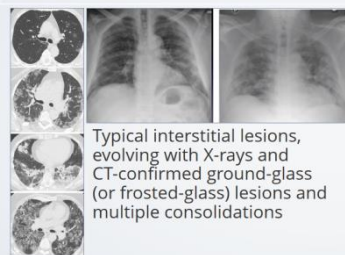
- People with COVID-19 can have no symptoms or develop mild, severe, or fatal illness
- The ACE2 cellular receptor is critical, since COVID-19 adheres to enter the cell
- Kids may have less severe disease (only 2% of confirmed cases in China occurred among those <20 yrs; in Italy, so far only 1.6% are <19 yrs)
- Current case fatality rate in COVID-19 adults 2%–8%, <1% in children
- Risk factors for severe illness may include:
 - Older age
 - Underlying chronic medical condition(s)
 - Obesity

Slide 9 – What about COVID-19 Infections? Risk Factors and Severity

COVID-19 Pneumonia

Risk factors for severe illness include older age, underlying chronic medical conditions, and comorbidities and obesity. Pneumonia is the most well-known disorder produced by this virus, and historically has been the first feature detected when these epidemics spread. Pneumonia by COVID-19 is characterized, as you all know, by typical interstitial lesions, evolving with CT-confirmed ground-glass lesions and multiple consolidations. Its diagnosis relies, as of today, only on PCR on nasopharyngeal swab.

COVID-19 Pneumonia



RT-PCR, reverse transcription polymerase chain reaction.



Diagnosis through COVID-19 RT-PCR on nasopharyngeal swab

Slide 10 – COVID-19 Pneumonia

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What is the burden in children? Is it a problem in children? Let's look at children first. The children—and with children, I mean babies older than 1 month and younger than 18 years—have actually limited burden and a limited severity, as we were alluding to earlier on.

Is COVID-19 also a problem in children, infants, neonates, and/or pregnant mothers?

CHILDREN

Limited Burden, Limited Severity

- In China, a review of 72,314 cases by the Chinese Center for Disease Control and Prevention showed that <1% of the cases were in children <10 years of age
- In the same report, no ICU cases occurred in children
- In Korea, only 0.7% of cases occurred in children <9 yrs
- In Italy, only 1.2% of COVID cases occurred in children <18 yrs
- The course of infection is generally mild to moderate
- No confirmed deaths attributed to COVID-19 so far in Italian children, except a debated case of a 16-yr-old female adolescent
- Severe disease requiring ICU admission and mechanical ventilation mainly in children affected by pre-existing complex disorders and comorbidities (ie, BMT, leukemia, immunodeficiencies, etc)

BMT, bone marrow transplant.

Slide 11 – Is COVID-19 also a problem in children, infants, neonates, and/or pregnant mothers?

In China, we have more than 70,000 cases stated, but only 1% of the cases occurred in children less than 10 years [of age]. In Korea, less than 1%. In Italy there were 1.2% of COVID-19 cases occurring in children less than 18 years. But regardless of the figures, the cause of infection is generally described as mild to moderate, and, so far, crossing figures, no confirmed deaths attributed to COVID-19 occurred in Italian children.

We only had a very debated case of a 16-year-old female adolescent who, regretfully, died of COVID-19, but still there is no autoptic finding to confirm that COVID-19 was the actual cause of death. Let's keep in mind that severe disease, like from many other viruses, can occur in children [and] in adolescents already affected by having comorbidities, like bone-marrow transplantation, leukemia, immunodeficiencies. And this is no surprise at all.

Italy ICU Case Study

When we look at Italy's situation, I'd like to show you, these very recent...last weeks' study in

Lombardy.⁶ This is a record from the network of ICU in Lombardy—a record involving 1,500 critically ill patients admitted in 1 month. All 99% underwent respiratory support, but only 4 out of 1,500 and more were less than 20 years old.

Demographic and Clinical Characteristics of Patients in the First 24 Hours of ICU Admission for COVID-19 in Lombardy, Italy: only 0.3% were children

- Retrospective, huge case series that involved 1,591 critically ill patients admitted from February 20–March 18, 2020, to one of the ICUs of the Lombardy network for severe COVID-19 infection
- 99% of them required respiratory support, including endotracheal intubation in 88% and noninvasive ventilation in 11%; ICU mortality was 26%
- Out of 1,591 patients, only 4 were <20 yrs old
- None of those 4 adolescents died, none had significant comorbidities



Grasselli G, et al. JAMA. 2020. [published online ahead of print April 6, 2020]

Slide 12 – Demographic and Clinical Characteristics of Patients in the First 24 Hours of ICU Admission for COVID-19 in Lombardy, Italy: only 0.3% were children

None of these 4 adolescents died; none had significant comorbidities. This is a very important finding that can be reassuring for us and can be telling us that the burden of the disease is limited, and that the risk for severe outcome is limited, as well.

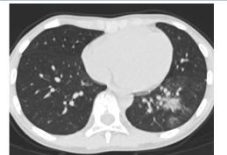
Typical Pediatric Features

We know there are typical features in pediatric patients with COVID-19 infections. CT images, or CT imaging, shows more frequently consolidation with a surrounding halo sign [Slide 13], and this is considered typical in pediatric patients. Also, coinfections are treated more commonly than in adults.⁷

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Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults^[1]

- Consolidation with surrounding halo sign is considered a typical sign in pediatric patients
- Coinfections are more common than in adults



Note: 10 years old. Chest CT showed consolidation with halo sign in the inferior lobe of the left lung, surrounded by ground-glass opacities. COVID, coronavirus disease; CT, computed tomography.

Findings	Number of Patients (%)
Pulmonary lesions	
Null	4 (20%)
Unilateral	6 (30%)
Bilateral	10 (50%)
Subpleural lesions	
Seen	20 (100%)
Not seen	0 (0%)
Consolidation with surrounding halo sign	10 (50%)
Ground-glass opacities	12 (60%)
Fine mesh shadow	4 (20%)
Tiny nodules	3 (15%)

1. Xia W, et al. *Pediatr Pulmonol*. 2020;55(3):1169-1174. [published online ahead of print March 5, 2020]

Slide 13 – Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults

I don't know if the disease is attributable to the fact that the pediatricians who usually test with multiple virus testing rather than physicians [for adult]. But, as a matter of fact, COVID-19 has been seen in our cases in Italy frequently together with other respiratory viruses.

Now I'll show you 3 slides reporting the main case series that describes, so far, from the 3 important countries with this epidemic: China, Italy and the USA. These reports from China were published in the *New England Journal of Medicine* last month⁸ and described the 171 pediatric cases, all of them having a course mild to moderate. I draw your attention with a balance distribution of age range between 1 and 15 years.

Epidemiological and Clinical Characteristics of COVID-19 Pediatric Cases in Italy (n=168)^[1]

Characteristic	Value	Characteristic	Value
Age		Signs and symptoms (continued)	n (%)
Median age, years (IQR)	2.3 (0.3-9.6)	Dyspnea	16 (9.5)
Age groups n (%)		Pharyngitis	9 (5.4)
<1 yr	66 (39.3)	Vomiting	9 (5.4)
1-5 yrs	38 (22.6)	Conjunctivitis	6 (3.6)
6-10 yrs	24 (14.3)	Chest pain	4 (2.4)
11-17 yrs	40 (23.8)	Fatigue	3 (1.8)
Gender n (%)		Non-febrile seizures	3 (1.8)
Males	94 (55.9)	Febrile seizures	2 (1.2)
Females	74 (44.1)	Hospital admission	110 (65.1)
Signs and symptoms n (%)		Age groups n (%)	
Fever	138 (82.1)	< 1 yr	52 (47.3)
Cough	82 (48.8)	1-5 yrs	24 (21.8)
Rhinitis	45 (26.8)	6-10 yrs	13 (11.8)
Diarrhea	22 (13.1)	11-17 yrs	21 (19.1)

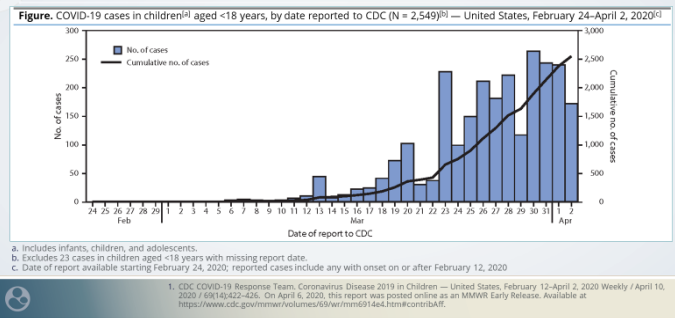
1. Boccia G, et al. *Emerg Infect Dis*. 2020;26(4):e200349. [published online ahead of print April 11, 2020].

Slide 14 – Epidemiological and Clinical Characteristics of COVID-19 Pediatric Cases in Italy (n=168)

I will note, just like in adults, even in children, males are more frequently represented, and this is something that was a concern. In Italy, we have been able, so far, thanks to our pediatric registry run by the Italian Society of Pediatric Infectious Disease, to describe the 168 patients in this paper that is in press. Again, here we have a balanced distribution of ages.⁹

Again, here we have this slight-prevalence of males, and the same occurs in the USA. Here you have the record from the CDC [Slide 15], published 10 days ago, with cumulative cases, day by day, and the breakdown of symptoms and signs in pediatric patients in the USA.¹⁰

Epidemiological and Clinical Characteristics of a Series of COVID-19 Pediatric Cases in USA (n=291)^[1]



Slide 15 – Epidemiological and Clinical Characteristics of a Series of COVID-19 Pediatric Cases in USA (n=291)

In summary, when taken together—the case series from China, Italy, and the USA—the main differences in children compared with adults are that the children feature less fever, less cough, less dyspnea, less headache, less myalgia, but similar incidence of gastrointestinal symptoms. If we compare, and this is something that it is in press and will be published later,¹¹ if we compare the case series from these 3 countries, we see that the median age of reported cases is quite different from China, the USA, and Italy.

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Epidemiological and Clinical Characteristics of a Series of COVID-19 Pediatric Cases in USA^[1] (continued)

Main differences in children compared with adults:

- Less fever
- Less cough
- Less dyspnea
- Less headache
- Less myalgia
- Similar incidence of gastrointestinal symptoms

Table. Signs and symptoms among 291 pediatric (age <18 years) and 10,944 adult (age 18–64 years) patients^a with laboratory-confirmed COVID-19 — United States, February 12–April 2, 2020

Sign/Symptom	No. (%) with sign/symptom	
	Pediatric	Adult
Fever, cough, or shortness of breath ^b	213 (73)	10,167 (93)
Fever ^b	163 (56)	7,796 (71)
Cough	158 (54)	8,775 (80)
Shortness of breath	39 (13)	4,674 (43)
Myalgia	66 (23)	6,713 (61)
Rhiny nasal ^c	21 (7)	757 (6.9)
Sore throat	71 (24)	3,795 (35)
Headache	81 (28)	6,335 (58)
Nausea/Vomiting	31 (11)	1,746 (16)
Abdominal pain ^d	17 (6)	1,329 (12)
Diarrhea	37 (13)	3,353 (31)

^a Cases were included in the analysis if they had a known exposure to a case of COVID-19, a positive result on a laboratory-confirmed test, or a history of contact with a case of COVID-19.

^b Includes all cases with one or more of these symptoms.

^c Includes only cases with rhinorrhea or other respiratory symptoms from nasals and/or eyes.

^d Includes only cases with abdominal pain or diarrhea.

^e Symptoms and additional pain were less frequently reported than other symptoms (fever, cough, shortness of breath, and myalgia).

In USA as of April 2: 2,572 cases in children <17 yrs (1.7% of all ages)

1. CDC COVID-19 Response Team. Coronavirus Disease 2019 in Children — United States, February 12–April 2, 2020 Weekly / April 10, 2020 / 69(14):422–426. On April 6, 2020, this report was posted online as an MMWR Early Release. Available at <https://www.cdc.gov/mmwr/volumes/69/worrell04e4.html#resourcelink>.

Slide 16 – Epidemiological and Clinical Characteristics of a Series of COVID-19 Pediatric Cases in USA (continued)

In Italy, we have a median age younger than China, and much younger than the US. I don't know why, but this is what we are reporting. The high frequency of gastrointestinal symptoms in all 3 countries is very important. It's also an important fact that pneumonia, as the main symptom, occurs in 40%–70% of patients, with 40% in Italy, where the course of the infection in children is quite similar to a very routine viral respiratory infection, or viral gastrointestinal infection.

Also, I draw your attention to the presence of lymphopenia. In Italy, this has been described in 2% of cases, and in China 3.6%.¹¹ To be honest, this is much lower than what is reported in adults, especially in Italy; lymphopenia in adults is present in much higher proportions.

Main Clinical Characteristics in Children A Comparison: CHINA vs USA vs ITALY^[1]

Characteristic	CHINA	USA ^(a)	ITALY
Median age	6.7 yrs	11 yrs	2.5 yrs
Asymptomatic	15%	NA	2.4%
Underlying chronic diseases and comorbidities	NA	NA	19.6%
Pneumonia	70%	67%	40%
Gastrointestinal symptoms (vomiting, diarrhea, etc)	15%	29%	19%
Lymphopenia (lymphocyte count <1.200/liter)	3.6%	NA	2%
Fever	42%	56%	82%
Conjunctivitis	NA	NA	3.6%
Seizures	NA	NA	3%

^a This US report includes only symptomatic cases.

1. Manzoni P. (unpublished, submitted to *NEJM*)

Slide 17 – Main Clinical Characteristics in Children A Comparison: China vs USA vs Italy

Once we know that children and infants are moderately affected, both for severity and burden [of disease], it remains, nonetheless, a need for prevention and the need for limiting the spread of this virus from child to child, and from children to adults and caregivers.

Tips to Limit Spread in Infants and Children

1. From experimental decay and virus survival models, we know **aerosol and fomite transmission** of SARS-CoV-2 is plausible, because the virus can remain viable and infectious in aerosols for hours and on surfaces up to days (depending on the inoculum shed), thus possibly producing nosocomial spread and super-spreading events. (van Doremalen, et al. *N Engl J Med.* 2020)
→ **SOCIAL DISTANCING AND HYGIENE**
2. Although the predominant symptoms of COVID-19 are respiratory, gastrointestinal (GI) manifestations can occur and may be overlooked, as well as **fecal-oral transmission**. A meta-analysis of 60 studies with data on GI symptoms + stool viral RNA (n=4243), pooled prevalence of GI manifestations was 18%. Anorexia (27%), diarrhea (12%), nausea and vomiting (10%), abdominal pain (9%) were the most common symptoms. Prevalence of GI symptoms was similar among adults, children, and pregnant women. The overall concomitant viral RNA positivity rate of stool and respiratory samples was 48%, and very frequent positivity of stool RNA was persistent even after respiratory tests had become negative. (Cheung KS, et al. *Gastroenterology.* 2020.)
→ **HYGIENE + PRECAUTIONS WITH DIAPERS AND STOOLS**

1. van Doremalen N, et al. *N Engl J Med.* 2020; NEJM2004973. [published online ahead of print March 17, 2020]
2. Cheung KS, et al. *Gastroenterology.* 2020. pii: S0016-5085(20)30448-0. [published online ahead of print April 3, 2020]

Slide 18 – Tips to Limit Spread in Infants and Children

There are 2 basic points I want to underline for you. The first one is that according to the evidence, we know that aerosol and fomite transmission of COVID is plausible, because the virus remains viable and infectious in aerosols for hours, and on surfaces for hours or even days. So, social distancing and strict hygiene measures are absolutely recommended and compulsory, also for children and infants.

The second point is that due to the very high frequency of gastrointestinal compromise in children with COVID-19, it is plausible that there is fecal-oral transmission, not only respiratory transmission. These points have been nicely debated in a recent paper in *Gastroenterology* where in adult patients with COVID-19—out of 60 studies—the prevalence of gastrointestinal manifestation was extremely high, and the positive rate from stool and respiratory samples for COVID-19 RNA was up to 48%.¹² Stool RNA was persistently positive even after respiratory tests had become negative.

These findings and claims call for great attention, from us pediatricians and from parents. Hygiene,

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and deep precautions with a person's stool [are necessary], because babies can spread the virus through the stool without showing symptoms and signs.

Peculiar Presentations in Children

Now I want to show you some peculiar presentations in children. I already described the typical frequency of the halo sign in the CT scan, and in the lung CT scan. But as I was telling you earlier, the gastrointestinal symptoms and morbidities are frequent, as testing for peripheral vasculitis ultimately show a skin lesion.

I want to highlight those 2 points by showing this case, a record that we described last week, which is currently submitted to the *New England Journal of Medicine*,¹¹ but I can disclose it. It's an uncommon presentation in a 7-year-old child we admitted to our unit. This child, she had no underlying comorbidities, and she was actually hospitalized for persistent diarrhea and increasingly severe abdominal pain, but no history of cough or fever.

Possible presentation 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.

Submitted to the New England Journal of Medicine

THE NEW ENGLAND JOURNAL OF MEDICINE

Please review the Supplemental Files folder to review documents not compiled in the PDF.

Uncommon presentation of COVID-19 infection in a child

Journal: New England Journal of Medicine
Manuscript ID: 20-09338

Manzoni P. (unpublished, submitted to NEJM)

Slide 19—Possible presentation as severe gastrointestinal disorders ultimately leading to acute ischemic gastrointestinal disease

We performed a complete workup, and due to the epidemic spread, we included a nasopharyngeal swab that was positive for COVID-19, just like the family of that child. And the chest X-ray, despite the absence of symptoms, showed the typical viral pneumonia patterns. Due to the increasing abdominal pain, and due to the increasing severity


of the clinical picture, she was referred to surgery. [She] underwent exploratory laparoscopy, and ultimately was revealed to have phlegmonous appendicitis with peritonitis. No pathogens grew from any culture. The child was treated empirically, and she recovered well. Finally, we are thinking that this virus was present, and might occur in many children, by producing severe diarrhea and gastrointestinal disorder. Ultimately it was associated in promoting the surgical outcome.

Skin Lesions

More frequently, in Italy, we are seeing and detecting skin lesions of many kind. At least the 5 types: urticaria, livedo reticularis, vesicular lesions, petechiae, and acral ischemia. (I will talk to you about acral ischemia in the next slide.) If you take a look, and you know the pathology of these lesions, the common denominator of these lesions is the occurrence of vasculitis associated with microthrombi and ischemia of the referral vessels.

Possible Association of COVID-19 With Skin Lesions

- COVID-19 associated rashes and skin lesions are being reported in Northern Italy in up to 20% of patients
- The skin lesions are mainly of 5 types:
 1. Urticaria
 2. Livedo reticularis
 3. Vesicular → chickenpox-like vesicles on erythematous base
 4. Petechiae
 5. Acral ischemia
- The common denominator of these lesions is occurrence of Microthrombi and Ischemia of peripheral vessels



Slide 20 - Possible Association of COVID-19 With Skin Lesions

You know very well that COVID-19 disease is emerging as a systemic vasculitis disease, associated with an abnormal inflammatory response. As such, it is curious to report these actual skin lesions in asymptomatic children. Those lesions are being frequently described, just like in epidemic in the last couple of weeks, in children with an average age of 10 years, usually affecting the feet, less presented in the hands. The fingers are

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typically affected, not all concomitantly, but usually 2 or 3 fingers, often separated by fingers not affected.

The lesions have a purplish-red or bluish color, they can evolve also with crust, but with *restitutio ad integrum* through recovery, typically in a couple of weeks. Limited testing for COVID-19 has been done, but many cases are reported as family clusters, or were positive to the swab.

The main feature of skin involvement in COVID-19 infection: Acral ischemic lesions in asymptomatic children

- The first report appeared in Italy on March 29, 2020, ie, 5 weeks after the first COVID-19 case
- In the last 3 weeks, there was an epidemic of reports of acral ischemic lesions in asymptomatic children ~10 yrs of age throughout Italy, with dozens of overlapping cases of intensely painful, new cases reported weekly, to date
- The lesions usually affect feet, sometimes the hands; the fingers are typically affected, not all concomitantly, but usually 3 fingers, often separated by fingers not affected; the lesions have initially a purplish-red or bluish color; they can evolve with bullae or blackish crusts
- *Restitutio ad integrum* typically occurs within 2 weeks
- Limited testing for COVID-19 has been done, but many cases are reported as family clusters, or swab positives, or both

Rationale → COVID-19 disease is emerging as a **SYSTEMIC VASCULITIS** disease associated with abnormal inflammatory response



<https://www.farpediatrico.com/doi/10.1016/j.covid.19.e-arrondissement-dia-in-bambini-acrosclerite-acral/>
<https://www.farpediatrico.com/wp-content/uploads/2020/04/acrosclerite.pdf>

Slide 21 – *The main feature of skin involvement in COVID-19 infection: Acral ischemic lesions in asymptomatic children*

In summary, data from China, Italy, and the USA suggest the **pediatric coronavirus disease may be less severe than cases in adults, and children might experience different symptoms than adults**. In these preliminary descriptions of pediatric cases, relatively few children with COVID-19 are hospitalized.

In Summary

- Data from China, Italy, and the USA suggest pediatric coronavirus disease 2019 (COVID-19) cases might be less severe than cases in adults, and children might experience different symptoms than adults.
- In these preliminary descriptions of pediatric COVID-19 cases, relatively few children with COVID-19 are hospitalized.
- Pediatric COVID-19 patients might not have fever or cough. In general, fewer children than adults experience fever, cough, or shortness of breath.
- Severe outcomes have been very rarely reported in children, and only 3 deaths in the USA have been described.
- Nonetheless, patients with less serious illness and those without symptoms (ie, children) likely play an important role in disease transmission. Consider fecal transmission from carrier children!

Slide 22 – *Module 2 Summary*

Pediatric patients might not have a fever or cough. In general, fewer children than adults experience fever, cough, or shortness of breath. Severe outcomes are not common in children. Only very few deaths have been reported so far. But children may be a reservoir for spreading and dissemination, even when they have a less serious illness, or are actually asymptomatic. Consider fecal transmission from children who are carriers, without knowing that.

MODULE 3

With this in mind, I will now move to the third module. I want to update you about COVID-19 in pregnant women through delivery and good practices in the NICU.

Is COVID-19 a problem in infants and neonates? Once more, this model is true, because infants and neonates have very limited burden with very limited severity. [There are] 2 main case series so far from China and Italy. But in both of them, up to 90% of neonates and infants are asymptomatic, and only 10%–20% have only mild respiratory symptoms, feeding instability or unspecific features.

Is COVID-19 also a problem in children, infants, neonates, and pregnant women?

INFANTS and NEONATES

Very Limited Burden, Very Limited Severity

Two main case series, so far:

- China → 37 neonates
- Italy → 12 neonates
- 80% to 90% are asymptomatic
- 10% to 20% have only mild respiratory distress, feeding instability, sometimes fever and rash

Slide 23 – *Is COVID-19 also a problem in children, infants, neonates, and pregnant women?*

This slide and the next one [Slides 24–25] report a table that a group of researchers, including myself, led by Shalish and Sant'Anna from Canada, had performed by reporting all together...all the papers described in positive mothers who delivered (in

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slide 23), and infant(s) who were positive in the first year of life.¹³ By skipping from one side to the other, you can see that usually mothers who are positive deliver babies who prove negative to the test, and who do not need any support of any kind, with very limited exceptions.

Characteristics of infants born to mothers with positive SARS-CoV-2 infection

Study	N	Region, Country	GA Range	Infant Testing	Respiratory Support	Adverse Events
Infants with negative testing; pending testing or not tested for SARS-CoV-2						
Chen H et al.	9	Wuhan, China	36 to 39 ⁺	Negative (6/9)	None	Increased myocardial enzymes (1/9)
Chen S et al.	3	Wuhan, China	35-37 ⁺ /38 ⁺	Negative	None	None
Chen Y et al.	4	Wuhan, China	37 ⁺ to 39 ⁺	Negative (3/3)	CRF for TTN (1/4)	None
Fan C et al.	2	Wuhan, China	37/36 ⁺	Negative	None	Mild neonatal pneumonia (2/2)
Isabel L et al.	1	Washington, DC	39	Negative	None	None
SIN-ISN	7	Northern Italy	34 ⁺ to 40 ⁺	Negative (4/4) ^a	NIV for prematurity (1/7)	None
LJF et al.	1	Zhejiang, China	35	Negative	None	None
Liu D et al.	11	Wuhan, China	34 to 38	Not done	None	None
Liu H et al.	16	Shanghai, China	Not specified	Not done	None	None
Liu W et al.	3	Wuhan, China	38 ⁺ to 40 ⁺	Negative	None	None
Liu X et al.	10	Outside Wuhan	32 to 38 ⁺	Not specified	None	Stillbirth for maternal AROS and shock (1/10)
Wang X et al.	1	Souzhou, China	30	Negative	None	None
Yu N et al.	6 ^a	Wuhan, China	37 to 41 ⁺	Negative (2/2)	None	None
Zeng H et al.	4	Wuhan, China	Not specified	Negative	None	None
Zeng S et al.	30	Wuhan, China	1 (27), 9 (3)	Negative	None	RDS (5/30), cyanosis (2/30), asphyxia (1/30)
Zhang L et al.	10	Wuhan, China	35 ⁺ to 41 ⁺	Negative (9/10)	Not reported	Bacterial pneumonia (3/10)
Zhu H et al.	10	Wuhan, China	31 to 39	Negative (9/9) ^b	IMV on DOL 6 (1/10); NIV after birth then IMV on DOL 3 (1/10)	Shortness of breath (6/10); pneumothorax (1/10); RDS (2/10); Shock, multiple organ failure, DIC and death on DOL 6 (9/10); respiratory distress after birth then DIC on DOL 3 (1/10)
Infants with unreported test results for SARS-CoV-2						
Dong L et al.	1	Wuhan, China	34 ⁺	Negative RT-PCR	None	None
Zeng H et al.	2	Wuhan, China	Not specified	High IgM/IgG	None	None
Infants with positive testing for SARS-CoV-2						
Wang S et al.	1	Wuhan, China	39 ⁺	Positive at 36 ⁺	None	Lymphopenia and transaminitis
Zeng L et al.	3	Wuhan, China	Term (2/3) Preterm (1/3)	Positive at <48h	NIV for prematurity (1/3)	1 infant: 37 ⁺ weeks, foetal distress, asphyxia, low Apgar scores, RDS, pneumonia, bacteremia

Shalish W, et al. Am J Perinatol. 2020. [in press]

Slide 24 – Characteristics of infants born to mothers with positive SARS-CoV-2 infection

Only very few positive cases at birth and during the first 2–3 days of life have been described from positive mothers. We had a couple of them in Turin and a couple of additional more in Lombardy, described here in the SIN-ISN network. But the majority of those cases listed here in the first year of life, as you see, occurred in babies older than a few days, that is, outside of the neonatal period.

Characteristics of neonates and infants <1 year of age with positive COVID-19 testing

Study	N	Region, Country	Age range	Need for Respiratory Support	Symptoms/Outcomes
Ca J et al.	2	Shanghai and Hubei, China	3 and 7 months	None	Fever and mild URTI symptoms
Ca J et al.	1	Guangxi, China	50 days	Oxygen therapy	Pneumonia, increased myocardial/ liver enzymes
Dong Y et al.	37	Mainland China	0 to 1 year	Not specified	7 (2%) asymptomatic 205 (54%) mild 127 (34%) moderate 23 (6%) severe 7 (2%) critical
SIN-ISN					
LJF et al.	5	Northern Italy	2 to 44 days	Oxygen (1/5)	Fever and/or mild URTI symptoms/conjunctivitis
Li H et al.	1	Hanoi, Vietnam	9 months	None	Mild URTI symptoms
LJW et al.	1	Zhejiang, China	10 months	None	Asymptomatic
Liu H et al.	2	Shanghai, China	2 and 11 months	Not specified	Both had mild pneumonia, one infant also had pleural effusion and was RSV positive
Liu X et al.	31	Wuhan, China	0 to 1 year	1 infant required IMV due to intubation and multi-organ failure (6 weeks after admission)	0 asymptomatic 6 (19%) URTI symptoms 25 (81%) pneumonia 1 (3%) death 4 (13%) asymptomatic/mild 6 (20%) moderate 1 (3%) severe
Qiu H et al.	10	Zhejiang, China	0 to 5 years	Oxygen therapy (1/10)	Asymptomatic
Wu M et al.	9	Mainland China	280 to 1y	None	Fever or mild URTI symptoms
Xu W et al.	9	Wuhan, China	0 to 1 year	Not specified	Neonates: asymptomatic (4/3) Others: asymptomatic or mild pneumonia
Zeng L et al.	1	Wuhan, China	17 days	None	Mild symptoms (fever, vomiting, diarrhea)
Zhang Y et al.	1	Hubei, China	3 months	None	Mild URTI symptoms

Shalish W, et al. Am J Perinatol. 2020. [in press]

Slide 25 – Characteristics of neonates and infants <1 year of age with positive COVID-19 testing

As a matter of fact, in the literature that we could access, so far, there are reports of 140 COVID-

positive mothers who gave birth to only 8 COVID-positive neonates: 5 from China and 3 from Italy. These children, those neonates, were mostly asymptomatic, and when they showed mild symptoms of respiratory distress, instability or sepsis-like symptoms, it's absolutely uncertain whether these symptoms were attributable to other concomitant conditions. One of them was premature, another developed bacterial sepsis. All were attributed to the virus.¹³

COVID-Positive Mothers and Neonatal Outcomes

- In the literature noted, there are reports of **140 COVID-positive mothers** who gave birth to only **8 COVID-positive neonates** (5 from China and 3 from Italy)
- Infected neonates were mostly asymptomatic
- A few had mild respiratory distress, instability, sepsis-like symptoms, likely attributable to concomitant conditions (such as prematurity or sepsis)

Shalish W, et al. Am J Perinatol. 2020. [in press]

Slide 26 – COVID-Positive Mothers and Neonatal Outcomes

Respiratory Strategies

There are few questions we are asking ourselves as neonatologists: Can we continue to use current respiratory strategies with neonates born to COVID-19-positive mothers? Or mothers who are uncertain of their COVID-19 status in a time when the epidemic is spreading?

Can we continue to use current respiratory strategies with neonates born to COVID-19-positive mothers?

- Yes, with a few suggested modifications to address the possibility of aerosol generation and exhaled air dispersion during oxygen administration and ventilatory support.
- To date, the only recommended modification for contemporary respiratory care is the use of **bacterial/viral hydrophobic** filters located at the expiratory part of the systems.
- Any strategy in such neonates should be tailored to the individual patient, rather than to the disease.

Shalish W, et al. Am J Perinatol. 2020. [in press]

Slide 27 – Can we continue to use current respiratory strategies with neonates born to COVID-19-positive mothers?

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The general response is yes, but we need to make sure that some modifications have been taken to address the possibility of aerosol generation and exhaled air dispersion during the administration of oxygen. As a matter of fact, the only recommended modification, the main recommended modification, is to use bacterial and viral hydrophobic filters located at the expiratory part of the systems. We will get back to that, because this is a part of a network of recommendations that are nicely depicted in this review paper that our group is publishing in the *American Journal of Perinatology*. As you see, endotracheal intubation is the most dangerous activity and procedure associated with a higher risk of contamination.

Practical Approach in the Delivery Room	
Bag and mask/ T-piece and mask ventilation	Delivery room and NICU should continue to be used as recommended by the NRP with all protective measure in place for suspected or confirmed COVID-19 cases. A small viral/bacterial filter should be placed in between the T-piece resuscitator or anesthesia bag and the mask or in the expiratory limb before the PEEP valves of a self-inflating bag. Normally, the filter should be replaced every 8-12 hours. NOTE: When placed between the T-piece or anesthesia bag and mask, the filter adds significant dead space. For that reason, the smallest available filter should be used and prolonged ventilation using this apparatus should be avoided.
Suction (oropharyngeal area and ETT)	Non-intubated infant —continuous suctioning reduces aerosol spread better than several episodes of intermittent suctioning. In this respect, open airway toileting should be performed with continuous suctioning. Mechanically ventilated infants: a closed-circuit suction should always be utilized and used for endotracheal suctioning.
Continuous positive airway pressure	Delivery room and NICU should continue to be used as recommended by the NRP with all protective measures in place for suspected or confirmed COVID-19 cases. A viral/bacterial filter should be placed in the expiratory limb (before the water reservoir for the bubble system) or before the ventilator exhalation valve. Normally, the filter should be replaced every 8-12 hours.
Non-invasive positive pressure ventilation	Delivery room and NICU is acceptable as long as all protective measures are in place for suspected or confirmed COVID-19 cases. A viral/bacterial filter placed in the expiratory limb of the system. NOTE: If those measure are not available or reliable, then intubation and invasive mechanical ventilation is a reasonable option.
Endotracheal intubation	Delivery room and NICU is the procedure associated with higher risk of contamination. Therefore, the operator should have experience and be properly protected. If possible, use a video laryngoscopy system to maintain some distance from the patient airway.
Mechanical ventilation	NICU —Should continue to be used in the NICU as per unit protocols as long as all protective measures are in place for suspected or confirmed COVID-19 cases. There are no data to recommend a specific mode. A viral/bacterial filter should be placed in the expiratory limb before the ventilator exhalation valve (not feasible with but high-frequency oscillatory ventilation). Normally, the filter should be replaced every 8-12 hours. A closed ETT suction apparatus should be used.
ETT, endotracheal tube; NRP, National Reading Panel.	
Shalish W, et al. <i>Am J Perinatol</i> . 2020. [in press]	

Slide 28 – Practical Approach in the Delivery Room

Precautions and different approaches need to be taken, but also the use of mask and bag, in the delivery room, suctioning from nonintubated or mechanically ventilated infants, and administration of the CPAP or mechanical ventilation needs to be tailored and fully reviewed in light of the risk of aerosol transmission and contamination.

Pregnancy and Delivery

Getting back to pregnancy and delivery. As neonatologists, we are often consulted by obstetricians and pregnant mothers with 2 main questions: **Can COVID-19 be passed from a pregnant woman to the fetus or newborn?** The

response so far is, no. **No confirmed vertical transmission has occurred, so far.**

I know [one], but it is off the record, that one specific case is described occurring in a European nation, but as of today, no consistent report of vertical transmission exists. If you think about this, it is not a surprise because almost all respiratory viruses do not have a high burden of occurrence through vertical transmission.

Is COVID-19 a Problem During Pregnancy or Delivery?

We do not know at this time if COVID-19 would cause problems during pregnancy or affect the health of the baby after birth.

Can COVID-19 be passed from a pregnant woman to the fetus or newborn?

No confirmed maternal-neonatal vertical transmission, so far.

We still do not know if a pregnant woman with COVID-19 can pass the virus that causes COVID-19 to her fetus or baby during pregnancy or delivery.

No infants born to mothers with COVID-19 have tested positive for the COVID-19 virus. In these cases, which are a small number, the virus was not found in samples of amniotic fluid or breast milk.

If a pregnant woman has COVID-19 during pregnancy, will it hurt the baby?

We do not know at this time if any risk is posed to infants of a pregnant woman who has COVID-19.

There have been a small number of reported problems with pregnancy or delivery (eg, preterm birth) in babies born to mothers who tested positive for COVID-19 during their pregnancy.

It is not clear, however, that these outcomes were related to maternal infection.

 Procanoy RS, et al. *J Pediatr (Rio J)*. 2020.

Slide 29 – Is COVID-19 a Problem During Pregnancy or Delivery?

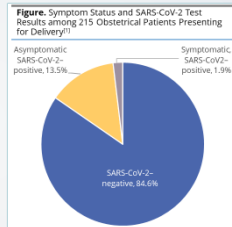
The second [question] is **if a woman has COVID-19 during pregnancy, will this hurt the baby?** Again, the response is probably no, but we need to admit that we don't know, at this time, if any risk is posed to infants. Our experience is too short and too limited, so far, to discard [the contention] that damages can occur.¹⁴

Also, taking into account that the epidemiology now for pregnant mothers being positive for COVID-19 is huge. This is a paper from the USA, Universal Screening in New York City during 2 consecutive weeks in late March/early April, disclosed that 50% of pregnant women tested were actually COVID-positive despite the fact that only 1.9% of them were symptomatic.¹⁵

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What is the current prevalence of COVID-19 in pregnant women at delivery?^[1]

- Universal screening in a New York academic setting during 2 consecutive weeks in late March–early April
- 215 pregnant women tested at admission for delivery
- Main findings:
15.4% COVID-positive
but only
1.9% COVID-symptomatic



Key Takeaway: Risk of underestimating COVID-19 positivity in women delivering

1. Sutton D, et al. Universal Screening for SARS-CoV-2 in Women Admitted for Delivery. *NEM*. April 13, 2020.

Guidance for Neonatal Management in the Nursery and for Breastfeeding

- **AAP document (USA)** → Recommends to consider separating mother and neonate in many situations (Puopolo KM, et al. *Pediatrics*. 2020)
- **SIN-UENPS document (ITALY-EUROPEAN UNION)** → Recommends not to separate mother and neonate, unless in very limited situations (Davanzo R, et al. *Matern Child Nutr*. 2020, in press) (Davanzo, ADCFN 2020, in press)
- **BRAZILIAN PEDIATRIC SOCIETY document** → the same as Europe (Procianny, Silveira, Manzoni, Sant'Anna. *J Pediatr*. 2020, in press)

Slide 30 – What is the current prevalence of COVID-19 in pregnant women at deliver?

This means the risk of underestimating positivity for COVID-19 in women who are admitted for delivery is very high. My advice in this epidemic era is to consider precautions and adoption of measures in times and settings where the epidemic is occurring heavily.

Breastfeeding and Neonatal Guidance

A final, or a pre-final point is, "What are we doing with neonatal management in the nursery, in the rooming-in and for breastfeeding?" I summarize here, 3 main documents that came to my attention. The American Academy of Pediatrics' document, published in *Pediatrics* by Karen Puopolo a few weeks ago,¹⁶ is basically recommending to not exclude separating mother and neonate, in some situations. It's more aggressive than the European and Italian document published through a consensus between the Italian Society of Neonatology and the UENPS (the Union of European Neonatal & Perinatal Societies) and published in *Archives of Disease in Childhood*.¹⁷

Slide 31 – Guidance for Neonatal Management in the Nursery and for Breastfeeding

This document, our document, recommends not to separate the mother and neonate except in very limited situations. The same approach has been taken also by the Brazilian Pediatric Society, with which I collaborated, and this document is in press in the *Jornal de Pediatria*.¹⁸

I want to summarize here what we are doing in Italy and Europe, and what we are recommending for delivering mothers and neonates. As you see [Slide 32], in the majority of cases, we do not recommend separating mother and infant, and we recommend providing direct breastfeeding, as well.

Breastfeeding and COVID-19^[1]

Health status of the mother	Pharyngeal swab for COVID-19 on the mother	Pharyngeal swab for COVID-19 on the neonate	Isolations of the mother	Management of the neonate during hospital stay	Advice on direct breastfeeding	Preventative measures for mother-neonate transmission
Asymptomatic or paucisymptomatic to be COVID-19 positive	Already done	Yes	Yes In an isolated and dedicated area of postpartum ward	In a rooming-in regimen, in an isolated and dedicated area of postpartum ward	Yes	Yes
COVID-19 paucisymptomatic mother under investigation	Yes	Only if maternal test is positive	Yes In an isolated and dedicated area of postpartum ward, pending result of lab test	In a rooming-in regimen, in an isolated and dedicated area of postpartum ward, at least until result of the lab test	Yes	Yes
Mother with symptoms of respiratory infection (fever, cough, secretions) and too sick to care for newborn, COVID-19+ or under investigation	Yes or already being done	Only if maternal test is positive	Yes In an isolated and dedicated area of postpartum ward, pending result of lab test	Neonate isolated and separated from the mother at least until the result of the lab test. Neonate placed in a dedicated and isolated area in the Neonatology Unit (if asymptomatic) or in the NICU (if symptomatic; eg, with respiratory disease)	No use of expressed milk. Pasteurization not recommended	Yes

Davanzo R, et al. *Matern Child Nutr*. 2020e13010. doi:10.1111/mcn.13010. [published online ahead of print April 3, 2020]

Slide 32 – Breastfeeding and COVID-19

Of course, no situation will strengthen the need to recommend preventative measures for prevention of mother-neonate transmission—prevention of the horizontal transmission. Only in one specific situation do we recommend isolating the mother

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from the infant, and to express the milk, and to give the milk by bottle; but it is only expressed maternal milk, and not pasteurized. This situation would include a mother with severe symptoms of respiratory infection and fever, cough, secretions, who is too sick to care for a newborn. In this situation it's a matter of common good sense to separate the mother and the infant—to take all these measures we are describing here.

Also, we recommend instituting in every NICU a checklist of measures that need to be taken to limit the spread of the epidemic. These measures are related, and we need to include the mother, newborn, health care providers, and parents, as well.¹⁹

How to manage a tertiary-level NICU in the time of COVID-19? A summary of the lessons learned from a high-risk zone in Italy

- Official policy issued by the Academic and Institutional Committees of a large tertiary NICU in Northern Italy
- NICU, Department of Women's and Children's Health, University Hospital of Padua, Venetian Region

Table. Checklist of preventive measures in our NICU during COVID-19 pandemic	
Maternity service	Mother
	Isolation if symptomatic or with a recent history of close contact with an individual testing positive for COVID-19
	Isolation of mother and baby until rapid test results are available
	Changing only without breastfeeding; rapid test results are available
NICU	Newborn
	Respiratory/airway swabs on admission and weekly thereafter
	Close frequent observation of signs in the event of contact with an individual testing positive for COVID-19 or showing symptoms
	Quarantine zone for symptomatic patients or those who have been in contact with an individual testing positive for COVID-19
	Thermistor-controlled crib
	Health care providers
	Weekly nasopharyngeal swabs
	Isolation in the event contact with an individual testing positive for COVID-19 or showing symptoms
	Surgical masks and gloves
	Protective clothing, gloves, and face shields for COVID-19 positive or suspected reasons
	Avoidance of close contact with other colleagues and parents
	Supportive psychological services available
	Parents
	Triage
	Nasopharyngeal swabs on admission and weekly thereafter
	Restricted access
	Avoidance of close contact with parents
	Standardized procedures for hand cleaning and wearing protective clothing before accessing the NICU
	Supportive psychological services available

Cavicchio ME, et al. *Pediatr Pulmonol*. 2020;1-3.

Slide 33 – How to manage a tertiary-level NICU in the time of COVID-19 A summary of the lessons learned from a high-risk zone in Italy

Current Treatment Options

In summary, in this disease, including adults and children, this table provides an overview of all the treatments now in use for COVID-19 [Slide 34]. Basically, these are anti-inflammatory, immunomodulatory treatments. These are anti-viral treatments, treatment for prevention of coagulopathy and thromboembolic complications, as secondary to an inflammation storm. Respiratory management, and inhibitors for viral entry into cells.

Summary of Current Treatment Options and Management for Adults and Children

	Type of treatment	Drugs used
Anti-inflammatory, immunomodulatory treatment	Symptomatic	Vitamin D Chloroquine Tocilizumab Steroids (?)
Anti-viral treatment	Untargeted	Lopinavir-Ritonavir Remdesivir
Prevention of coagulopathy and thromboembolic complications secondary to inflammation storm	Symptomatic	Heparin NAO
Respiratory management	Supportive-symptomatic	Oxygen ECMO
Inhibitors of viral entry into the cells	(Un)targeted	Chloroquine ACE2 inhibitors

+ NO COVID-19-SPECIFIC TREATMENT CURRENTLY EXISTS

Slide 34 – Summary of Current Treatment Options and Management for Adults and Children

But as you see, there is no COVID-19-specific treatment currently. As you all know, and as you see, the type of treatment is always either symptomatic or untargeted, [for] either drug you are using. The point now is to understand whether, in the next weeks or months, if something will arise that will enable us to switch our ability to cure infants, children, and adults with COVID-19.

I want to give you a quick review of 4 drugs under investigation.

Waiting for a vaccine: Are there any potentially innovative/alternative treatments?

- Resveratrol
- Lactoferrin
- L-asparaginase
- Hyperimmune plasma from donor

Slide 35 – Waiting for a vaccine: Are there any potentially innovative/alternative treatments?

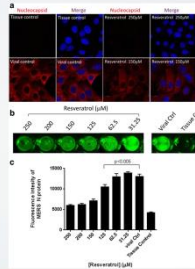
Resveratrol, *in vitro* significantly inhibits MERS-coronavirus infection by 3 main pathways, 1 of those being the upregulation of the ACE2 gene expression.²⁰ By enabling the MERS-coronavirus, researchers are excited to test its ability, also, on coronavirus, which is very close to MERS.

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RESVERATROL

Resveratrol *in vitro* significantly inhibits MERS-CoV infection by 3 main pathways:

1. Upregulation of the ACE2 gene expression
2. Decreasing the expression of nucleocapsid (N) protein essential for MERS-CoV replication
3. Down-regulating the apoptosis induced by MERS-CoV



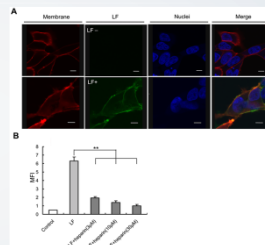
Li Y, et al. Appl Biochem Biotechnol. 2005.

Slide 36 – RESVERATROL

Lactoferrin, the same with the SARS pseudovirus is inhibiting the heparan sulfate proteoglycans that are a cell-entry protein, very critical for entry of the cell by these viruses.²¹

LACTOFERRIN

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



Lang J, et al. PLOS ONE. 2011;6(8): e23710. Used under the terms of the Creative Commons Attribution License.

Slide 37 – LACTOFERRIN

But probably more sound is the point of L-asparaginase. **L-asparaginase** is an enzyme that is capping and blocking asparagine, which is an amino acid placed in a position in the cell membrane protein critical for an ACE2 receptor. The point is that when we eliminate the amino acid asparagine from the cell membrane protein, we likely prevent binding of the virus to its specific cellular receptor.

L-ASPARAGINASE

Background and Rationale →

- COVID-19 links with the sites of ACE2, using this cellular receptor to enter the cells of the lung, digestive system and the genitourinary tract of man.
- Most of the attack sites of ACE2 are glycosylation areas where sugar molecules bind to a cell membrane protein.
- The last amino acid of the cell membrane protein is almost always asparagine.
- By using the enzyme L-asparaginase, we can eliminate the amino acid asparagine, thus preventing the binding of the virus to its specific cellular receptor.
- Once asparagine has been eliminated, COVID no longer has any point of attack.

Suggested Combination Treatment
(currently patented in USA by Italian researchers; RCTs ongoing):
L-asparaginase
+
Chloroquine
+
Heparin

Slide 38 – L-ASPARAGINASE

As a matter of fact, and this is of course off-label, it is suggested that combination treatment with L-asparaginase and chloroquine and heparin has been very recently patented in the USA by Italian researchers, with randomized clinical trials from Wuhan.

In Italy, it's getting increasingly popular and increasingly good results from plasma transfusion of convalescent donors. The rationale is obvious: formerly positive COVID-19 patients may become donors of a hyperimmune plasma once they recover and return negative.²²

PLASMA TRANSFUSION from Convalescent Donor

Background and Rationale →

- COVID-19 formerly positive patients may become donors of hyperimmune plasma once they have recovered and returned negative
- The potential for this treatment has been tested in previous coronavirus epidemics (specifically, SARS and MERS) in Asia
- Preliminary experiences in China, Italy and Spain in the last weeks look promising
- COVID+ ICU patients are described to recover much faster after receiving hyperimmune plasma
- Some 22 patients have been treated so far in Mantua Hospital (Lombardy) with good results and no adverse effects (personal communication)
- RCTs ongoing in the Lombardy ICU Network

SARS, severe acute respiratory syndrome; MERS, Middle East respiratory syndrome.

Bloch, EM, et al. J Clin Invest. 2020. [published online ahead of print April 7, 2020]

Slide 39 – PLASMA TRANSFUSION from Convalescent Donor

Also, in previous coronavirus epidemics, the potential for this treatment has been tested positively, with preliminary experience during this epidemic in China and in Spain, with promising results. I know, from personal communication, that

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in Mantua Hospital in South Lombardy, some 22 patients had been treated already with these strategies with very good results. All of them were ICU patients, and they recovered much faster. Usually recovery occurs in 15 to 22 days, and in these 52 patients the recovery occurred in 5 average days.

A randomized clinical trial has been started, last week, in Lombardy's ICU network. We're very excited to see whether this could be a good bullet to shoot away COVID.

Key Messages

So, as a final take-home list of messages, I want to remind you, and disease consideration is that the COVID-19 epidemic is an unprecedented challenge for all of us, and all health care systems worldwide.

As pediatricians, we need to know that children may be affected, but usually with less severity, despite the high likelihood of children being carriers of the virus, even though [they may be] asymptomatic.

Gastrointestinal symptoms and fecal-oral transmission are frequent in children and should raise concerns when taking precautions and prevention.

No vertical transmission from pregnant mother to child has been demonstrated to date.

Neonates can occasionally experience mild-to-moderate forms of the disease, but no consistent feature of neonatal disease attributed to COVID-19 has been described, so far.

Key Takeaways

- The COVID-19 epidemic is an unprecedented challenge for all health care systems worldwide.
- Pediatricians need to know that children MAY be affected, but usually with less severity.
- Children MAY be carriers of the virus.
- Gastrointestinal symptoms and fecal-oral transmission are frequent in children.
- No vertical transmission demonstrated to date.
- Neonates can occasionally experience mild-to-moderate forms of the disease.
- No specific treatment, nor vaccine exists to date.

Slide 40 – Key Takeaways

Finally, there is no specific treatment. No vaccines exist to date. We are all trying our best to manage this epidemic with the drugs we have, and we hope that we'll be through it quickly because this epidemic is affecting all of us very severely.

QUESTION & ANSWER

Editor's Note: This is a transcript of audience questions together with Dr. Manzoni's responses from the April 24, 2020 audio webcast.

What can we learn specifically from RSV-related immunology in newborn infants that may apply to COVID-19?

Dr. Manzoni: Well, I think the major point is the fact that maternal antibodies pass through the placenta and may protect the child for 2–3 months. The model, as a respiratory virus, could be similar in that COVID-19-positive pregnant mothers could transfer their antibodies to the child, to the offspring, and in doing so protecting the baby, their baby, for the first weeks.

Do you have RSV vaccine given to the mother in Europe? We have [palivizumab] immunoglobulin given to newborns only in the US?

No. An RSV vaccine does not exist yet. There have been trials exploring the efficacy and safety of the maternal RSV vaccines, with contracting and somewhat positive result. But as a matter of fact, this vaccine is not yet out in the market. And

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palivizumab can be administered only to premature infants less than 35 weeks of gestational age and with additional comorbid conditions.

Did you see any cases of vertical transmission of COVID-19 from mother to infant?

Did the staff wear N95 masks for deliveries to rule out all COVID-positive mothers? What kind of PPE protection equipment was used?

As I outlined in my presentation, so far there is no vertical transmission case confirmed, and we stick to that. We know, historically, that respiratory viruses have a very low likelihood of vertical transmission, or at the very least that they are very unlikely to produce a congenital disease. And we expect similar findings from COVID-19.

Nonetheless, when COVID-19-positive mothers deliver, we, of course, take all measures to protect the infant and ourselves from horizontal transmission from the mother by using all PPEs that are applicable in that situation. One very important point is that the most protective mask, the so-called FFP3, or FFP2, according to the OMS, should be reserved for procedures generating aerosols, and conducting very close to the patient's mouth.

With the neonate, and I would dare to say, with younger infants and children, every procedure we are taking is by definition very close to the mouth of the patient, with a very high risk that aerosol generation occurs, because the baby or an infant can cry, can spit, can vomit, can exhale. So, my recommendation that I use in my unit, and that we, as neonatologists, use in the Italian network of neonatal intensive care units, is to get to the highest level of protection in delivery room, and at all times when approaching a neonate with possible respiratory disorders, or possible uncertain status for COVID-19.

Did you bring the children in for routine vaccinations at the height of your surge?

Routine vaccination is absolutely recommendable. There is currently no recommendation either to withdraw or support more. So, as a matter of fact, the normal course of vaccinations should be emphasized as routine.

What precautions should a COVID-19-positive mother take to prevent transmission during breastfeeding?

A mask... washing and disinfecting hands, and a mask. There is no demonstrated transmission through breast milk. So, once the mother cleans her nipple with the usual systems, and once the mother uses [something to] protect her from aerosol transmission to the baby, and reinforces hygiene with disinfectant gel on her hands, I think that is done.

In theory, I outlined in my talk, fecal transmission from the diapers should be targeted. But so far, we have so very few neonates affected by COVID-19 that it's much more likely that the mother would transfer the virus to the baby, rather than the opposite.

Do you recommend using donor milk if maternal breast milk is not available?

I have no problems with donor milk because of what I was saying earlier: there is no demonstration of transmission from human milk; however, the maternal donor should not be positive for COVID-19. Of course, donor milk for premature infants is better than formula milk, provided that donor milk is handled and processed in a high-quality [manner].

Would the benefits of breastfeeding outweigh the risk of a COVID-19-positive mother breastfeeding her child?

Absolutely, yes. They outweigh [the risk] by far. I always remind everyone that the OMS and the WHO recommend breastfeeding also HIV-positive mothers in some low-income countries, where the

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protection offered by breastfeeding outweighs the risks related to not receiving human fresh milk. So, with COVID-19 even more.

Considering that fecal transmission can occur, is it recommended to wear gloves when changing a child's diaper? Or, is immediate hand washing sufficient?

I think it's okay to immediately hand wash and disinfect with alcohol-based gel.

Do neonates require resuscitation, and was the resuscitation done in the same room as the birth from COVID-19-positive mothers?

No. We have separated areas. But this is true, at least in my NICU, we have separated areas, and this is true for all situations. If the baby is requiring resuscitation, usually they're taken at least 2 to 3 meters away from the mother, so any risk of transmission is avoided. Also because the room is equipped with laminar flow, which should prevent transmission by air.

Are there any changes to basic cardiopulmonary resuscitation algorithms for children with documented or suspected COVID-19?

To my knowledge, no. To my knowledge, not yet. In Turin, my colleagues in the ICU of Turin admitted 2 children very severely affected. One of them needed intubation, but they had very severe comorbidities, and the question of these incidents remains anecdotal, I would dare to say.

What are the reasons which explain the less symptomatic children, or the neonates, in comparison to adults?

Oh, well, there are several theories. The most popular theories are, number 1, that the experience of infants and children with coronaviruses of any kind are very recent; and therefore, there could be a cross protection, thanks to having gotten into contact with other coronaviruses, more frequently than adults, and more recently than adults.

The second idea is that the ACE2 receptor is less represented and less active in infants and children. The third theory is that the course of vaccination somewhat enables a better pattern of immune defenses, thanks to the high level of activity of the immune system, which the child unavoidably has.

Can you describe a typical presentation you've seen in children presenting with COVID-19, in your experience?

Well, in my experience I saw 3 cases of COVID-19. I personally saw 3 cases, and all of them had a very uncommon presentation. The one I described [earlier in the presentation] had severe diarrhea, lasting for more than a couple of weeks. Another had myalgia and nothing else, and another had cough, but with a very mild rhinitis. I think this is very much representing the universe of presentations in children and infants with this virus.

I would dare to say that the presentation of COVID-19 in infants is absolutely no different, roughly speaking, from other respiratory or gastrointestinal viruses that we are very familiar with as pediatricians.

For children who present with GI symptoms, what is the frequency of vomiting and diarrhea?

It's very frequent. In our case series in Italy, we described 19% of children having these symptoms as the main ones. But off the record, I recognized that this proportion may be even higher, maybe up to 30%–40%. Also, I can vouch for a frequent occurrence of diarrhea during this epidemic in children who were not tested but were living in households together with COVID-19-positive patients. So, in my opinion, the burden of the GI symptoms is even higher than what we have described.

As adults are wearing masks, practicing hygiene, and social distancing, how do you suggest parents protect their newborns from leaving the

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hospital to going to doctors' visits, after delivery and from the hospital?

Well, this is a highly debated point. As a matter of fact, our government, the Italian Government, issued rules to prevent patients going to hospitals for situations that are not extremely urgent or severe. But, nicely enough, did not touch the so-called maternal-infant area. Meaning that mothers and neonates and infants in the first weeks of life can and continue to receive the same services as ever, because it is a higher risk leaving them unattended rather than acquiring the infection.

Of course, precautions need to be taken. And I mean disinfection, social distancing, wearing masks, gloves and gowns, and so on. Once we do that, I think that as pediatricians, we need to provide assistance for mothers and infants in the first weeks of life.

Can you confirm when to hold mother's milk? I think one slide said for her to pump but not feed the milk until confirmed positive or negative?

The Italian and European recommendation for COVID-19-positive and severely sick mothers is to express the milk and to give this expressed milk, fresh—not pasteurized—with a bottle, until the mother has recovered. In no cases recommendations rule out the need for mothers to give their milk. The only limitation is for severely sick mothers, and in such a case, breastfeeding is recommended but bottle feeding with maternal milk.

Can children without symptoms be significant sources of transmitting infection to adults who will have more severe symptoms?

Well, this is likely, but it's debated. In the very first stages of the epidemic there was a kind of dogma in saying that only symptomatic patients spread the virus, but later—after a few weeks from the onset of the epidemic—it has become clear, that also asymptomatic infant(s), and patient(s) as a whole,

can disseminate the virus and hence transmit the disease.

This is certainly occurring also for children. Let's say that the children after undergoing the lockdown of schools and day cares are closed, now since very early March, are less likely to acquire this virus, unless in a familial setting. So, now it's much more likely that children get the virus from adults, who somehow continue to work, or continue to see other adults, despite the lockdown, rather than the opposite situation.

Are you having COVID-19-positive moms, clean, or sterilize their breast prior to breastfeeding?

Clean, clean.

Are you empirically giving anticoagulants to hospitalized pediatric patients?

I didn't, but it's recommended for those who evolve very severely. One of my 3 patients, it had been suggested by the infectious disease specialist, be given heparin. But we didn't do [that] because this child had a very good course, with fast improvement. But in settings where sicker children have been admitted, heparin has been used. I'm personally very, very convinced that coagulopathy, and thrombophilic changes of this disorder, is emerging actually as one of the main features, ultimately determining the severity of the disease.

Editor's Note: This is a transcript of audience questions together with Dr. Manzoni's responses from the April 30, 2020 audio webcast.

Would the benefits of breastfeeding outweigh the risks of a COVID-19-positive mother, breastfeeding her child?

Yes, it is for sure because breastfeeding is providing antibodies against COVID-19, and the only way for the baby to get protected is to receive some antibodies for pathogens it's meeting for the first time.

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This model occurs also with other viral infections. Let's think of HIV in a specific setting where the benefits of breastfeeding from an HIV-positive mother outweigh the risk of acquiring HIV in babies, who have a very high risk of getting sick, extremely sick at the risk of death, if they don't receive antibodies.

Can expressed milk from COVID-positive mothers be held in the same refrigerator as expressed milk from COVID-negative mothers?

Well in theory, yes. Provided that you secure all the necessary hygiene measures and handle with safety and ultimate hygiene. Nonetheless, as a practical approach, we store these samples in different shelves of the same refrigerator or, if possible, in different refrigerators.

What isolation procedures do you use for infants admitted to the NICU from COVID-suspected or positive mothers?

We use the same isolation procedures that we implement when a transmittable disease is suspected or demonstrated with a newborn. Let's think of RSV, let's think of HIV, as well. So, we have isolation rooms with dedicated staff, nursing and doctor staff looking after the patient until the results of the tests are available, and they can rule out or confirm the suspected [case].

If Mom is COVID positive and symptomatic, should we test the infant?

Surely yes, of course. This is the worst possible situation in which we are absolutely compelled to test the baby, while keeping the baby separate from the mother and isolated from the other NICU patients until the test results are available.

Can you comment on whether pregnant COVID-positive mothers in China and Italy were tested, or only if they had symptoms or other risk factors?

Yes, certainly. This policy was implemented as the evidence was arising. In these epidemics we can understand that probably not the best strategies were implemented from the beginning, because the full awareness and the availability of the PPEs and equipment to cohort and isolate were not yet available from the very first minute.

As a matter of fact, the first recommendations in Italy and China were to test only positive patients or patients with proven contacts with other positive individuals. As such, we performed probably less [tests] than needed, and we obtained fewer positive [cases] than the number that was probably real.

One case in *The New England Journal of Medicine* reported intubation to limit aerosolization. In order to limit aerosolization for those with respiratory failure, do you recommend intubation with cuffed inflated endotracheal tube?

Yes and no. Should the intubation be absolutely unavoidable, yes, this is the way. In addition, provide the equipment with the viral filters and the respirator. But more generally speaking, I'm skeptical about the approach of intubating infants who do not need to be intubated in order to limit aerosolization.

I think that intubation is a procedure that needs to be reserved only for patients who actually need it. If we need to reduce aerosolization procedures, we'd better look at alternative strategies and the precautions that can be implemented without having the child undergo an invasive measure.

We had a 31-week gestational age infant who tested positive for COVID-19. Mom was positive prior to delivery. The staff at delivery was in full PPE. The infant was removed immediately after birth and placed in isolation. What would the route of transmission be in this situation?

Well, this is a very interesting case. I wonder which kind of delivery occurred in that situation. Should it

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be a spontaneous delivery, there is room for a possibility that the baby became positive during the delivery. Let's keep in mind that the presence of viral copies have been reported in the amniotic fluid, as well. So, these could be the 2 possible ways for him to become positive, in my opinion.

To minimize fecal oral transmission, are there any precautions with diapers we should be doing additionally to reduce exposure?

I don't see any additional major [actions] other than strict and repeated hygiene measures and the use of barriers to protect the baby's caregiver.

Is there any evidence of birth defects associated with COVID-19 positive mother?

No. And I would say, not yet. I'm confident that this will not occur, because we know from other respiratory viruses that this risk is very, very uncommon.

How long after delivery do you recommend newborns are bathed?

I don't see any specific recommendation here. I think that this can be done as per standard of care in each setting.

Given the data showing minimal risk for neonates from COVID-19, what is the AAP's rationale for separating newborns from mothers who test positive?

Well, I'm a little uncomfortable with this question because actually I don't see a strong rationale. I'm very much supportive of the Italian and European approach. Our approach is aiming at saving and endorsing breastfeeding whenever possible. And I think, just as I was telling you earlier, I think that the benefits of breastfeeding in this situation very much outweigh the possible risks.

Can you speculate as to the main reasons why infants and children are largely protected from severe COVID disease?

I would say, I can list 3 or 4 popular areas, that are usually addressed in order, to explain that. The first is that ultimately this virus is a coronavirus and coronaviruses are not unknown to infants and children, because they have already been in contact with [the virus], probably more frequently and more recently than adults.

Another possible explanation is that usually ACE2 receptors that are critical for adhesion of the virus are less present in infants and children. Another idea is that the routine schedules of vaccination may be providing an enhanced immune response to the infant that can defend them against pathogens of other kinds.

Is the 17-week duration of protection—provided by maternal antibodies during gestation—for full-term infants or both full-term and early preterm infants?

The 17-week duration is based on the average half-life of the antibodies that pass through the placenta. The point is how many antibodies did pass actually, because once they pass their half-life, as an average, should be the same both in term and in preterm infants. The problem for preterm infants is that they had little time for their mothers to have their antibodies pass through the placenta.

What are considered aerosol-generating procedures in pediatrics and neonates?

I think that in this view, we'll need, as pediatricians, to be very pragmatic and flexible. I would dare to say, and this is my approach in my unit, that every time we approach a child or an infant and check him through a physical exam, we are at risk of undergoing an aerosol-generating procedure with the baby because if we explore his mouth or his tongue or his nose, we are unavoidably very close to his face and exposed to the risk that the baby is crying, spitting, or swallowing, or coughing, and therefore these are procedures that generate

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aerosols. As such, they need to be included in the procedures that require protection.

How many days into the viral process do you see the skin lesion issues present?

Several days, and not the very first day. Usually, the course of the disease is around 2–3 weeks. At some point these skin lesions appear, but usually not at the very beginning.

Were all infants, neonates with positive COVID-19 born to mothers who were also positive?

Almost all of them, but not all because, if I remember, at least a couple of cases reported that the mother was not positive. But we have to keep in mind that the sensitivity of the swab is around 70%, so a false negative may be there.

Have you seen the atypical Kawasaki[like] disease in Italy now described by several pediatric centers in the UK and the USA?

Yes. I didn't see any actually personally, but I am in contact with other pediatricians in Lombardy having described an increase in reports of such Kawasaki-like syndromes and features, in conjunction with the epidemic. So, the point is they are also here.

Are you recommending any treatments for finger and toe symptoms? Do patients have other symptoms of COVID with these findings?

I don't recommend any specific treatment, only symptomatic ones. And yes, some of them, according to the records, had other symptoms of COVID, such as fever or myalgia and influenza-like symptoms.

From the US: I had a patient who lived with her family member, who tested positive a week prior to her delivery. We tested the new mother and secluded her with the baby after the birth of her child in a room down the hallway. One nurse was assigned to her specifically and the new mother was asymptomatic. She was not in

a reverse-isolation room. Was this the best practice in your eyes?

I think that roughly speaking, yes, in a situation like that, we assign the mother and the child to an isolation room. We allow rooming-in of the child, and we have a limited number of rotating nurses and midwives assisting them.

Do the team members admitting a premature neonate born to a COVID-positive mother, need to don full PPE, including N95 respirator, if the admission takes place in a standalone resuscitation admission room?

Yes. The team needs to be protected with PPE, such as the FFP2, such as masks, gowns and gloves. Resuscitation and admission rooms need to be prepared specifically for these activities.

Other than contact precautions, have you seen any preventative therapies used that are supported? For example, taking certain dietary supplements or probiotics? If so, how much and what strains?

No. I love probiotics, as probably many of you know, but in this context, no probiotics prove to be effective, so far. The only nutritional supplement that has been consistently prescribed is vitamin D. Vitamin D is supposed to have good antiviral and anti-inflammatory activity. So, as a supportive treatment, this can be taken.

Do you allow skin-to-skin for neonates with COVID-positive mothers?

No. Skin-to-skin is avoided in this context if mothers are positive.

Are there specific nutrition-related interventions for the NICU pediatric population with COVID?

No. Unless the mother is too sick and too severely affected not to be able to breastfeed, or not to be able to express her milk. If the mother is able, at the very least, to express her milk, we give the

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expressed milk by bottle. If she is so sick that she's not even able to do that, we give formula.

What is the median duration of fecal viral [shedding] in children?

We don't know exactly because there is still uncertainty about the data. We suppose it's many, many days, but we still don't know.

What do we know about immunity after COVID-19 with symptoms or asymptomatic?

We don't know anything so far because the experience for us is still too limited to allow us to have a cohort being tracked for a good number of months. I hope I will be able to answer this question in the next month.

When testing neonates for COVID-19, is it more beneficial to send a stool sample rather than a respiratory sample?

I think respiratory sample, yes. Respiratory samples would be better.

What would be the ideal test in a patient with skin symptoms: PCR or serology?

PCR, for sure. Serology, so far is not helpful. PCR confirms that the virus is there, at the moment, and is the most important one, rather than seeing whether the baby has antibodies.

Do you recommend universal testing for all patients in labor and delivery?

I would like very much to have this as a possibility, but unfortunately this goes, at the moment, beyond our possibilities, not only in Italy but everywhere.

If you have a COVID-positive mother and infant in the NICU who were tested and negative on admission, is there a need to repeat the test at any point?

This is a difficult question. Honestly, I don't have a consistent position on that. I would consider this, but honestly, I can't say anything.

How long after exposure to COVID will a nasopharyngeal test report positive?

This is variable. We have cases that remain positive for weeks and weeks, confirming positivity to repeat testing week after week. So, it's unpredictable to some extent.

At what point do you let a COVID-positive mom visit a premature baby in the NICU? And what about the father?

This is a very good and important question. We test mothers, but fathers should have a role in that, just like in the child's life, but also in this moment they should have a role. Different policies on admitting fathers both in the delivery room and in the ward, are followed in this moment, in different settings and in different countries. We recommend fathers use the PPEs and to take all precautions needed to minimize the risk for cross-transmission.

Do you have an opinion about using Ibuprofen for fever in COVID-positive patients?

No, I don't, but I prefer to use paracetamol at the moment. This is the most followed approach, at least in Italy. But so far we don't have any data stating that Ibuprofen may be dangerous.

Do you recommend a specific dose of vitamin D for supportive preventative care?

Yes, 800 international units per day.

Abbreviations

AAP	American Academy of Pediatrics	PCR	polymerase chain reaction
ACE2	Angiotensin-converting enzyme 2	PPEs	personal protective equipment

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FFP	Filtering Face Piece	RNA	ribonucleic acid
ICU	Intensive Care Unit	RSV	respiratory syncytial virus
NICU	Neonatal Intensive Care Unit	SIN	Società Italiana di Neonatologia
		UENPS	Union of European Neonatal & Perinatal Societies

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