Delta Variant in Children: what are the risks?

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Discussion will cover

- COVID-19 case presentations and management - Adult versus Pediatric care protocols
- General overview of data in terms of incidence, hospitalizations, severity of illness
- Common myths debunked
- Is in-person school safe
- Vaccine efficacy and safety profile in the pediatric population

The Pandemic from Two Sides

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- Managing Acute Hypoxemic Respiratory Failure in Adults vs Kids with COVID-19
  - HFNC considerations
  - Timing of intubation
  - Proning and ideal PEEP strategies
  - When nothing is working: Rescue therapies
  - MISC - challenges in identification and management

Adults: ARDS, but make it COVID

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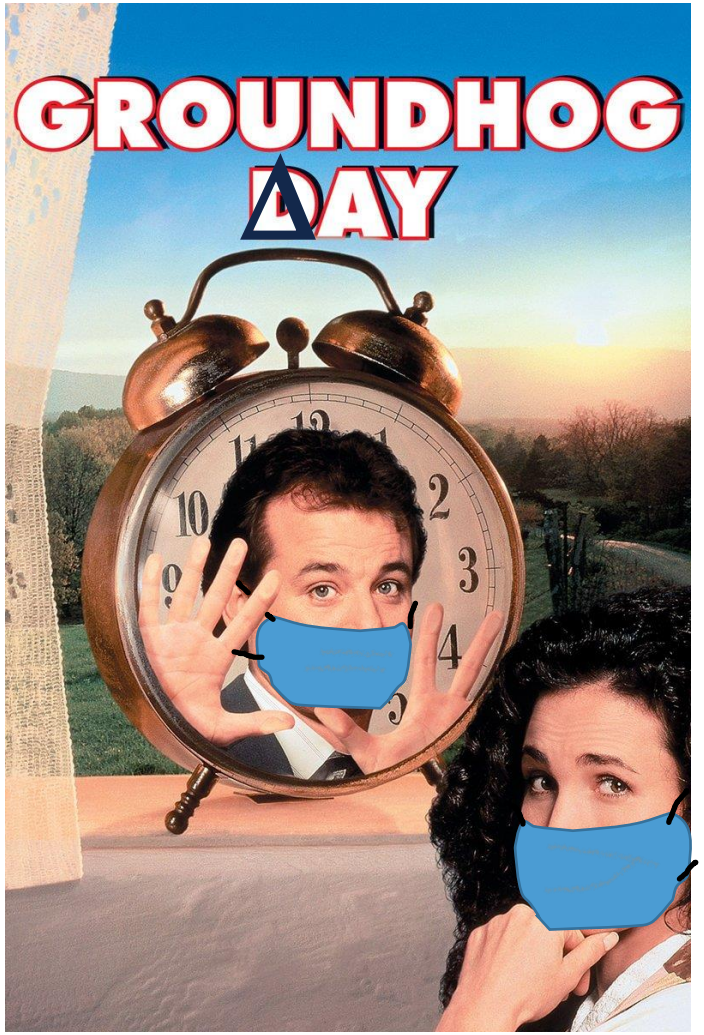
From emerging entity to protocolized practices that continue to evolve

- Experiences of other providers, evidence-scarce zone
- Sticking with the basics of ARDS
- Revisiting new and emerging data
- Continuing to play critical care defense
- Groundhog day with Delta Variant



Pre-Intubation management

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- Self-proning
- Role for HFNC and NIPPV
- Timing of Intubation:

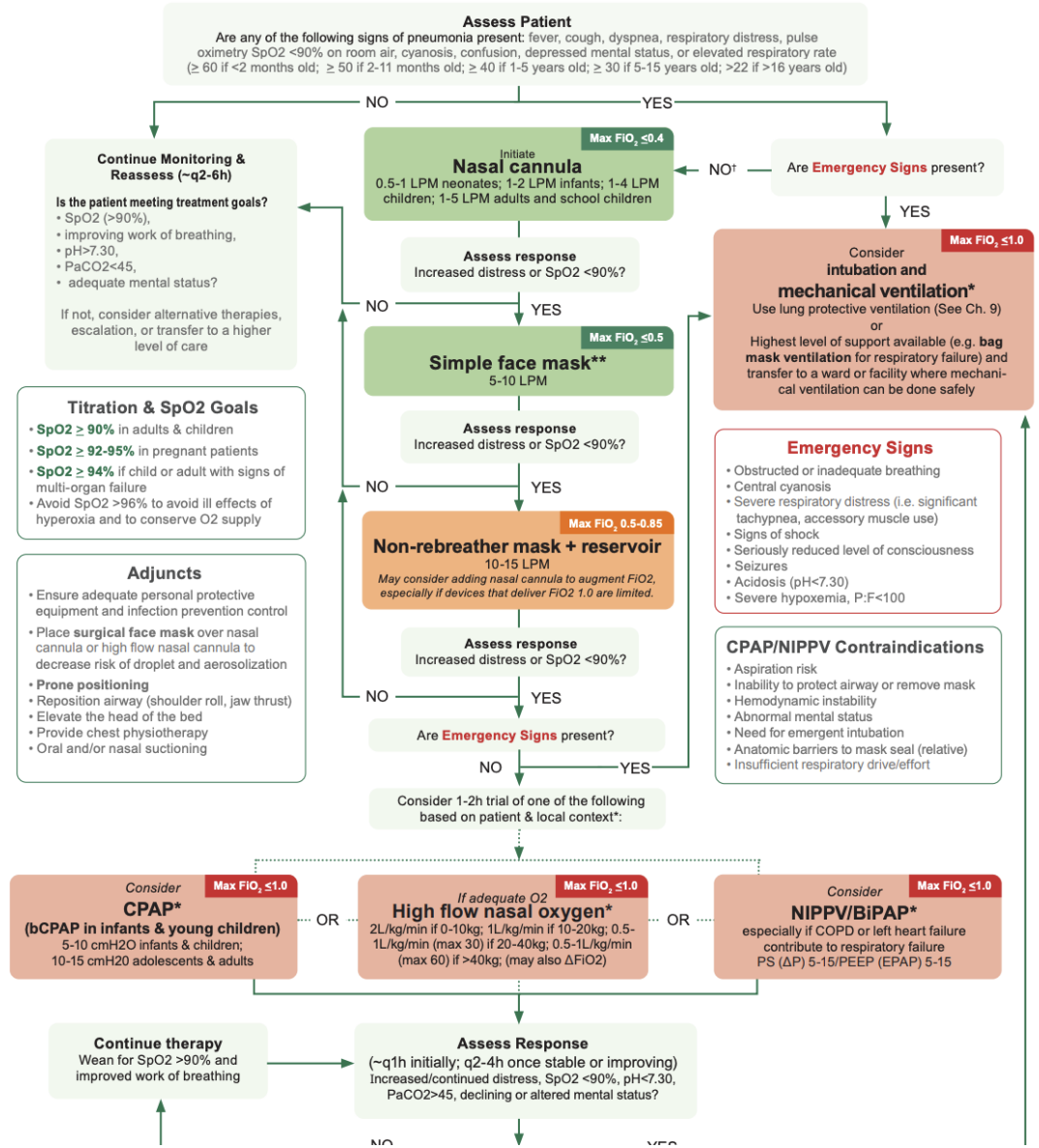
Intubate Early!

- Aerosolization with NIPPV and PPE shortages
- Transfer safety
- Prolonged periods of NIPPV, P-SILI

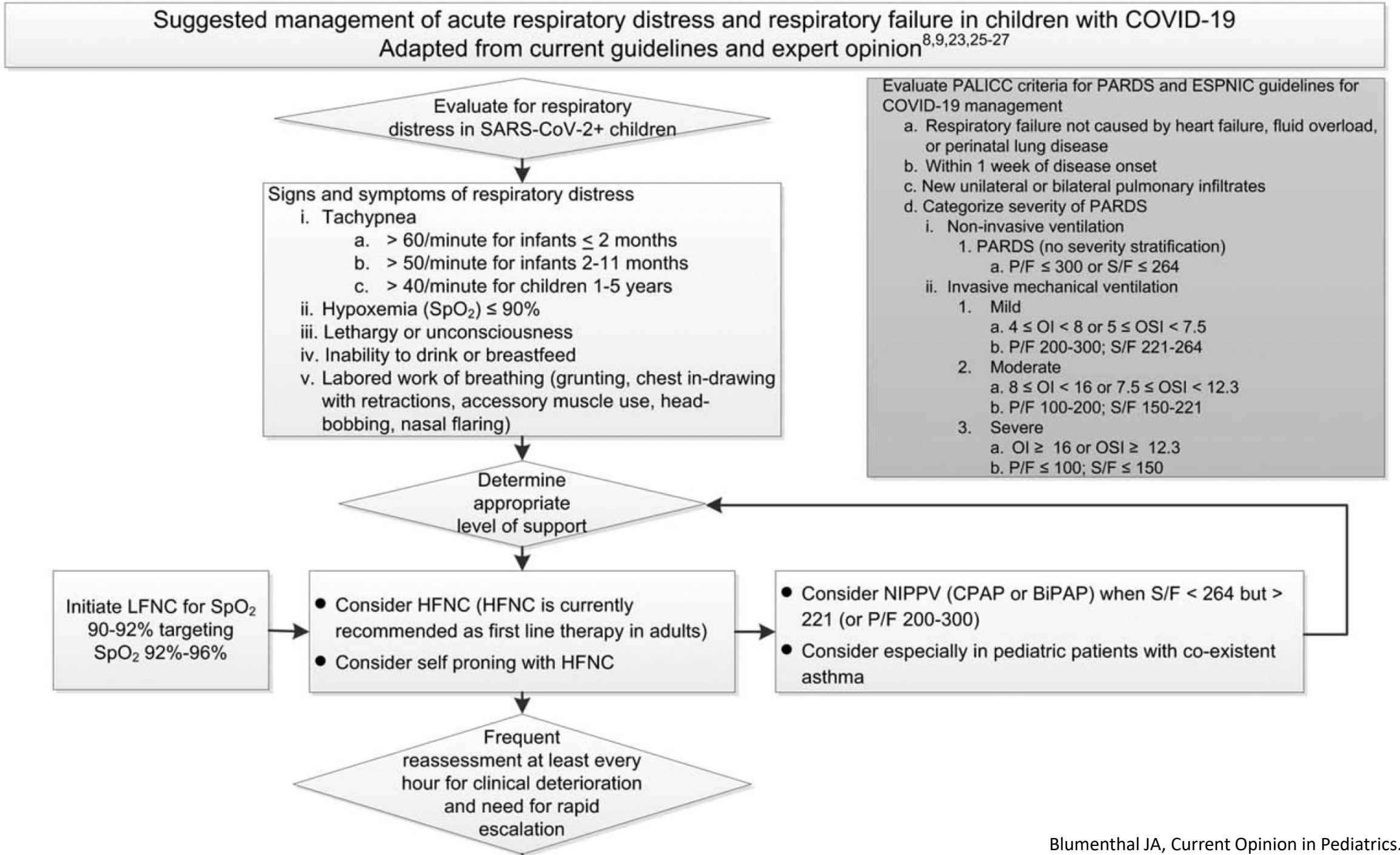
Delay intubation!

- Concerns about ventilator shortages
- Exposures to high amounts of sedation, paralytics
- Complications on the ventilator

Oxygen therapy escalation algorithm



USAID FROM THE AMERICAN PEOPLE · STAR · WFSA World Federation of Societies of Anaesthesiologists · OC2 Open Critical Care.org · UCSF Center for Health Equity in Surgery & Anesthesia chesa.ucsf.edu



Blumenthal JA, Current Opinion in Pediatrics. 2021

Delayed Intubation: how to decide

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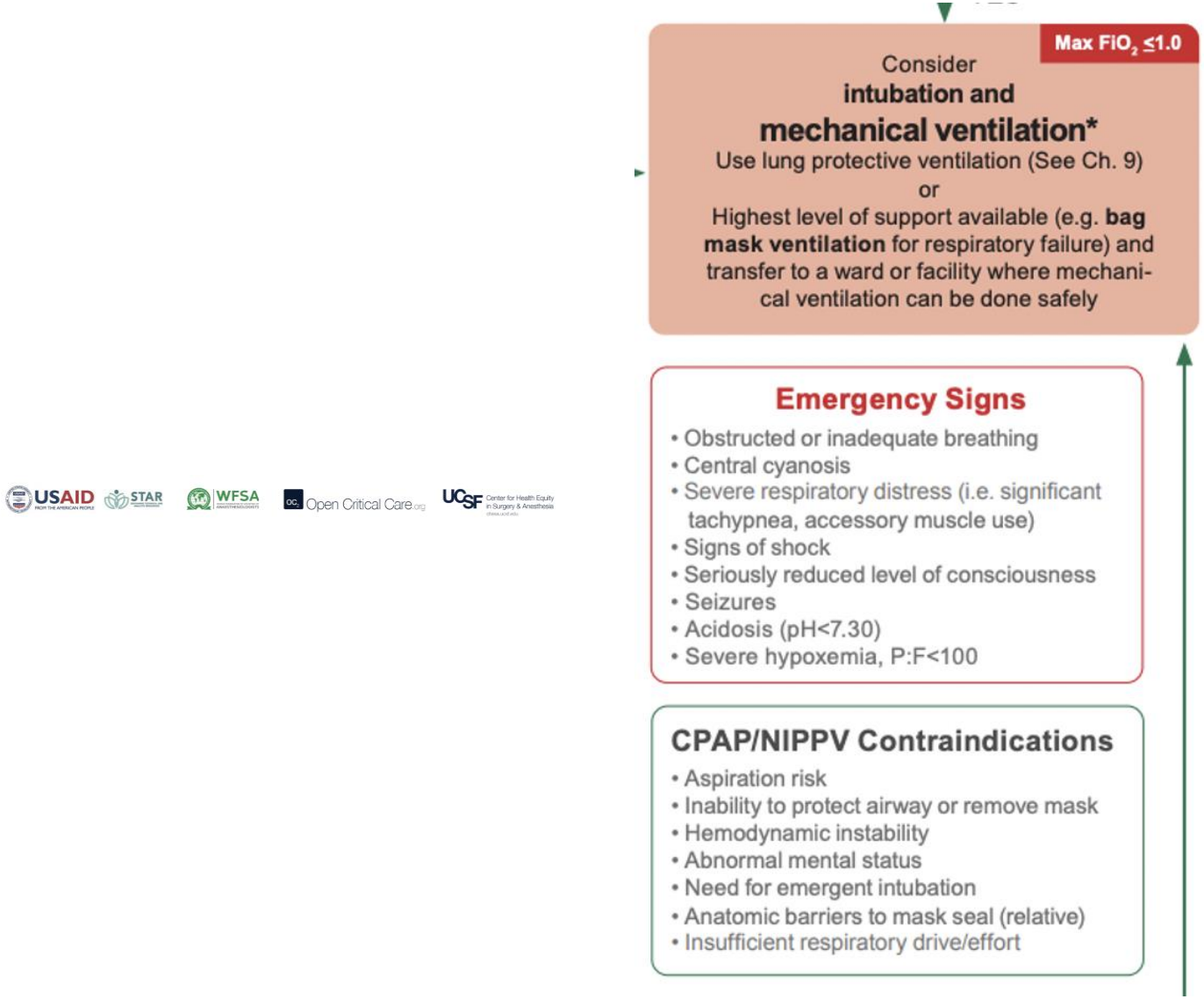
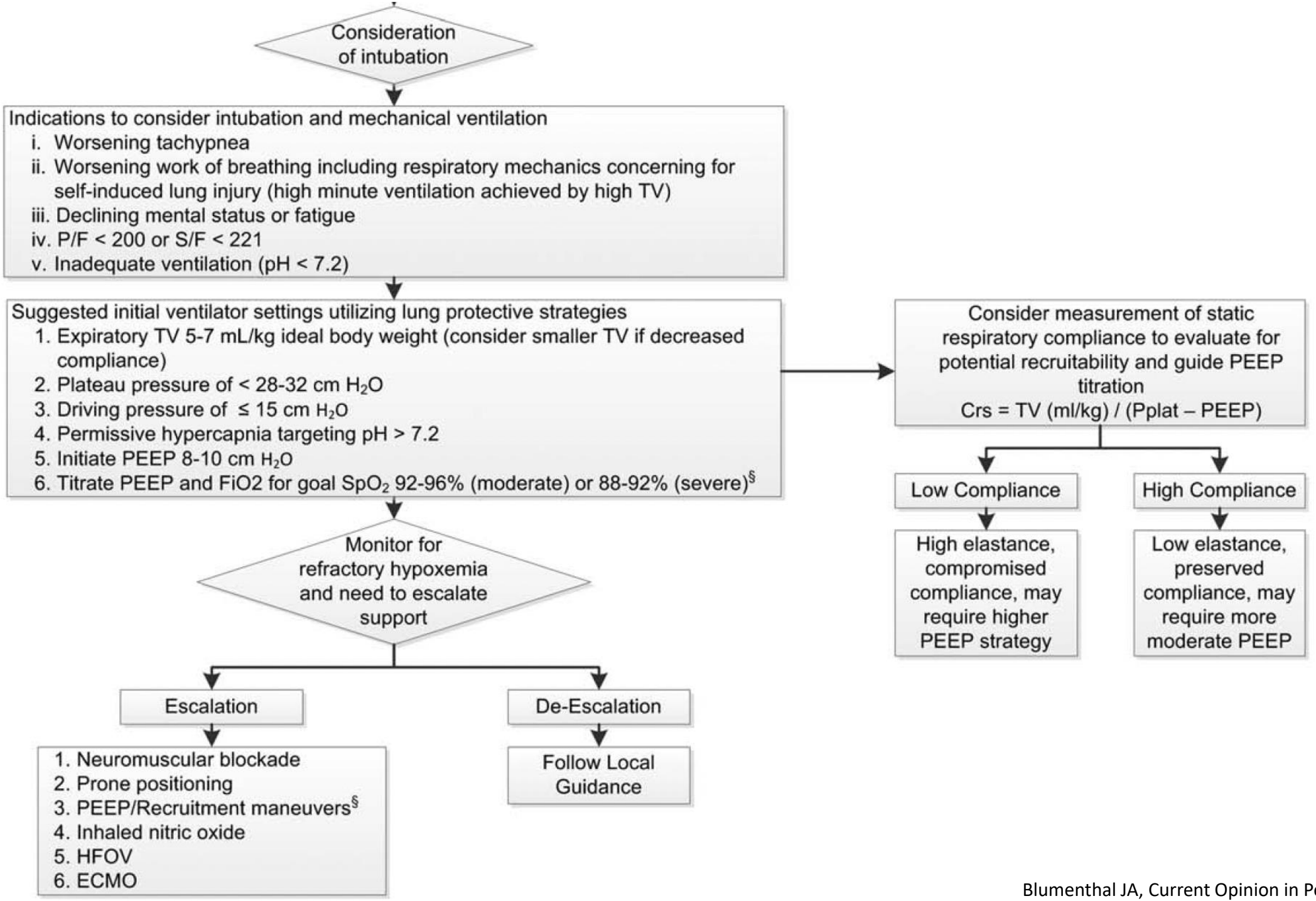
Pre-Intubation management: Intubate… sometime in between?

- Concerns about prolonged periods of NIPPV at high settings
  - P-SILI (patient self-inflicted lung injury)
- Challenging discussion with patients and family members
- If tolerating NIPPV comfortably: **reassuring**
- If can take breaks on HFNC for periods of time: **reassuring**

Sometimes – you are forced to intubate





Blumenthal JA, Current Opinion in Pediatrics. 2021

ARDS: Back to Basics in Adults

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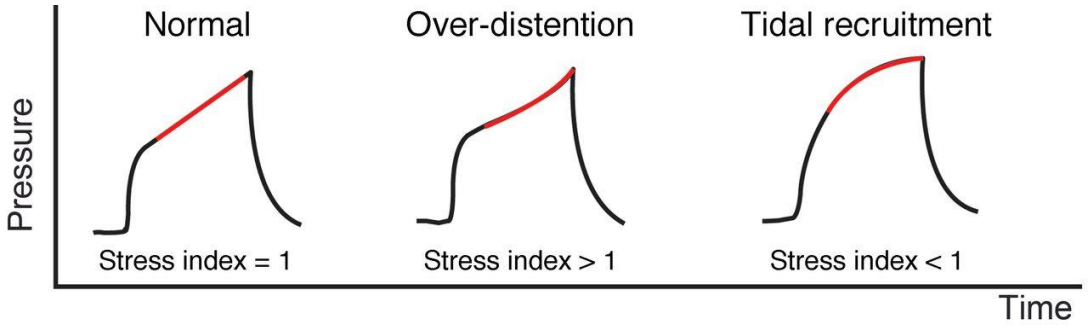
- Lung protective ventilation as in Pediatric ARDS management
  - PEEP and Driving pressure (ΔP)
    - ARDSNet Tables
    - Driving pressure to determine ideal PEEP
    - Esophageal balloon
    - Stress Index



Lower PEEP/higher FiO2

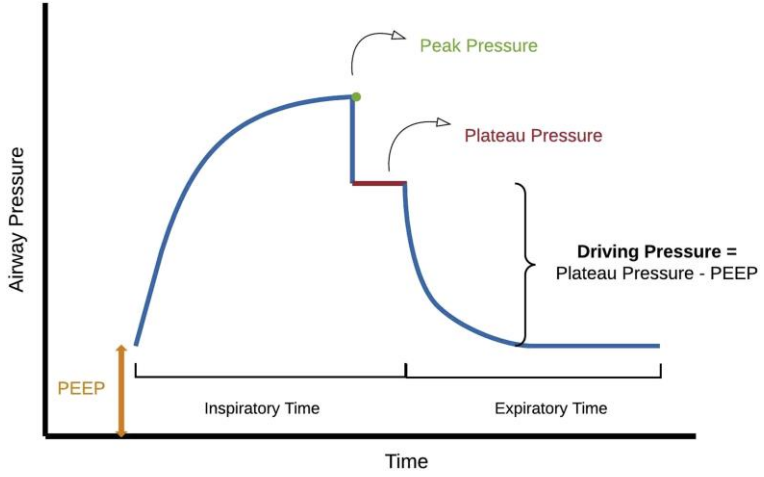
FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12

FiO_2	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	14	14	14	16	18	18-24

Higher PEEP/lower FiO2

FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5
PEEP	5	8	10	12	14	14	16	16

FiO_2	0.5	0.5-0.8	0.8	0.9	1.0	1.0
PEEP	18	20	22	22	22	24



Respiratory System Compliance = Tidal Volume / (Plateau Pressure - PEEP)

Gattinoni L, et al. Intensive Care Med (2020)
Amato MB, et al. New Engl J Med (2015)

ARDS: Back to Basics in Adults

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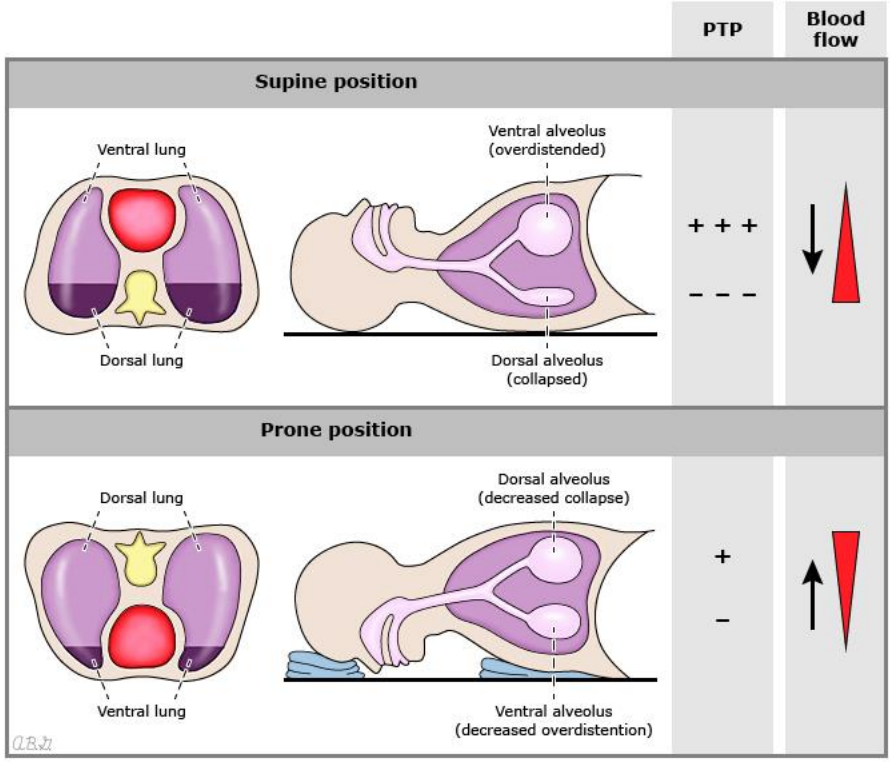
- Prone Positioning
  - P:F <150 if ventilated
  - goal of prone positioning 16h/day
  - work down ventilator settings to low/safe as possible
  - Technical considerations if team not familiar with procedure and care
  - Challenge of being unable to safely supinate patients
- Sedation, Paralytics



Carsetti A, et al. Crit Care (2020)
Menk M, et al. Intensive Care Med (2020)

What if nothing is working

- Adult vs pediatric thoughts on
  - Tracheostomy
  - iNO, inhaled Epo
  - HFOV
  - ECMO

Pediatric ECMO

Table 2. Relative Contraindications, Conditions With Poor Prognosis (*ELSO Red Book*, 5th Edition, Chapter 19)

Conditions rendering patient unlikely to benefit from ECLS:
Large intracranial bleed with mass effect or need for neurosurgical intervention
Hypoxic cardiac arrest without adequate CPR
Irreversible underlying cardiac or lung pathology (and not a transplant candidate)
Pulmonary hypertension and chronic lung disease
Chronic multiorgan dysfunction
Incurable malignancy
Allogenic bone marrow recipients with pulmonary infiltrates
Conditions with worse prognosis in respiratory ECLS:
Hepatic or renal failure
Pertussis infection in infants
Fungal pneumonia
Immunodeficiency
Relative contraindications:
Vessel anomalies or having previously been clipped or ligated for prior ECMO
Localized site infection

CPR, cardiopulmonary resuscitation; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation.

Maratta C. ASAIO Journal (ELSO). 2020

More than One Road to ECMO

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- 5 year old previously healthy girl presented to outside ED with 5 days of fever, abdominal pain, vomiting, sore throat, new rash.
  - Hypotensive, tachycardic, tachypneic on exam, pink maculopapular over trunk
  - CXR with bilateral hazy opacities
  - COVID-19 nasal swab PCR positive
  - Vasopressor support initiated and transferred to UNC
  - O2 support initiated in route for hypoxemia

More than One Road to ECMO

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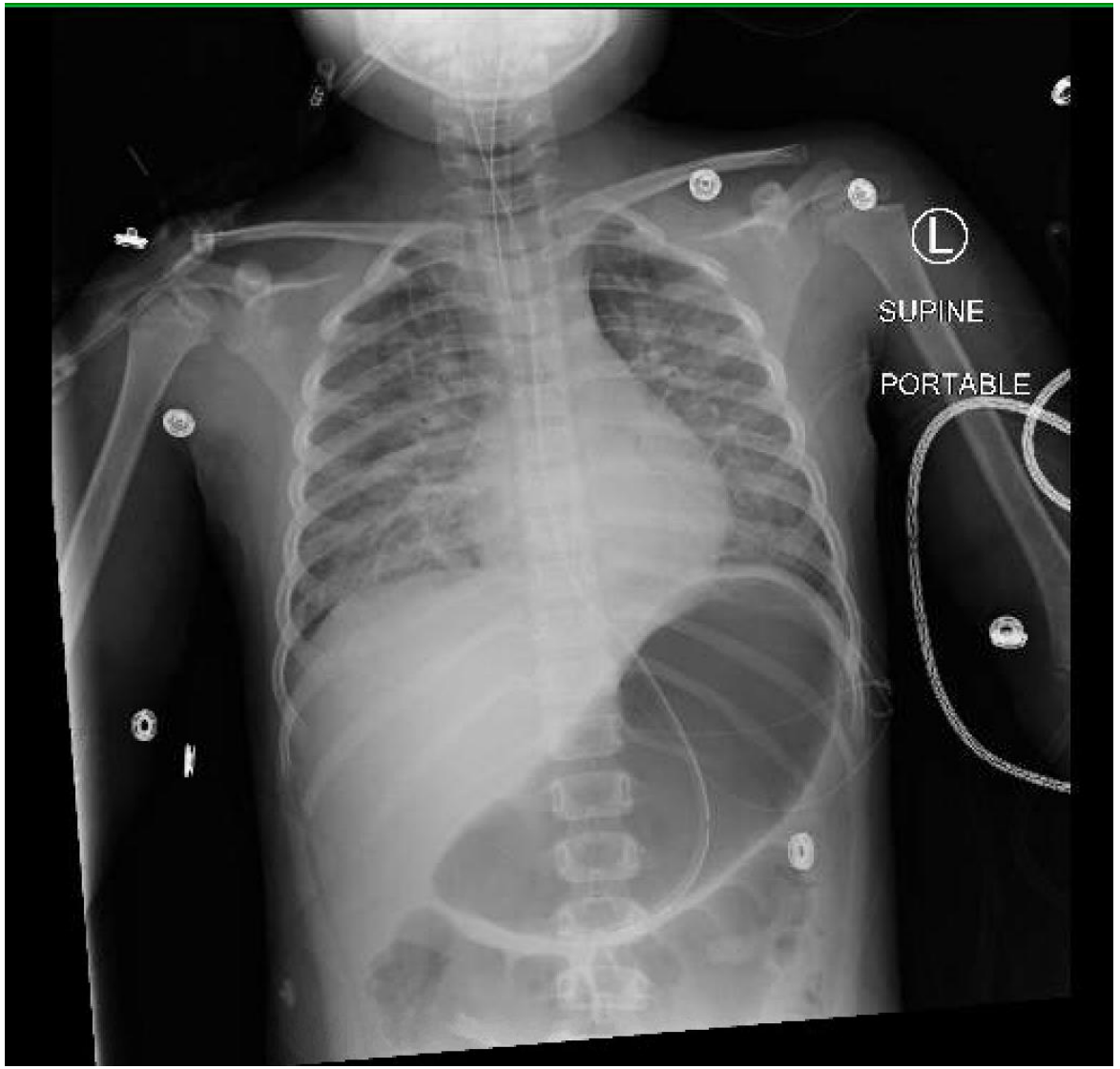
Additional laboratory data

- WBC 14.7, 3+ left shift
- ESR 32, CRP 179
- Pro-BNP 10,400
- D-dimer 1209
- Troponin 0.599
- Albumin 2.5, AST 94, ALT 86
- PT 15.4, aPTT 40.4



Multisystem Inflammatory Syndrome in Children (MIS-C)

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- Age <21
- Fever
- Lab evidence of inflammation (elevated ESR, CRP, LDH, ferritin, fibrinogen, procalcitonin, IL-6, elevated neutrophils, low lymphocytes, low albumin)
- Clinically severe illness requiring hospitalization
- Multisystem organ involvement

AND

- No alternative plausible diagnosis (may fulfill partial criteria for Kawasaki)
- Positive for current or recent SARS-CoV-2 infection, or exposure to suspected or confirmed COVID-19 case within 4 weeks prior to symptom onset

Management with immunosuppression, and supportive care for organ systems involved

https://www.cdc.gov/mis/hcp/index.html
Henderson LA et al. Arthritis Rheumatol (2020) https://onlinelibrary.wiley.com/doi/10.1002/art.41616

Severe Acute COVID-19 vs. MISC

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- Age can be clue
- Cardiac involvement (+/- respiratory involvement) → **think MISC**
- Mucocutaneous involvement → **think MISC**
- Patients with more comorbidities → **think severe acute COVID-19**
- Patients with neuro, GI, hematological involvement WITHOUT cardiac involvement or mucocutaneous involvement → **think severe acute COVID-19**

Feldstein LR et al. JAMA (2021)

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- Common myths debunked
- Is in-person school safe
- Vaccine efficacy and safety profile in the pediatric population

Multisystem inflammatory syndrome in children (MIS-C)

Last updated with cases reported to CDC on or before August 27, 2021*

TOTAL MIS-C PATIENTS MEETING CASE DEFINITION*	TOTAL MIS-C DEATHS MEETING CASE DEFINITION
4,661	41

*Additional patients are under investigation. After review of additional clinical data, patients may be excluded if there are alternative diagnoses that explained their illness.

Summary

- The median age of patients with MIS-C was 9 years. Half of children with MIS-C were between the ages of 5 and 13 years.
- 61% of the reported patients with race/ethnicity information available occurred in children who are Hispanic/Latino (1,316 patients) or Black, Non-Hispanic (1,362 patients).
- 99% of patients had a positive test result for SARS CoV-2, the virus that causes COVID-19. The remaining 1% of patients had contact with someone with COVID-19.
- 60% of reported patients were male.

https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance

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Vaccines approved in the US

And pediatric ongoing trials

Vaccine	Approval age limit	Ongoing trials	Hopeful timeline for further approval
Moderna	18	01/2021 – EUA requested (12-17 yo)	For 12-17 likely soon
Pfizer	12	03/2021 worldwide phase 1/2/3 trials began in 6m-2y, 3y-5y, 5y-11y	EUA request likely towards end of Sept/early Oct and approval likely a few weeks later (towards the end of October for 5 y -11 y)
Johnson and Johnson	18	Underway	Unsure

Pfizer trial details (& why is it taking so long)

- March 24-25 – started enrollment
- 2 doses given at 21 days apart *trialed 3 dose ranges in 3 age ranges
  - Puts us at late April to May to realistically be giving second doses to anyone
- FDA asked for 4-6 months of safety data (adverse event data) before consideration
  - Adult approval was given with 2 months of safety data
- September 27th - Date of final data collection for primary outcome measures
- September 28th - Data submitted to the FDA for EUA
- FDA to scrutinize data

Pfizer data - released September 20 to the public

2,268 children 5-10 y who received a 10microgram dose in a two-dose series

- Neutralizing antibody geometric mean titer was 1,197 – a strong immune response (1 mo post 2nd dose) though unknown protection level
  - The GMT in the 16-25 yo range was 1,146 for comparison when given a 30microgram dose for 2 doses

- Side effect profile seems similar to 16-25 yo age group (control group)

Moderna trial details (adolescents)

Overview of Moderna COVID-19 Vaccine (mRNA-1273) in adolescents (P203)

Overview

- Phase 2/3, randomized, observer-blind, placebo-controlled study to evaluate the safety and effectiveness of mRNA-1273 in **healthy adolescents 12 to <18 years of age**

Data updates

- Primary endpoint of non-inferior immunogenicity versus the Phase 3 study adult comparator group was met
- No cases of COVID-19 observed after two doses of vaccine using the primary case definition, consistent with a vaccine efficacy of 100%
- Safety and tolerability generally consistent with Phase 3 COVE study in adults

Regulatory Updates

- Authorized for adolescents in United Kingdom, European Union, Japan, Canada, Switzerland, Taiwan, Saudi Arabia, Australia and the Philippines
- Data submitted in United States and other countries

TeenCove STUDY™

Trial Design

100 µg mRNA-1273
N=2,486

Placebo
N=1,240

Slide 7

Ali, Keshaf, et al. "Evaluation of mRNA-1273 SARS-CoV-2 Vaccine in Adolescents," *NEJM* (August 2021), https://doi.org/10.1056/NEJMoa2109522

moderna

Moderna trial details (children)

Overview of Moderna COVID-19 Vaccine (mRNA-1273) in children (P204)

Overview

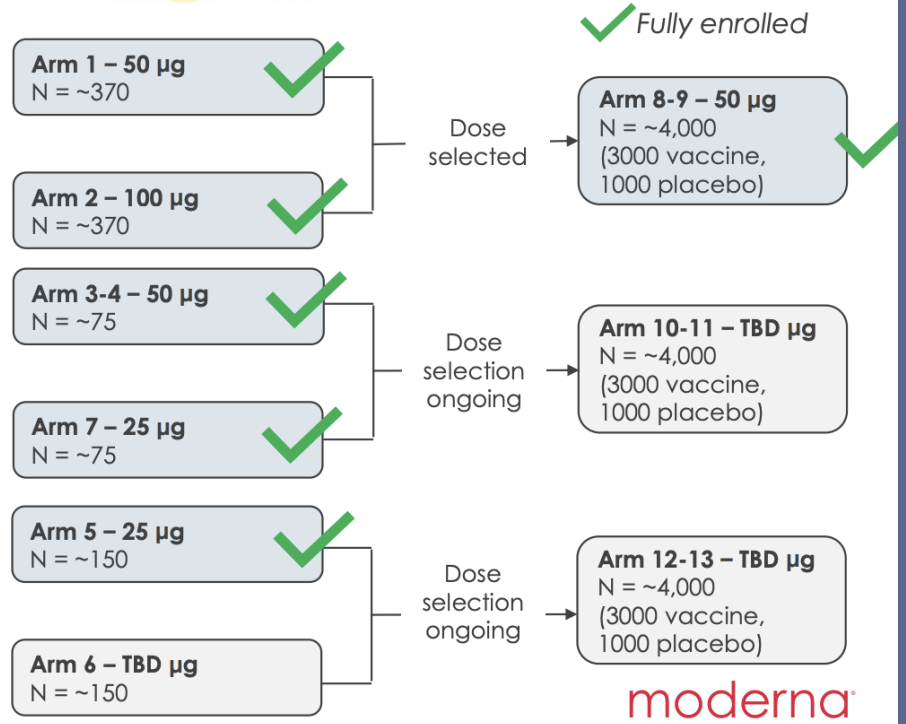
- Phase 2/3 expansion study to evaluate the safety and effective of mRNA-1273 in children aged 6 months to less than 12 years ongoing
  - 2-part, open-label, dose-escalation, age de-escalation, randomized, observer-blind, placebo-controlled

Updates

- We selected a dose and expanded enrollment in the 6 years to less than 12 years old cohort, and Part 2 of the study (Arms 8 & 9) is fully enrolled (N=4,000)
- Dose selection studies are still underway for 2 to <6 years old and 6 months to <2 years

KidCove STUDY

Trial Design



moderna

Slide 8

Side effects of COVID vaccines

Side effects after getting a COVID-19 vaccine are **normal signs** that a person's body is building immunity

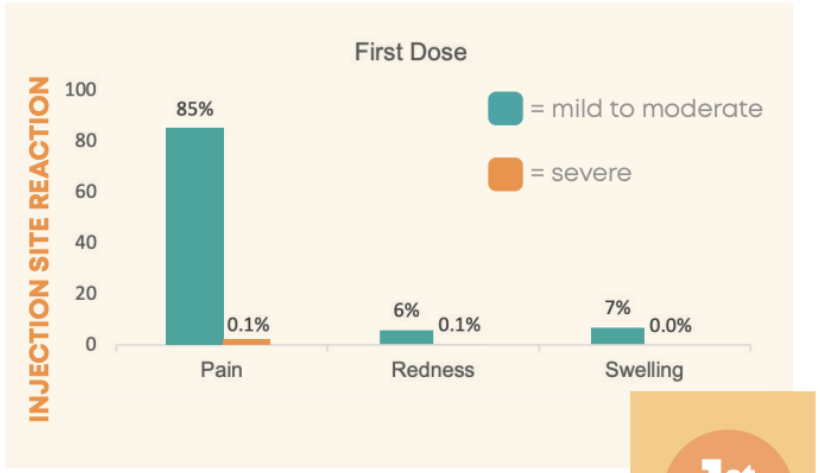
- **The most common side effects from the COVID vaccines are**
  Fatigue
  Redness/swelling/soreness at site of injection
  Headache
  Muscle aches
  Fever or Chills

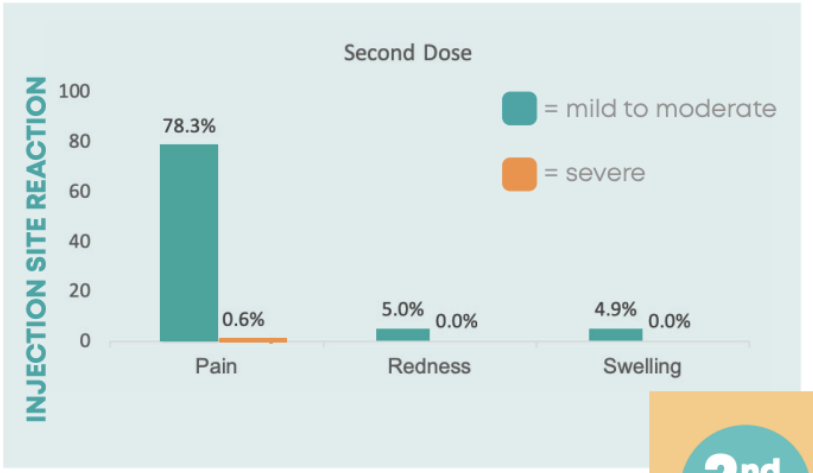
- They occur usually within the first week, most common at 1-2 days post receipt

SE in 12-15 yos (Pfizer data)
Injection site pain 91%
Fatigue 77.5%
Chills 49%
Muscle pain 42%
Fever 24%

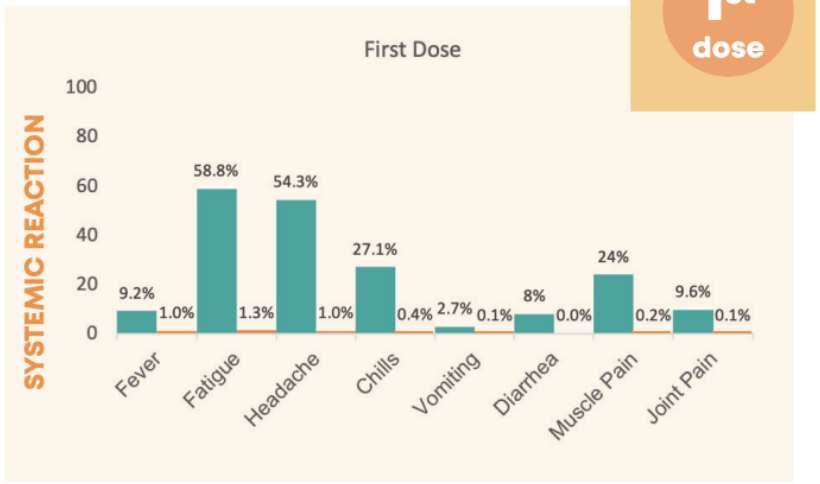
WHAT TO EXPECT:

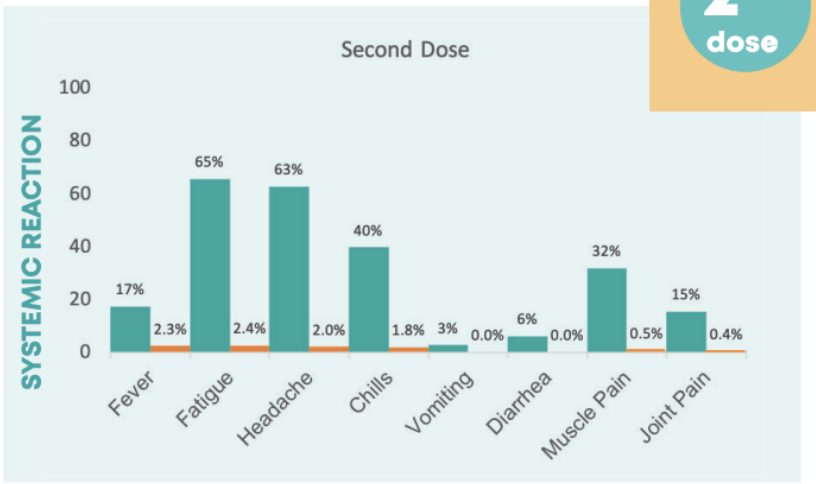
PFIZER COVID-19 VACCINE SIDE EFFECTS, AGES 12-15





1st dose





2nd dose

Frequency of Solicited Local and Systemic Reactions Within 7 Days After Each Vaccination, as Percentage of Phase 2/3 Trial Participants

Uncommon side effects

Rare – but serious

- Acute Allergic reactions including anaphylaxis occurs in 2-5 people per million in the US
- Guillain Barre Syndrome –
  - associated with J&J vaccine
  - 195 cases after 14.5 million doses given
  - Usually, 2 weeks post dose
  - Mostly in men over 50 y
- Thrombosis with Thrombocytopenia Syndrome
  - Associated with J&J (2 cases following 362 million doses of Moderna – not above baseline population rate)
  - 46 cases after 14.5 million doses given
  - Almost exclusively in women under 50 y
- Myocarditis/Pericarditis

CDC.Gov

Myocarditis and Pericarditis following COVID vaccine

- Associated with mRNA vaccines
- Associated with male adolescents and young adults
- Usually within a few days of the second dose (myocarditis) or further from second dose (pericarditis)
- Almost all patients resolved completely

Symptoms/signs include –

Chest pain
Shortness of breath
Palpitations
ST segment changes
Troponin elevation

Myocarditis, Pericarditis, and Myopericarditis by the most recent numbers

- 2,574 reports in all ages/age groups
  - Myopericarditis: 1,903 reports
  - Pericarditis alone: 671 reports
- Median age
  - Dose 1 – 26 y
  - Dose 2 – 20 y
- Median time to symptom onset
  - Dose 1 – 3 days
  - Dose 2 – 2 days
- Between 72-82% male

Manufacturer	Reports after dose 1	Reports after dose 2	Reports after unknown dose
Pfizer-BioNTech (n=1,282)	169	922	191
Moderna (n=557)	133	339	85
Janssen (n=49)	33	1	15
Not reported (n=15)	2	9	4
Total (N=1,903)	**337**	**1,271**	**295**

Expected vs. Observed reports after mRNA vaccination dose 2, 7-day risk period (N=765)*

Age group, years	Females		Males	
	Cases of myopericarditis, expected	Cases of myopericarditis, observed	Cases of myopericarditis, expected	Cases of myopericarditis, observed
12–15*	0–3	12	1–5	117
16–17*	0–2	15	0–3	121
18–24*	1–8	24	1–11	213
25–29*	1–6	16	1–9	56
30–39	2–21	10	2–19	72
40–49	2–22	22	2–19	45
50–64	4–40	15	4–35	13
65+	4–44	6	4–36	8

* As of Aug 18, 2021; assumes a 7-day observation window, with 765 of 897 reports after mRNA vaccines occurring during Days 0–6 after vaccination; counts among 12–29 years from reports meeting case definition for myopericarditis; expected estimates for females 12–29 years adjusted to reflect reduced incidence in this age group

7

Outcomes after myocarditis/pericarditis

Of those that met CDC case definition *(742)

- 701 were hospitalized
- 667 were discharged
  - 77% of those had recovered
- 18 were still hospitalized

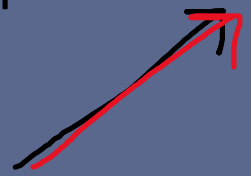
- Thus enhanced monitoring set up within the VAERS system including surveys to determine functional status and ongoing clinical symptoms as well as need for further treatment

- Patients being followed by Cardiology division at BCH

Reporting adverse events

Vaccine providers enrolled in the federal COVID-19 vaccination program are responsible for mandatory reporting of the following events `

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events* (irrespective of attribution to vaccination)
- Cases of multisystem inflammatory syndrome (MIS)
- Cases of COVID-19 that results in hospitalization or death



-Death
-A life-threatening adverse event;
-Inpatient hospitalization or prolongation of existing hospitalization
-A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
-A congenital anomaly/birth defect
-An important medical event that based on appropriate medical judgement may jeopardize the individual and may require medical or surgical intervention to prevent one of the outcomes above.

https://vaers.hhs.gov/reportevent.html

Thank you for joining us!