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Podcast Contributor Show Notes

COVID Therapeutic Options in Children

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"How confident are you about therapeutic options in pediatric #COVID19? Listen to this FREE bonus piece with @ChildrensLA experts @bradgoldbergmd and peds ID doc Michael Smits as they share their insights and practice. [hyperlink and artwork]"

Summary

Earlier this month, we discussed new outpatient treatment options for COVID. In this bonus segment, we take a deeper dive from a pediatric perspective. The co-chairs of the Special Pathogens Program from Children's Hospital Los Angeles, Brad Goldberg, MD (Pediatric Emergency Medicine) and Michael Smit, MD (Pediatric Infectious Diseases), sit down with our host Sol Behar, MD to discuss pediatric-specific issues related to COVID therapeutics. Which medications can and are being used in children?

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1. What therapeutic options are there in kids with covid?
   - Oxygen :) , Heated High Flow Nasal Cannula (HHFNC) is Fantastic
   - Dexamethasone (for any O2 requirements, ventilation requirements
   - Monoclonal Antibodies (outpatient), however in the age of Omicron only Sotrovimab is indicated. FDA updated the EUA for RGEN-COV during the last week of 1/2022 to limit it's use to only when a patient is likely to have been infected or exposed to a pre-omicron variant.
     - Given previous monoclonal REGEN-COV (Casirivimab and imdevimab) "markedly reduced activity against Omicron variant and because real time testing to identify rare, non-omicron variants (<1% of Circulating US variants) is not routinely available."
   - Remdesivir
     - Acts to inhibit SARS-CoV-2 RNA-dependent RNA polymerase thus making it difficult for the virus to effectively replicate. It is effectively an analogue of ATP (adenosine triphosphate) that incorporates itself into the viral RNA. This incorporation of the drug instead of ATP results in delayed chain termination which disrupts replication. This is different than PAXLOVID which inhibits the virus specific protease enzyme.

2. Dexamethasone- who should get it, how much?
   - There are now multiple clinical trials in hospitalized adults demonstrating mortality benefits for patients with COVID-19 requiring supplemental oxygen or mechanical ventilation.
   - There was no benefit for those hospitalized without a supplemental oxygen requirement.

- Many will remember the first landmark COVID-19 therapeutics trial named RECOVERY published by the Europeans early in the pandemic. 6,425 Randomized adults, 2,104 received dexamethasone and 4,321 received usual care alone. 28 day mortality was lower in those receiving dexamethasone (Risk Ratio 0.83, those who received dex were .83 times likely to be dead by 28 days compared to the standard care group).
- The benefit of dexamethasone does seem to increase in the subset of critically ill patients.
- There have since been other trials with similar results including the CoDEX trial in Brazil.
- Per the NIH COVID-19 Treatment Panel Dexamethasone can be considered in children admitted with COVID-19 and an oxygen demand. Technically, the panel recommends for high flow oxygen needs or mechanical ventilation. Most institutions are offering for any patient requiring supplemental oxygen of any rate.
- Dexamethasone 0.15mg/kg (max: 6mg Daily) for up to 10 days. It should be stopped on discharge or earlier in hospitalized patients who improve rapidly and no longer require supplemental oxygen.
- Limitations: No major pediatric specific studies.

3. Monoclonal abs- what different therapeutic meds are there, what is approved, in what ages and what indications? Does it matter the strain of covid (omicron vs delta?)

- What are Monoclonal Antibodies?
    - mAbs are laboratory-made proteins that mimic the immune system's ability to fight off harmful pathogens. Like the circulating antibodies made by your body's immune system, mAbs can bind to SARS-CoV-2 virus blocking its ability to efficiently enter cells in your body.

- Omicron was a real curveball this fall. In addition to it's well known ability to cause breakthrough infections in the vaccinated, it has been shown to be resistant to many of the available monoclonal antibody products currently available. This has been mainly shown through neutralizing antibody assays. In these assays most of the available products lost almost all of their ability to neutralize omicron while some now needed to be given at concentrations orders of magnitude higher.
    - Sotrovimab proved to neutralize omicron although at what seems to be slightly less efficient compared to previous strains. Omicron has many mutations to the spike protein that uses the ACE-2 receptor on cells to gain entry. Sotrovimab appears to target a specific receptor binding domain on the spike protein that was preserved from previous strains.

Prophylactic / Pre-exposure Monoclonal Antibodies for SARS-CoV-2

- New mAb available called Evusheld which is two separate intramuscular injections given at the same time to prevent or reduce severity of a future COVID-19 infection. The two different components are **tixagevimab** and **cilgavimab**.
- Targets the SARS-CoV-2 spike protein

- It is approved to prevent COVID-19 infections in patients with moderate to severe immune compromise due to a medical condition or immunosuppressive medications AND may not mount an adequate immune response to COVID-19 vaccination OR to patients for who vaccination with any COVID-19 vaccine is not recommended due to history of severe adverse reaction.

- The evidence / Phase III trials were called PROVENT and STORM CHASER
    - PROVENT is an ongoing double blinded, placebo controlled in unvaccinated subjects 18 years of age and older that were COVID-19 negative and no serological evidence of COVID-19 antibodies. 3,441 subjects received Evusheld and 1,731 received placebo. Prior to day 183 subjects with PCR positive symptomatic illness was 8 (0.2%) in the Evusheld group and 17 (1.0%) in the placebo group for a relative risk reduction of 77% (45, 90). Of the 8 positive patients in the Evusheld group none had severe/critical COVID-19 events (pneumonia, hypoxemia, or severe resp distress, death) compared to 1 severe/critical illness and 2 COVID-19 related deaths in the placebo group. If you are interested take a look at the published Kaplan Meyer curve, it's quite compelling

    - STORM CHASER is the other ongoing Phase II randomized double blinded, placebo controlled trial in adults 18 years and older. Enrolled unvaccinated subjects following potential exposure (within 8 days) to an individual with lab confirmed COVID-19 infection. At current there is no demonstration of benefit for Evusheld in preventing symptomatic COVID-19 as a post-exposure prophylaxis hence only being approved for pre-exposure.

    - Studies were initiated and data based on pre-omicron wave subjects. However, in-vitro studies demonstrate retained neutralizing activity against omicron unlike many of the previous monoclonal antibodies developed.

    - SImilar to all the other outpatient COVID-19 EUA therapeutics, it is approved for ages 12 and older AND having a weight of at least 40kg.

    - Initially there was a very limited supply, although slowly improving. Large medical centers are being given allotments with institutions crafting highly specific priority tiers for the most at risk patients. Typically patients with organ transplants and moderate/severe immunocompromised states, whether it from a condition or ongoing therapy.

4. Oral paxlovid- what is it, how does it work, indications to prescribe it? Age groups you'd use it? When will it be available? Dosing/duration? Side effect profile? Any contraindications?

- PAXLOVID is actually two separate oral tablets that are taken together and prescribed as a package for outpatients diagnosed with COVID-19 that are "high risk" for progression to severe disease.
- The two seperate tablets are nirmatrelvir (nir-ma-trelvir) and ritonavir.

    - Both are protease inhibitors. Protease is an enzyme made by human cells and viruses that are used to cleave proteins. In the case of viruses, protease inhibitors target and bind the viral protease to prevent viral replication. The best known examples are probably their use in HIV and Hepatitis C.

    - With PAXLOVID, the nirmatrevlir (nir-ma-trelvir) specifically targets the main protease (Mpro) of SARS-CoV-2.

    - Interestingly, ritonavir is a HIV-1 protease inhibitor and has no known direct activity against SARS-CoV-2 protease. It does however inhibit a the CYP3A cytochrome which in turn raises the the serum levels of the SARS specific protease inhibitor nirmatrelvir (nir-ma-trelvir)

- The evidence: A double blinded placebo controlled trial was conducted in patients 18 years of age and older. All subjects had at least one risk factor for progression to severe disease which included: Diabetes, overweight (BMI >25), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically-related technological dependence, or were 60 years of age and older regardless of comorbidities.

- Subjects were randomized in a 1:1 ratio between PAXLOVID and Placebo. 1,039 subjects got PAXLOVID and 1,046 got placebo. At day number 28, 66 subjects (6.3%) were hospitalized in the placebo group and 8 subjects (0.8%) were hospitalized in the treatment group. All cause mortality at day 28 was 12 subjects in the placebo group and 0 in the treatment group. Based on this a relative risk reduction of 88% (CI 75%-94%) was assigned for PAXLOVID.

- One drawback was this study was completed pre-omicron surge and 98% of the subjects had Delta. However there have been multiple *in vitro* studies demonstrating that nirmatrelvir (nir-ma-trelvir) remains effective in inhibiting the highly conserved protease (Mpro) in SARS-CoV-2. This takes place intracellularly and doesn't have the same resistance issues seen with monoclonals that were targeting the rapidly mutating spike protein extracellularly prior to binding with the cell.

- As of now PAXLOVID is EUA approved for patients 12 years and older and weighing at least 40kg. It is currently available by prescription

- Rx: Nirmaterelvir (nir-ma-trelvir) 150mg Oral Tablets. Take 2 Tablets PO Twice Daily for 5 Days. Ritonavir 100mg Oral Tablets. Take 1 Tablet PO Twice Daily for 5 Days.

- The proportion of patients who discontinued treatment due to adverse event (side effects) were 2% in the PAXLOVID group and 4% in the placebo group. There were signals suggesting dysgeusia (all things tasting sour, bitter, metallic, or sweet), diarrhea, and hypertension may be slightly more prevalent in the PAXLOVID group.

- The cautions and contraindications are many, mostly related to other medications patients may be taking that will have altered serum concentrations due to clearance dependence on the CYP3A cytochrome which PAXLOVID inhibits.

Are you seeing bacterial superinfections with covid? If so, what makes you suspect it and what overage do you add?

- Personally, I have not been seeing significant instances of bacterial superinfections in acute COVID-19. This includes bacterial pneumonia. I think if you are suspicious you should use your typical antibiotic choices.
- On the flip side, although we have seen bacterial infections in MIS-C. One example was an infant who had a culture positive UTI but continued to spike fevers and was diagnosed with MIS-C at a subsequent encounter and ended up quite ill with cardiac complications. This is what scares me.

Several people are asking about treatment of covid related croup- how should we treat these kids?

Croup was another new pediatric manifestation of COVID-19 that I do not think any of us had on our pandemic bingo card. Pediatric Emergency Medicine physicians everywhere quickly began seeing exploding cases with rising omicron case numbers.

- I have personally ordered full viral panels on many of these kids early during omicron when we were still trying to figure out what was going on, the vast majority of these viral panels were negative for the typical croup culprits like parainfluenza virus.

- This new finding of croup with omicron makes sense with the emerging body of literature suggesting that omicron shows increased preference (tropism) for upper airway cells compared to previous variants.

- All emergency departments I have been in communication with appear to have been using their standard dosing of dexamethasone and inhaled racemic epinephrine for COVID-19 associated croup.

- Dex generally is given 0.15-0.6 mg/kg PO or IM as a one time dose. The dose given may vary some depending on your practice or department. The takeaway is whatever your standard therapy for croup may be, this seems to be adequate for COVID-19 croup.

- Racepinephrine 2.25% inhalation solution given by nebulizer 0.25mL for patients under 5kg and 0.5mL for patients over 5kg diluted in 2mL of NS is what is used at my institution.

Can we shut the door on ivermectin already? Is there even a plausible mechanism by which this might help someone infected with covid? How should we handle a family demanding we

give it (and other therapies pushed by less than scientific groups)when there are no studies to support using this (so we can avoid being shot/harassed/threatened)?

There is no evidence for evidence being an effective treatment for covid infection. We must stick to the adage of first do no harm and hold steadfast and not prescribe this medication for covid outside of clinical trials.

Does omicron cause as much MIS-C as delta? I have not seen as much, but what data is there on this?

- It is still a bit early to know. I have heard rumblings of increasing case numbers at a large health care system in the NYC area. Also keep in mind NYC is probably 1-2 weeks ahead of the West Coast.

- On the brighter side, during Jan.-Feb. 2021 our institution ---over those two months we saw 66 MIS-C patients. In Dec. 2021 and January 2022 we saw about 17 patients. So I would say so far we have seen less, however we do not want to speak too early and we are holding our breath for the next few weeks.

- The total number of MIS-C cases our institution has reported to the LA Dept. of Health during the entire pandemic sits around 177. Of that 177, 64 (36%) required ICU level of care.

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