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HCFI DR KK AGGARWAL RESEARCH FUND

IMA DMA NDB Meet on "COVID Update, Immune Signature of COVID-19, Treatment Strategies"

COVID UPDATE

- Cases in India are rising but hospitalizations are low. In the UK, 58% of cases were incidentally found cases.
- Coronavirus disease 2019 (COVID-19) *per se* is now behaving like any other virus and humans too are behaving immunologically as they would to any other virus.
- Singapore, Israel and UK, highly vaccinated countries, had the highest daily new confirmed cases per million people as of April 21, 2022. France had the highest number of COVID-19 patients in hospital with 24,894 admissions, followed by UK (17,748), Italy (10,289), US (9,964) as of April 16, 2022.
- In Delhi, the hospital bed occupancy is <1% and ICU admissions are <0.1%.
- Omicron has given robust natural immunity.
- We have to now start moving from infection to disease. The virus is going to find ways to evade immunity and the body will continue to find ways to deal with the virus.
- The daily new confirmed deaths per million people are quite low at 0.04.
- India is doing around 6,000 tests for every confirmed case. Whereas, the US is doing around 20 tests per one confirmed case, UK (13.4), Singapore (10.10), Israel (9.80) and Japan (2.60).
- The effective reproduction rate in the UK has been consistently going down to <1%. But in India, RR is steadily rising and has increased from 0.35 in February this year to 1.32 as of April 19, 2022.
- In the last week, Germany, South Korea, France, Italy and the US were reporting the maximum new infections each day, but they are now showing a decline.
- Europe is the lead driver of infection followed by Asia, US and Canada.
- Transparency in data reporting is important.
- In the UK, which is currently 12% of its peak and falling, even a nationwide lockdown did not prevent the Omicron surge. Despite opening up now, the numbers have not gone up.
- India is <1% of its peak. Despite no lockdown, the Omicron wave did not cross the Delta wave. The rising cases however merit a close watch.
- The US, which is at 5% of its peak, had a partial lockdown (local and in sectors, not nationwide) till very recently, yet made no difference to the waves.
- South Korea had nearly 90% of population vaccinated. India has vaccinated around 75% of its population, but in terms of number of people vaccinated, India is at the top.
- In India, the new cases and recoveries are following very close to each other. Currently the infected cases are less than 15k.

- The 7-day average in India showed a decline from mid-March to mid-April but is again showing a rising trend near the end of April.
- However, the numbers are still low considering the huge population, so no cause for panic yet. There is no indication of a sharp rise.

ABOUT VIRUSES

- Viruses are not always harmful; about 8% of our genome is viral in origin. They are obligate intracellular parasites as they need the host cell machinery to multiply.
- The immune response to any intracellular parasite is either Th1, Th2 or Th17 response. If the body does not recognize the pathogen, the response can be delayed, skewed, hyperinflammatory in terms of magnitude or persistence.
- The Th1 response is largely for intracellular bacteria or viruses and can result in organ specific autoimmunity such as Crohn's disease, *Helicobacter pylori* gastritis and acute renal transplant rejection. It is a phagocyte-mediated immune response.
- The Th2 response is for intestinal nematodes and results in strong antibody production, marked activation of eosinophils and inhibition of several functions of macrophages. It is a phagocyte independent immune response.
- Interleukin (IL)-12 and interferon (IFN)-alpha and gamma from macrophages and natural killer (NK) cells favor Th1 response.
- Early production of IL-4 by a still unidentified cell type favors Th2 response.
- Interferons are the key drivers to immune response to virus. They have several actions. They induce arginine vasopressin (AVP) production by host cells and degrade viral RNA leading to inhibition of viral protein synthesis. They activate NK cells leading to enhanced killing of infected cells by NK cells and enhance MHC expression by host cells leading to enhanced killing of infected cells by cytotoxic T cells (CTLs).
- In COVID, Th17 and Treg cell function is significantly altered.
- Immune response is an interplay of various T cells. There is significant increase in Th17 leading to increased expression of cytokines (IL-17, IL-23, retinoic acid receptor [RAR]-related orphan gamma) and decrease in T regs and also reduced expression of P3-FoxP3, IL-17 and transforming growth factor (TGF)-beta.
- The Th17/Treg and IL-17/IL-10 ratios are strongly predictive of pathology and decreased survival in COVID patients.
- Control inflammation by Day 3 and thrombo-inflammation definitely by Day 10.
- The immune signature of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) includes lymphopenia driven by decrease in T CD4 and CD8, immune imbalance, increased inflammatory cytokines, hyperinflammation, thrombosis. The disease can resolve or persist; the pathology can be local or systemic as seen in long COVID.
- Monitor C-reactive protein (CRP); if rising then act to reduce it. Early and aggressive treatment will improve outcomes.
- IL-6 is the main regulator molecule for all intracellular viruses and bacteria. It activates CTLs, Th1, Th17 cells which secrete perforins, granzyme and trigger release of cytokines leading to pro-inflammatory response.
- Cytokine-mediated hyperinflammation has been strongly correlated with reduced survival.
- IL-6 increases Th17 activity and reduces Treg activity. IL-6 is elevated in autoimmune diseases like rheumatoid arthritis.
- The increased number and function of Th17 cells drive hyperinflammation. They reduce the number and function of Tregs hampering the ability for anti-inflammation.
- Tregs are marked by increase in CD3, CD4, CD25 and low CD127 and Fox P3. Tregs induce immune tolerance and prevent autoimmune disease.
- Tregs are of two types: n (natural) and i (inducible).
- The nTregs develop in the thymus and protect against autoimmunity, while the iTregs develop outside the thymus and their differentiation depends upon contact with non-self antigen, IL-2 and TGF.
- Tregs inhibit activation of both innate and adaptive immune cells; they also inhibit maturation of antigen presenting cells (APCs), decrease available IL-62 and create a pool of memory cells for response at secondary challenge.
- The immune response to SARS-CoV-2 and mechanism of immunopathological changes in COVID-19 are thus driven by a balance between

IL-2, 6 and 17 and between T cells populations with Tregs.

- If the Th1 response can be controlled in 3 days and definitely within 10 days, the cytokine storm can be controlled.
- Early treatment prevents inflammation and progression to thromboinflammation.
- Control measures at population level are personal protection, risk stratification, isolation, vaccination and early detection.
- Fever can be managed with mefenamic acid, respiratory/nasal secretions by H1 block, bronchodilator; inflammation by nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, doxycycline, azithromycin; hyperinflammation by steroids, colchicine; thromboinflammation by aspirin, non-vitamin K antagonist oral anti-coagulants (NOACs) and antiplatelets; monoclonal antibodies by IL-2 and 6 and antivirals.
- Prevention is better than cure. If you want to dodge the bullet, control metabolic dysfunction, treat chronic diseases adequately, fortify mitochondrial health, get adequate good quality sleep, follow anti-inflammatory and vagal lifestyle and create health and wellness.

(*Excerpts from a presentation by Dr Nidhi Dhawan, April 24, 2022, Sunday*)

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FSSAI Faces Opposition Against its New Star Rating System

When the world is moving towards a healthy lifestyle, Food Safety and Standards Authority of India (FSSAI) has also decided to join in with their new star rating system for packaged food and beverages rather than warning the companies to label products based on ingredients.

Consumer Voice, People's Vigilance Committee, Consumer Unity & Trust Society (CUTS) and several other associations have decided to oppose this move stating that nutritional warnings on food packets are an "urgently required intervention" to protect public health. CUTS chief states that these new regulations are in favor of large food companies, not consumers. Also, the rating models are misleading as the healthier nutrients will cover up the unhealthy ingredient in the rating algorithm.

AIIMS briefed that the consumers prefer direct labeling to warn them about excess salt, sugar, and fats in the packaged food based on a study. Also, the consumers are ready to make healthier choices but star ratings will be difficult to comprehend. (*Source: https://health.economictimes.indiatimes.com/news/policy/fssais-new-star-rating-system-for-packaged-food-faces-a-revolt/90789563*)

Chronic Kidney Disease: A Burden on Public Healthcare Sector

The large disparity stills existing in our nation with our healthcare sector lauded globally along with a severe shortage in the number of healthcare professionals in rural areas, a fact that was brought to light during the emergency of the pandemic. Lifestyle changes and migration has led to a hike in noncommunicable disease with 50% of spending on in-patients which has increased the demand for specialized care.

As per a WHO report, 1 out of every 4 Indians is at the risk of dying from noncommunicable disease before reaching the age of 70. CKD is the sixth fastest-growing cause of death globally with expensive treatment options such as dialysis, and renal replacement being the major setback. The deaths reported due to kidney failure were greater in lower and middle socioeconomic groups in India.

According to a study, more than 60% of the patients had to travel more than 50 km to receive dialysis. The government has eased the situation by introducing the "National Dialysis Program" and setting up dialysis facilities in 688 districts to support the low socioeconomic groups. While fighting COVID-19, our healthcare sector is also building back by providing accessibility and availability to all and actively working to meet the UN's sustainable development goal to reduce premature mortality for noncommunicable diseases.

(*Source: https://health.economictimes.indiatimes.com/news/industry/public-health-challenge-of-chronic-kidney-disease/90789819*)