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CONGENITAL NEPHROTIC SYNDROME: A CASE REPORT

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ABSTRACT

Congenital nephrotic syndrome (CNS) is a rare kidney disorder characterized by severe protein urea, hypo-protein aemia, and edema commencing shortly after birth. The majority CNS type often discovered is Finnish by common indication of prematurely born infant with a large placenta. Prenatal diagnosis can be through the detection of high levels of Alfa fetoprotein in the amniotic fluid.

The infant aged one month 18 days had abdominal swelling that was noticeable from 21 days after birth. The infant hospitalized at Kolaka Hospital had anasarca edema, hypo-albuminemia (albumin 1.0 g / dl), protein urea (+++), and hyper-lipidaemia (209). Patient's history of receiving albumin transfusions. Referring to the anamnesis and physical examination, the infant endured a CNS started less than three months after birth, and the onset factor of symptoms led to primary CNS due to genetic disorders.

The diagnosis is made based on history, physical examination, and supporting investigations. The patient accepts the treatment of intravenous albumin transfusion followed by intravenous antibiotics for secondary infection.

KEYWORDS Congenital, Nephrotic syndrome, Child Health.

Introduction

Nephrotic syndrome (NS)is one of the most common glomerular disorders in childhood. [1.2.3]Its incidence is reported to be 2 -3/100000 children in Western countries, slightly higher (2-7/100,000) in children of South Asian origin and its prevalence is 12-16/100,000 children. In Indonesia, the incidence was reported 6 per 100,000 per year in children < 14 years with the sex ratio of boys and girls 2: 1.[1]

In Asia, a higher incidence of 9–16 cases per 100 000 children per year has been found. Approximately 90% of the nephrotic syndromes in children are idiopathic and steroid sensitive, with a favorable prognosis, while the remaining 10% do not respond and are defined as steroid resistant. Abnormal T-cell functions leading to release of certain cytokines and lymphokines, which cause altered glomerular basement permeability and hence protein urea, may be involved in the pathogenesis of nephrotic syndrome and its relapses[2] .Relapse in NS is defined as recurrence of severe protein urea (greater than 40mg/m^2/h or urine protein dipstick 2+ or more for 3 consecutive days), often with recurrence of edema[3]

Many infections can induce relapse in nephronic syndrome. Acute respiratory infections (ARI) and urinary tract infections (UTI) are the most frequent infectious triggers of relapse.Amongs the infectious triggers, respiratory tract infection consistently ranks as the most prominent and frequent factor irrespective of geographical setting . The average prevalence rate of respiratory tract infection as a trigger of relapse was approximately 66.9%. It is currently recognized that at least 50% of relapses are triggered by a viral upper respiratory tract infection; which may be linked to non-specific host response to infection (cytokine release) rather than to viral antigen or antibody response. Thus, other infection such as urinary tract infection (UTI), diarrhea, peritonitis and skin infections have also been implicated.[4]

Recently, *Corona virus disease 2019 (COVID-19), an acute respiratory illness first discovered in Wuhan,* China in Dec*ember* 2019, *has rapidly spread not only in China but the world.* It's *become trending issue because* it's *high infectivity and* mortality, *WHO has defined it as a global pandemic. As of April 7, corona virus disease 2019 (COVID-19), caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), has been confirmed in .1.25 million people worldwide with a mortality rate of 5.7%.*[5]The novel corona virus disease (COVID-19) is one of the most threatening pandemics in history involving multiple organs, including the kidney.[6]On May 18 ,2020 , The Indonesian Health Ministry announced 693 new confirmed COVID-19 cases , bringing the total number of infections nationwide to 19,189.[7]

The pathogen of COVID-19 is SARS-CoV-2 , primarily spreading through respiratory droplets from an infected individual in close contact.[5,6,7] SARS-CoV-2 infection can cause elevated inflammatory cytokines suggest that a cytokine storm, also known as cytokine release syndrome(CRS),may play a major role in the pathology of COVID-19.Evidence suggests that CRS might play a major role in severe COVID-19. SARS-CoV-2 targets the lung and likely other organs as well, leading to multi organ damage by binding to the

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angiotensin-converting enzyme2(ACE2) receptor, a cell surface protein highly expressed in the lung, heart and kidney[8]

Here, we discuss the mechanism SARS-CoV-2 infection can induce relapse in nephritic syndrome with the concepts of 'immune deregulations or abnormal T-cell functions leading to release of certain cytokines (cytokine storm) and lymphokines by virus binding to ACE2 as the main host cell receptor of human pathogenic coronaviruses.[4]

It is important to further investigate SARS-CoV-2 induce relapse in patient with Nephrotic Syndrome due to therapy that may be needed to prevent SARS-CoV-2 binding to ACE2 in the kidney or effect the cytokine that released by other organs which infected by SARS-CoV2 that can affected the kidney .

Here also will slightly mention two controversial studies about coagulation system as one of complication of COVID-19 and new vision about PCR test that used for diagnostic test of COVID-19 disease.

1. Nephrotic Syndrome

Nephrotic Syndrome (NS) characterized by proteinuria that is severe enough to cause hypo-albuminemia and edema. The first description of a nephrotic child was published in 1484 , when Cornelius Roelans of Belgium described '' swelling of the whole body of child " as one of 52 common diseases of children. Outcome for children with NS were uniformly poor before the introduction of antibiotics in the 1930's, with mortality rates of approximately 67%.With widespread use of Sulfonamides and Penicillin to treat NS-Associated infection, mortality drop to 35% by 1950. The watershed moment in the history of NS was the introduction of steroids for the treatment of this disorder in the 1950s, which led to clinical remission in a majority of treated patients drop in mortality to 9% by 1960.[3]

NS is a clinical description of constellation of findings that can be caused by a large number underlying primary and secondary disorders. The International Study of Kidney Disease in Children (ISKDC) defined NS as massive protein urea (greater than 40mg/m^2/h, or 1000 mg/m^2/24h) leading to hypoalbuminemia (less than 2.5 g/dL), edema , and hyperlipidemia.[3]

Term used for clinical sub classification of NS is as follows: [3]

a. Relapse: Relapse in NS is defined as recurrence of severe protein urea (greater than 40mg/m^2/h or urine protein dipstick 2+ or more for 3 consecutive days), often with recurrence of edema

b. Steroid-Sensitive NS (SSNS): SSNS defined as complete remission in response to corticosteroid therapy alone. SSNS suggest Minimal Changes Nephrotic Syndrome (MCNS) on Histopathologic examination.

c. Steroid-Dependent NS (SDNS): SDNS some children who initially respond to steroid experience a relapse while still receiving steroid or within 2 weeks discontinuation of treatment and are classified as having SDNS

d. Frequently relapsing NS (FRNS): Finally, children who develop more than four relapses in 12 months are classified as having FRNR.

e. Steroid-resistant NS (SRNS) :children with SRNS do not achieve remission despite 4 to 8 weeks of high dose corticosteroid therapy

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Idiopathic nephrotic syndrome (INS) is a common glomerular disease in children. The exact patho physiology of this disease is not well understood. However, many studies have suggested that it is immune-mediated. These suggestions are based on the fact that most children with INS respond well to steroids and cyclo phosphamide, both work on cell-mediated immunity. The fact that most attacks are triggered by viral illnesses and there is an increased incidence of allergic diseases among INS patients also supports the immune-mediated pathology. The role of T-cell lymphocytes in pathogenesis of INS was the core of many studies over the last 2 decades. Initially, imbalance between Th1 and Th2 helper cells with the increase in Th2 cytokines was postulated to be the key abnormality in INS. The activation of T-cells leads to release of local cytokines that work as soluble circulating factors provoking increased glomerular permeability and podocytes' barrier dysfunction with subsequent proteinuria.[9]

Minimal changes disease is the most common cause of idiopathic childhood nephrotic syndrome.[1,3]Patients with Minimal Changes Nephrotic Syndrome often display a defect in *delayed-type hypersensitivity* (DTH) response, suggesting an abnormal Th1-dependent cellular immunity. Th1 cells produce IL-2, IFN-γ and tumor necrosis factor-beta (TNF-β), and promote both macrophage activation resulting into DTH, and production of complement-fixing and opsonizing antibodies. Th2 cells synthesize IL-4, IL-5, IL-6, IL-10 and IL-13 provide optimal help for antibody production, and promote both mast cell growth and eosinophil differentiation and activation causing humoral responses . Type 1 cytokines predominate in cell-mediated immunity and type 2 cytokines in atopy and class-switching of B-cells for production of IgG4 and IgE .The titer of IL-4 and IL-13 as the major Th2 detected increased in patient with relapse INS.[10]

Other study showed, the 3 pro-inflammatory cytokines, IL-1β, IL-6 and IL-8, play a major role during relapse in INS. Pro-inflammatory cytokines, IL-1β and IL-6, were specifically reported to be involved in the patho physiology of INS. The chemokine IL-8 was only recently documented to act as a soluble factor that increases glomerular basement membrane permeability[9]

Some of the previous studies have suggested that genetic variations in IL-4 may be associated with predisposition to Minimal Changes Nephrotic Syndrome (MCNS), and partially to the clinical course of MCNS. IL-4 production by peripheral Th2 cells is up-regulated in patients with MCNS and correlated with the severity of proteinuria. Increased systemic production of representative cytokines, chiefly interleukin-4 is also reported while in vitro studies suggest that podocytes express receptors for interleukin-4 and interleukin-13; activation of these receptors by the respective cytokines might disrupt glomerular permeability resulting in proteinuria[4]

Dysregulated IL-6 has been demonstrated to underlie a number of autoimmune and inflammatory diseases, metabolic abnormalities, and malignancies. This review provides an overview of basic concept of IL-6 signaling pathway as well as the interplay between IL-6 and renal-resident cells, including podocytes, mesangial cells, endothelial cells, and tubular epithelial cells.[11]

As we know that NS is defined by presence of high-grade protein urea, hypo albuminemia, and edema. Increased permeability of the glomerular filtration barrier (GFB) result in massive loss of protein in the urine that lead to constellation of renal and extrarenal finding characteristic of the disease. A major contributor to the GFB is the podocyte, and the

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disruption of the podocyte physiology is an important cause of NS. The podocyte also known as the glomerular visceral epithelial cell, is a terminally differentiated, highly specialized cell located at urinary side of the glomerular capillary tuft. It play role in; maintain ke GFB through preservation of a molecular filtration sieve, synthesis of the glomerular basement membrane (GBM) and regulation of other glomerular cell type. In many protein uric diseases, the podocyte become the target of immunologic or non immunologic injury .[3]

A hypothesis to unify these concepts of immune dysregulation, increased glomerular permeability and podocytopathy is yet to be proposed but the speculation that critical podocyte proteins are probably potential targets for T cell cytokines or vascular permeability factors still needs further confirmation. Nevertheless, the podocyte evidently plays a key role both in the maintenance of the glomerular filtration barrier and structural integrity, as its injury and loss contribute to protein urea and progressive sclerosis.[4]

2. SARS-CoV-2 Infection

Corona viruses are a family of viruses, including the common cold, which typically cause mild to moderate upper respiratory tract symptoms. These viruses are zoonotic, often originally circulating among animals; they occasionally spill over to humans through contact. There are currently seven corona viruses known to cause human disease, three of which Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), and COVID-19 are known to cause moderate to severe disease in human.[5] SARS and MERS are less contagious than COVID-19. The COVID-19 disease is very contagious, with lower mortality rate than MERS and SARS. At present, the novel corona virus has a mortality rate of about 2% to 3% but it possibly changes as the virus continues to spread, while SARS virus mortality is about 14% to 15%. Most deaths of COVID-19 occur in elderly people with other health problems such as heart disease, hypertension, and diabetes. According to statistics, this group of people is at greater risk of death than others due to diseases like the flu[6]

Similar to other corona viruses, COVID-19 has an incubation period of 2-14 days and cause fever, fatigue, cough and shortness of breath, but it may also progress to more severe respiratory illness.[12] The affected patient develop pneumonia and multi organ failure ending to death. Studies revealed the high rate of renal involvement in patient with COVID-19. Two common symptoms in COVID-19 patients with renal failure are hematuria and protein urea as albumin in the urine.[6]

The pathogen of COVID-19 is SARS-CoV-2, primarily spreading through respiratory droplets from an infected individual in close contact.[6, 12,13Because] droplet usually fall within a few meters, the like hood of transmission is decreased if people remain at least 2 m apart.[13]However, COVID-19 has also been found in anal swabs suggesting an additional oral-fecal route of transmission.[12]

Corona viruses are RNA viruses that are divided into four genera; alpha-corona viruses and beta-corona viruses are known to infect humans. SARS-CoV-2 is related to bat corona viruses and to SARS-Cov-1, the virus that causes severe acute respiratory syndrome (SARS). Similar to SARS-CoV-1, SARS-CoV-2 enters human cell through the angiotensin-enzyme 2 (ACE2) receptor. SARS-CoV-2 has RNA-dependent RNA polymerase and protease, which are targets of drugs under investigation.[13]ACE2 has the physiological functions of regulating heart and kidney function and controlling blood pressure. Recently, it has been found that

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human ACE2 promoted the entry of SARS-CoV-2 into the cells.[14]ACE2 is mainly expressed by epithelial cells of the lung, intestine, kidney and blood vessels.[10,14,15] ·It has been reported ACE2 is the main host cell receptor of human pathogenic corona viruses {severe acute respiratory syndrome corona virus (SARS-CoV), HCoV-NL63, and SARS-CoV-2 (COVID-19)} ,and play a crucial role in the entry of virus into the cell to cause the final infection . Wrap and colleagues recently provided the Cryo-EM structure of the virus spike protein, the known ligand for ACE2, and documented a 10 to 20 fold higher affinity of ACE2 for SARS-CoV-2 compared to previous SARS-CoV.[15]

Several significant differences in the frequency of distribution of ACE2 variant among different racial and ethnic lines have been described. A recent single-cell RNA sequencing (RNA seq) analysis indicated that Asian males may have a higher expression of tissue ACE2 .In another case control study conducted in the north eastern Chinese Han population , the serum ACE2 activity negatively correlated with body mass index (BMI), pulse pressure , and estrogen level in female EH (essential hypertension) patient. These observation point both to a cardiovascular protective effect of circulating levels of ACE2 and simultaneously prove that estrogens participate in the up regulation of ACE2 expression and activity levels. This might explain the relative protection of female vs. male in COVID infection.[15]

A putative trend toward this kind of association was also seen in children. Children generally have higher levels of ACE2 than adult. For example, ACE level in children (6 month to 17 years of age) 13-100U/L compared with 9-67 U/L in adult when using an FAPGG-based enzymatic activity assay. Of note is the fact that children with confirmed COVID-19 have generally presented with mild symptoms. Cases of corona virus disease (COVID-19) among children in China have been less severe than those in adult, according to new study. [15]

In our opinion, the explanation for the correlation between age and COVID-19 disease severity might be related not only to the immune decline of an aged immune system (termed *immune senescence)* but also to a peculiar ACE plasma profile that may characterize children from birth. Indeed in mid to late pregnancy in women, an increase in urine and plasma levels of ACE2 were found as well as an increase in local placental/uterine production and activity of ACE2, suggesting a systemic hemodynamic role in the enhancement of placental-fetal blood flow and rapid fetal growth.[8]ACE can pass through the placental, enabling the mother to transfer to baby her immunity and other kinds of protective soluble factors.[15]

Severe acute respiratory syndrome corona virus 1 (SARS-CoV-1) and SARS-CoV-2, which have been responsible for the SARS epidemic in 2002 to 2004 and for the more recent corona virus disease 2019 (Covid-19) pandemic, respectively, interface with the renin–angiotensin–aldosterone system (RAAS) through angiotensin-converting enzyme 2 (ACE2), an enzyme that physiologically counters RAAS activation but also functions as a receptor for both SARS viruses. ACE2 is a key counter regulatory enzyme that degrades angiotensin II to angiotensin-(1–7), thereby attenuating its effects on vasoconstriction, sodium retention, and fibrosis. Although angiotensin II is the primary substrate of ACE2, that enzyme also cleaves angiotensin I to angiotensin-(1–9) and participates in the hydrolysis of other peptides.SARS-CoV-2 appears not only to gain initial entry through ACE2 but also to subsequently down regulate ACE2 expression such that the enzyme is unable to exert protective effects in organs. It has been postulated but unproven that unabated angiotensin II activity may be in part responsible for organ injury in Covid-19.After the initial engagement of SARS-CoV-2

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spike protein, there is subsequent down-regulation of ACE2 abundance on cell surfaces. Continued viral infection and replication contribute to reduced membrane ACE2 expression, at least in vitro in cultured cells. Down-regulation of ACE2 activity in the lungs facilitates the initial neutrophil infiltration in response to bacterial end toxin and may result in unopposed angiotensin II accumulation and local RAAS activation. In a small study, patients with Covid-19 appeared to have elevated levels of plasma angiotensin II, which were in turn correlated with total viral load and degree of lung injury[10]

Genetic differences are well-known to contribute to individual variation in the immune response of pathogen. However, when the protective immune response is impaired, virus will propagate and massive destruction of the affected tissue will occur, especially in organs that have high ACE2 expression such as intestine and kidney. The damage cell induce innate inflammation in the lungs that is largely mediated by pro inflammatory macrophage and granulocyte.[16]

The elevated inflammatory cytokines suggest that a cytokine storm, also known as cytokine release syndrome(CRS),may play a major role in the pathology of COVID-19.Evidence suggests that CRS might play a major role in severe COVID-19. Inflammatory cytokines and chemokines, including interleukin-6 (IL-6), interleukin-1β (IL-1β), inducedprotein 10 (IP10) and monocyte chemoattractant protein-1 (MCP-1) were significantly elevated in COVID-19 patients, and some were more commonly seen in severe patients than in non severe patients .In COVID-19 patients with elevated inflammatory cytokines, post-mortem pathology has revealed tissue necrosis and interstitial macrophage and monocyte infiltrations in the lung ,heart and gastrointestinal mucosa . Moreover, severe lymphopenia with hyper activated pro inflammatory T cells and decreased regulatory T cells is commonly seen in critically ill patients, suggesting dysregulated immune responses. CRS refers to an uncontrolled and overwhelming release of pro inflammatory mediators by an overly activated immune system.CRS is a common immuno pathogenesis underlying many pathological processes. Exuberant production of cytokines, such as type I IFN, diminishes T-cell responses by inducing T cell apoptosis to aggravate CRS and lymphopenia, as observed in SARS patients. The overwhelming pro inflammatory cytokines and chemokines cause localized pulmonary injury characterized by diffuse alveolar damage with epithelial and endothelial apoptosis, dysregulated coagulation and pulmonary fibrinolysis. They may also leak into systemic circulation to cause extra pulmonary manifestations and eventually multiple organ dysfunction syndromes. The elevated cytokine levels may also be responsible for the lethal complications of COVID-19.As shown inTable1,patients with COVID-19, SARS or MERS presented distinct cytokine profiles. Patients with COVID-19 presented elevated T helper 2 cytokines (interleukin-4) in addition to T helper 1 cytokines compared to those in patients with SARS or MERS. [8]

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Table 1
The levels of cytokines in patients with COVID-19, SARS and MERS versus those in normal controls.

Cytokines	COVID-19	SARS	MERS
IL-6	↑ in some [36,58] or in severe cases [6,34,54]	↑	Unknown but ↑ in severe than in mild cases
IL-2	↑	↑ or NS	NS
IL-1β	↑	NS	Unknown
IL-8	↑	↑	Unknown
IL-17	↑	Unknown	↑
IFN-γ	↑	NS	↑
TNF-α	↑	NS	↑
IP10	↑	↑	Unknown but ↑ in severe than in mild cases
MCP-1	↑	↑ or NS	Unknown
IL-10	↑	NS or ↑ in convalescent cases	↑
IL-4	↑	NS or ↓ in convalescent cases	NS
Ref	[6,33,34,36,54,58]	[28,59–61]	[62,63]

Up or down arrows indicate higher or lower levels versus normal controls, respectively. Abbreviations: NS; no significant change versus normal controls, IL: interleukin, IFN-γ: interferon γ, IP: induced protein, MCP: monocyte chemoattractant protein, TNF-α: tumor necrosis factor α.

Recently there are two topics that become controversial and needs further investigation regarding involvement of coagulant system as complication of COVID-19 disease and new finding in PCR test as diagnostic for COVID -19 disease.

As mention before that disease severity is correlates with pro-inflammatory cytokines (i.e., IL-2, IL6, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A and TNF-α), although it is not yet clear what is the cause of such a cytokine storm. Here demonstrated that's there are close connection between thrombosis and inflammation; two processes that mutually reinforce each other. Indeed, both coagulation factors (pro- and anti-coagulants) and platelets are directly implicated in the modulation of the host immune response, displaying pro inflammatory functions that are independent from their haemostatic effects. All the above issues have been instrumental in spreading the feeling that COVID-19 is associated with the classical syndrome named disseminated intravascular coagulation (DIC) and the subsequent consumption coagulopathy.[17]

The clinical spectrum of the disease is very wide, ranging from minor, unspecific symptoms, such as fever, dry cough and diarrhea, sometimes combined with mild pneumonia and mild dyspnoea, to severe pneumonia with dyspnoea, tachypnoea and disturbed gas exchange, leading in approximately 5% of infected patients to severe lung dysfunction, a need for ventilation, shock or multiple (extra pulmonary) organ failure.[17]

Like other severe infections, COVID-19 pneumonia may induce sepsis-induced coagulopathy (SIC) and (if not controlled despite adequate medical therapy) progress to disseminated intravascular coagulation (DIC) .[18, 19] DIC is one of the severe complications identified in patients with pneumonia, septicemia, malignancy and other severe diseases. The clinical diagnosis of DIC is made on rapid progression of serious deterioration of organ functions resulting in a boost of intravascular thrombin generation and microthrombi with secondary parenchymal bleeding through endothelial leakage. Venous thrombo embolism (VTE) may develop in COVID-19 patients via immunologic and toxic activation of intravascular and platelet-released thrombin. DIC is one of the severe complications identified in patients with pneumonia and other infections, not surprisingly; the occurrence of DIC has also been described in COVID-19-driven pneumonia. However, diagnosis of DIC is suspected by deterioration of laboratory parameters documented by repeated determinations.[18]

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The most frequently determined parameters in COVID-19 patients have been the following: prothrombin time (PT) and activated partial thromboplastin time (APTT) both increase (suggestive of coagulation activation) and decrease (consistent with consumptive co-agulopathy), and fibrinogen increases (suggestive of acute-phase changes) and decreases (consumptive coagulopathy). Later stages of the disease are also characterized by increase in thrombin-antithrombin complex, fibrin-degradation products and D-dimers, with the degree of changes related with a risk of fatal outcome .Platelet counts increase in the acute phase of COVID-19 disease but may decrease in late stages of DIC (Table 1). About 71% of non-survivors and 0.6% of survivors showed evidence of overt DIC identified with a median time of 4 days after onset of interstitial pneumonia.[18]

Among the several clinical and biochemical parameters associated with poor prognosis, increased D-dimer levels have gained particular attention as a predictor of the development of acute respiratory distress syndrome (ARDS), the need for admission to an intensive care unit (ICU) or death.[17]

Of great interest is the determination of D-dimer levels. A pooled analysis including four studies showed that D-dimer values are three-fold higher in patients with severe COVID-19 than in those with milder forms. When D-dimer levels increased to levels higher than 3 µg/mL, the mortality rate increased three-fold. D-dimer reached maximum levels at a median time of 4 days after onset of interstitial pneumonia in 71% of non-survivors. A multivariable logistic regression model identified older age, higher SOFA score and D-dimer greater than 1 µg/mL at admission to be associated with increased probability of fatal outcome. Patients with COVID-19 pneumonia and PE documented by computerized tomography (CT) angiography had higher D-dimer levels compared to those without PE (median, 6.11 vs. 1.92 µg/mL). D-dimer had a sensitivity and specificity of 100% and 67%, for the presence of PE on CT angiography at a cut-off of 2.66 µg/ mL, respectively. Elevations of D-dimer have also been reported in severe courses of other viral infections, including human immunodeficiency (HIV) , Ebola , Zika and Chikungunya viruses .[18]

The acronym COVID-19 associated coagulopathy (CAC) is being used to describe the coagulation changes in infected patients. The SARS-CoV-2 virus does not appear to have intrinsic procoagulant effects itself, although more information is needed. As discussed, the development of coagulation test abnormalities seen in SARS-CoV-2 infected patients is most likely a result of the profound inflammatory response.[19]

The hypothesis of improving the clinical outcome of COVID-19 patients by simple and inexpensive antithrombotic drugs is very attractive, but several issues need to be addressed and clarified before adopting an aggressive anticoagulation approach. They include the appropriate timing of start of treatment, and the type and dosage of drug, while the impact of concomitant medications that are often taken by these subjects should also be taken into consideration. Moreover, it should be noted that approximately 50% of those patients who have died of COVID-19 in Italy had three or more co morbidities such as aerial fibrillation or ischemic heart disease, often requiring anticoagulant or ant platelet treatment; the management of these is particularly challenging due to the potential interactions of concomitant therapies, namely direct oral anticoagulants (DOAC).[17]

Second controversial issue, the sharp trend gets wider in such a way that the isolation of affected people can interrupt the chain of transmission. The standard method of COVID-19

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diagnosis is real time Reverse Transcription Polymerase Chain Reaction (r RT-PCR) now become controversial method that use to confirmed COVID -19.

Dr. Andrew Kaufman is an American natural healing consultant, inventor, expert witness and forensic psychiatrist who has been powerfully outspoken throughout the pandemic. Speaking counter to the mainstream media, Dr. Kaufman has stated that a virus is not causing a new disease, there is no evidence of increased mortality and modern medicine is the leading cause of death. His complaint that there is no specific gold standard for the RT-PCR test for SARS-CoV-2, is addressed in the current literature — it the reason it is called a novel coronavirus.In a nutshell, Dr. Kaufman believes that the corona virus is a hoax and does not pose any health threat. What we are being told is a dangerous virus, he says, is something that is actually beneficial to our health. Dr. Kaufman doesn't even attempt an explanation of how such a hoax could possibly succeed, or why it would inspire such loyal support from so many governments, international bodies, health authorities, research institutions, scientists, doctors, health workers, and journalists. Conspiracists often avoid discussing the strategies of their proposed deceptions because to so would be to expose how far-fetched their ideas really are. The pandemic, being such a deeply viscerally frightening event, is such fertile ground for paranoid story lines that all that the likes of Dr. Kaufman have to do to rack up the 'likes' is to poke holes in the accepted narratives. Is SARS-CoV-2 an exosmic ? Here his list about similarity SARS-CoV-2 and Exposure :[20]

Table.2 Similarity Exosome and COVID-19[20]

Category	Exosome	COVID-19
Diameter inside cell	500nm	500nm
Diameter outside cell	100nm	100nm
Receptor	ACE-2	ACE-2
Contains	RNA	RNA
Found in	Bronchoalveolar (lung) fluid	Bronchoalveolar (lung) fluid

Certain conditions that can induce exosome: 20

1. Toxic substance
2. Stress (fear)
3. Cancer
4. Ionizing radiation
5. Infection
6. Injury
7. Immune response
8. Asthma
9. Disease (unspecified in literature , many)
10. Electromagnetic radiation (5G)-no research

Dr. Kaufman concludes that the "supposed" Covid-19 disease is caused by conditions that produce exosomes, which emerge as the body's natural response to threat. These include poisoning, stress, infections (flu, pneumonia), and electromagnetic radiation (even though he acknowledges that there is no evidence for this). According to him, the coronavirus is actually exosomes rather than the cause of the illness. And exosomes are a good thing. The hundred thousand plus people who have died so far from the novel corona virus all actually

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died from stress, or some other disease. Or perhaps from 5G. No one would argue that a weak immune system doesn't factor in how a person responds to infection. This does not mean infection doesn't exist. In choosing one over the other, Kaufman reveals the stark limitations of the kind of either/or thinking that cannot tolerate a both/and scenario.[20]

This controversial topic very challenging that's needs further investigation from expert so public can also understand well about the COVID-19 disease.

3. **How SARS-CoV-2 infection induce relapse in Nephrotic Syndrome**?

SARS-CoV-2 targets the lung and likely other organs as well, leading to multi organ damage by binding to the angiotensin-converting enzyme2(ACE2) receptor, a cell surface protein highly expressed in the lung, heart and kidney. SARS-Cov-2 infection interface with the renin–angiotensin–aldosterone system (RAAS) through angiotensin-converting enzyme 2 (ACE2), down-regulation of ACE2 activity in the lungs facilitates the initial neutrophil infiltration in response to bacterial endotoxin and may result in unopposed angiotensin II accumulation. Elevated levels of plasma angiotensin II, which were in turn correlated with total viral load and degree of lung injury. Acute lung injury due to damage cell induce release cytokines and chemokines including interleukin-6 (IL-6), interleukin-1β (IL-1β), induced protein 10 (IP10) and monocyte chemo attractant protein-1 (MCP-1) suggest that a cytokine storm, also known as cytokine release syndrome(CRS). CRS refers to an uncontrolled and overwhelming release of pro inflammatory mediators by an overly activated immune system. Moreover, severe lymphopenia with hyper activated pro inflammatory T cells and decreased regulatory T cells is commonly seen in critically ill patients, suggesting dys-regulated immune responses.

However, when the protective immune response is impaired, virus will propagate and massive destruction of the affected tissue will occur, especially in organs that have high ACE2 expression such as intestine and kidney. Kidney involvement by two mechanisms:

- Tissue destruction by binding SARS-CoV-2 to ACE2 in kidney that can induce dysregulation of T-cell and suggest cytokine storm that can cause impairment of glomerular permeability
- Elevated pro-inflammatory agent including IL-4, IL-6 secondary to epithelial cell damage in lung , they may also leak into systemic circulation cause extra pulmonary manifestation. In kidney pro-inflammatory agent provoking increased glomerular permeability and podocytes' barrier dysfunction with subsequent protei nurea.

Two mechanisms of kidney involment in SARS-CoV-2 infection suggest as factors that can induce relapse in nephrotic syndrome.

Conclusions

It is important to further investigate of kidney involvement in patient with COVID-19 disease caused by SARS-CoV-2. Kidney as one of target organ of virus SARS-Cov-2 because it have high ACE2 expression as receptor virus to entry into cell. SARS-CoV-2 infection can induce release pro inflammatory agents especially IL-4 and IL-6 as result of T cell dys regulation, these agents can cause relapse in NS by provoking glomerular permeability subsequent as proteinuria.

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Patients with Nephrotic Syndrome who have COVID-19 diseases suggest will have tendency to frequent relapse compared to patient NS without COVID-19 disease.

Thus, further investigation of SARS-CoV-2 and its mechanism that can cause relapse in Nephrotic Syndrome are imperative for getting a full view of prevention and developing more effective drugs, also the diagnostic test to confirm the virus still need to discuss further .

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