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Our Mission

The Student Society of Pediatric Advocates is a student organization affiliated with the University of Georgia College of Pharmacy. We are a student group associated with the Pediatric Pharmacy Advocacy Group. The Mission of the SSPA is to bring awareness to the proper use of medication therapy in pediatric populations through various service and education-based initiatives. Service activities center around lending our medication-based knowledge to pediatric patients and their parents in our community. Educational activities are directed toward student members in an effort to safely and effectively extend pharmacy practice to pediatric populations by building relationships with mentors and professionals in the health care community, as well as supplementing didactic coursework with lectures by specialists and our peers. Overall, SSPA advocates for the safety and happiness of young patients while learning and having fun along the way. The purpose of our newsletter is to educate pharmacy students about pediatric pharmacy and advocate for pediatric patients within the University of Georgia College of Pharmacy.

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SPREAD LOVE, NOT VIRUSES: A COMPARISON BETWEEN THE 2019 NOVEL CORONAVIRUS AND THE 2019-2020 INFLUENZA VIRUSES

BY: NINA MURPHY, PHARM.D. CANDIDATE 2021

Human Coronaviruses

Human coronaviruses (HCoVs), named after the crown-like spikes on their surface, were first identified in the mid-1960s. They belong to the alpha and beta genera within the coronavirus subfamily and replicate by using a nested set of mRNAs. During epidemics, coronaviruses have been responsible for causing up to one-third of community-acquired upper respiratory tract infections in adults and a significant proportion of upper respiratory tract infections in children. Certain coronaviruses may also cause diarrhea in infants and children[1,6].

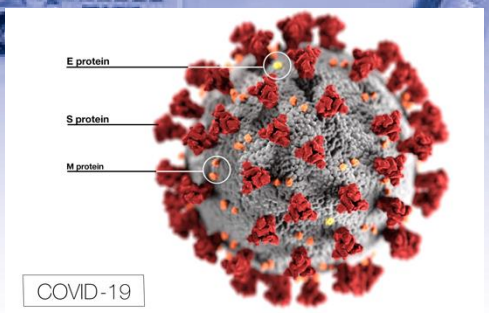

Figure 1. *Image displaying the ultrastructural morphology exhibited by coronaviruses. The protein particles E, S, and M located on the outer surface of the virus have been labeled. Source: https://phil.cdc.gov/Details.aspx?pid=23313*

Despite the discovery of HCoVs a little over half a century ago, it was not until the end of 2002 that coronaviruses became the center of attention due to the severe acute respiratory syndrome (SARS) pandemic. Within months, SARS had spread to nearly every continent. At the conclusion of the SARS pandemic in 2003, it had infected nearly 8,100 people, killed 774 individuals, and was estimated to have cost between $30 and $50 billion to the global economy[3,4]. Luckily, a worldwide pandemic was averted due to collaborative efforts between scientists, government officials, and healthcare professionals in the field[5].

2019 Novel Coronavirus

The 2019 Novel Coronavirus, or COVID-19, is a novel respiratory virus that was first identified in Wuhan, China in early December 2019 after 41 people developed idiopathic pneumonia that was unresponsive to existing treatment regimens. Thousands of laboratory-confirmed cases in China have since been reported, and numbers continue to rise. The majority of case reports originated from the Hubei Province and the other surrounding provinces, but numerous cases had also been reported throughout China. Shortly after, increasing cases had begun to be reported in countries overseas such as Europe, Australia, and the United States, mainly among travelers from China. The suspected origin of COVID-19 was thought to be associated with the Huanan Seafood Wholesale Market, where live rabbits, snakes, bats, and other animals were sold. Most of the infected patients had worked for or visited the market, and it was shut down for disinfection. However, the definitive origin of the virus is still under investigation.

When the coronavirus is spread from animals to humans, the virus evolves and becomes a new human coronavirus[2]. COVID-19 is the third zoonotic coronavirus, after

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV)[31]. So far, human-to-human transmission mainly through respiratory droplets is the suspected mode of transmission, but how easily or sustainably COVID-19 spreads between people remains unclear[6,13].

Figure 2. *Passengers wearing protective masks at a train station in Hong Kong. Source: https://www.wsj.com/articles/what-we-know-about-the-wuhan-virus-11579716128*

Public Health Emergency of International Concern

On January 30, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak as a Public Health Emergency of International Concern (PHEIC), making it the sixth time that a PHEIC has been initiated since the H1N1 pandemic in 2009[12]. Both the WHO and Centers for Disease Control and Prevention (CDC) released travel advisories recommending the avoidance of all nonessential travel to China. In particular, the WHO advised exit screening for international travelers from areas with active COVID-19 transmission to identify individuals with fever, cough, or potential high-risk exposure[6,9,10]**.** On February 2, 2020, the U.S. government suspended entry of foreign nationals (such as lawful permanent residents and aliens who are the spouses U.S. citizens or lawful permanent residents) who had been in China within the past 14 days[29]. U.S. citizens, residents, and their immediate family members who had been in the Hubei province and other parts of mainland China were permitted to enter the U.S., but were subject to health monitoring and possible quarantine for up to 14 days[13]. The CDC also expanded health screenings of passengers arriving from Wuhan from 5 to 20 airports in an effort to prevent further spread of COVID-19 in the country. In China, health officials announced a restriction of public transportation within Wuhan and a temporary halt of all air and rail traffic out of Wuhan and surrounding areas. As of April 15, 2020, at least 91% of the global population resides in countries with COVID-19 related travel restrictions, with approximately 39% residing in countries that have enforced complete border closures to foreigners[32].

Current Interventions to Control COVID-19

The CDC continues to closely monitor the situation and is collaborating with the WHO, state and local public health partners, and scientists in China to address this emerging public health threat[13]. Although similar coronaviruses from past outbreaks (SARS and MERS) were spread from symptomatic individuals, there is the possibility for asymptomatic individuals to transfer COVID-19 during the incubation period (up to 14 days)[6]. If the latter is the case, changes in the public health response will have to be implemented. On January 29, 2020, the Institut Pasteur, a French non-profit private foundation responsible for the monitoring of respiratory viruses, sequenced the whole genome of COVID-19 and submitted the sequence to the Global Initiative on Sharing All Influenza Data (GISAID) platform, which shares sequences and monitors the

genetic evolution of influenza viruses on a global scale. Hence, it is a vital component in determining the composition of the influenza vaccine. A special “coronavirus” tab has been created so that the scientific community can collaborate at a quicker pace. The CDC is also growing COVID-19 in cell culture, which will be necessary for further studies. Currently, a number of pharmaceutical companies such as Johnson & Johnson and Inova Pharmaceuticals are working to develop a vaccine[16,17,18].

Figure 3. *A close up on the COVID-19 sequence, performed at the Institut Pasteur (Paris, France). Source: https://www.pasteur.fr/en/press-area/press-documents/institut-pasteur-sequences-whole-genome-wuhan-coronavirus-2019-ncov*

COVID-19 Reported Cases

As of April 25, 2020, the CDC has reported a total of 928,619 positive cases and 52,459 deaths in a total of 55 jurisdictions within the U.S. All U.S. states and territories, except the American Samoa, Federated States of Micronesia, Palau, and the Marshall Islands, have had confirmed cases of COVID-19[33]. On a global scale, the WHO has reported 2,804,796 confirmed cases and 193,710 deaths and the global risk assessment is categorized as very high[15].

Influenza Virus

As of April 18, 2020, the CDC’s FluView, a weekly U.S. influenza surveillance report, stated that influenza severity indicators remain low overall, but hospitalization rates among children and young adults remain high. The CDC has estimated that there have been 39 million to 56 million influenza illnesses so far this season, of which 410 thousand to 740 thousand have required hospitalization. So far, approximately 24 thousand to 62 thousand people (including 169 children) have died from the flu[13].

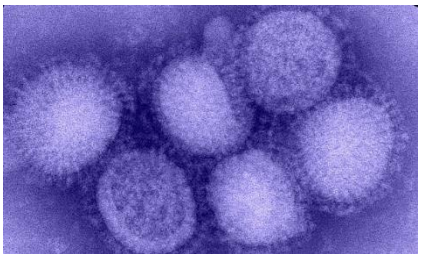

Figure 4. *Electron microscope image of H1N1 influenza virus. Source: https://www.cdc.gov/flu/pandemic-resources/index.htm*

In contrast to the discovery and pathogenicity of the COVID-19, the human influenza virus was isolated in 1933 and has had a reputation for causing numerous pandemics since its discovery[7]. It is important to remember that there are two main types of influenza virus (Types A and B) which routinely spread in humans through the inhalation of respiratory droplets. These two types are responsible for seasonal flu epidemics each year.

After thorough review and evaluation of epidemiologic data, antigenic characteristics of recent influenza isolates, serological responses to 2018-2019 vaccines, and the availability of candidate strains and reagents, the FDA's Vaccines and Related Biological Products Advisory Committee recommended that the 2019-2020 trivalent formulation influenza vaccines contain the following strains: an A/Brisbane/02/2018 (H1N1)pdm09-like virus; an A/Kansas/14/2017 (H3N2)-like virus; and a B/Colorado/06/2017-like virus (B/Victoria lineage). The advisory committee also recommended that the quadrivalent influenza vaccine include the following additional B strain: a B/Phuket/3072/2013-like virus (B/Yamagata lineage)[20]. The FDA noted that roughly 60% of the influenza virus specimens tested nationally to date have been influenza type B which, although less severe in adults, can cause more serious infections in children[28]. In contrast, type A influenza lineages are commonly more pathogenic and are responsible for pandemics[19]. Table 1 compares key clinical features and epidemiologic statistics between COVID-19 and the influenza virus.

Table 1. Clinical Features and Epidemiologic Statistics: COVID-19 versus Influenza Virus[6,8,11, 21, 22, 24,34, 35]

	COVID-19	Influenza Virus
Transmission	• Person to person through respiratory droplets from an infected person coughing, sneezing, or talking • Possibly via airborne route – Tiny droplets remaining in the air even after ill person is no longer near	• Person to person through respiratory droplets from an infected person coughing, sneezing, or talking
Most Common Symptoms and/or Clinical Findings	• Fever, chills • Cough • Shortness of breath or difficulty breathing • Myalgia • Fatigue • Sore throat • New loss of taste or smell • Bilateral infiltrates on chest imaging	• Fever or feeling feverish/chills* • Cough • Myalgia or body aches • Fatigue • Sore throat • Headaches • Severe malaise ** Note: Not everyone with the flu will have a fever*
Less Common Symptoms	• Sputum production • Headache • Hemoptysis • Diarrhea	• Runny or stuffy nose • Vomiting • Anorexia • Diarrhea
Complications	• Respiratory failure/ARDS • Septic shock • Acute cardiac injury • Secondary infection • Organ failure	• Pneumonia • Sinus and ear infections • Myocarditis • Encephalitis • Sepsis • Myositis, rhabdomyolysis • Multi-organ failure
Incubation Period	Within 14 days following exposure	1 to 4 days

Diagnosis	See Figure 5.
	
	Note: Case definitions and clinical criteria for diagnostic evaluation differ slightly between expert groups
	
	For patients who meet the CDC criteria, it is recommended to test for other respiratory pathogens and collect upper respiratory tract specimens (nasopharyngeal and oropharyngeal swab) and, if possible, lower respiratory tract specimens (sputum, tracheal aspirate, or bronchoalveolar lavage). Serum may also be collected.
	
	Once specimens are collected, they are sent to the CDC laboratory which subsequently performs polymerase chain reaction (PCR) to detect COVID-19.
		See Figure 6.
		
		• Diagnostic Tests:
		  ○ Rapid molecular assay
		  ○ Rapid influenza diagnostic test
		  ○ Direct and indirect immunofluorescence assays
		  ○ Molecular assays (including RT-PCR)
		  ○ Multiplex molecular assays
		  ○ Rapid cell culture (shell vial and cell mixtures)
		  ○ Viral culture (tissue cell culture)

Treatment/ Management	• Early recognition of suspect cases
	• Immediate isolation
	• Institution of infection control measures (standard, contact, and airborne precautions as well as eye protection)
	• Notification of public health officials
	• Supportive care – There is currently no other treatment recommended for coronavirus.
	
	Interim guidelines from both the WHO and CDC on surveillance case definitions, laboratory diagnosis, and clinical management are available.
		• Non-high risk patients:
		  ○ Symptomatic treatment
		  ○ Stay at home in order to minimize risk of infecting others
		  ○ Self-monitor for worsening signs and symptoms
		• For high risk patients:
		  ○ Neuraminidase inhibitors (NAIs) (Zanamavir, Oseltamivir, Peramivir)*
		  ○ Cap-dependent endonuclease inhibitors (Baloxavir)*
		• Supportive care:
		  ○ Hydration
		  ○ Antipyretics
		
		** Note: Benefits of NAIs and baloxavir are highly dependent on the timing of initiation, with an ideal period within 12 hours of influenza onset up to 48 hours.*

Number of U.S. Cases, Hospitalizations, and Deaths (As of April 25, 2020)	• 928,619 total cases • Cumulative hospitalization rate of 29.2 per 100,000 population • 52,459 deaths	• 39 to 56 million cases* • 410 to 740 thousand hospitalizations (rate of 68.6 per 100,000 population)* • 24 to 62 thousand deaths* ** CDC preliminary in-season 2019-2020 burden estimates*
Global estimates	• 2,804,796 cases • 193,710 deaths	• 1 billion cases • 290 to 650 thousand deaths

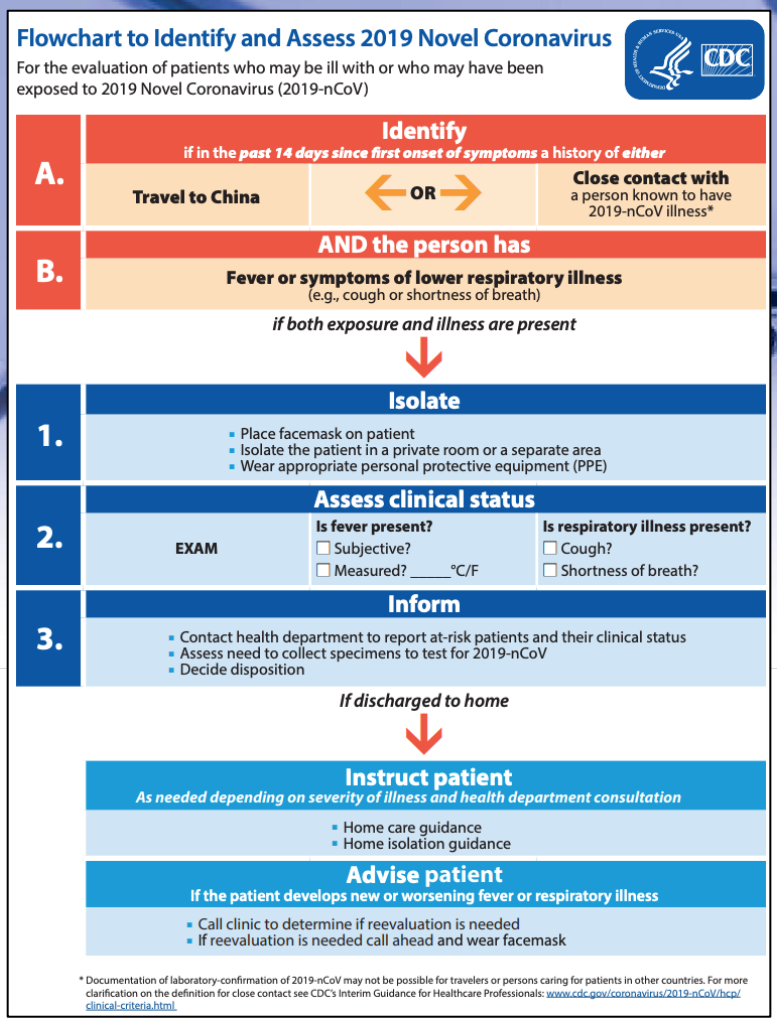

Figure 5. *CDC flowchart to identify and assess 2019 novel coronavirus. Source: https://www.cdc.gov/coronavirus/2019-ncov/hcp/identify-assess-flowchart.html*

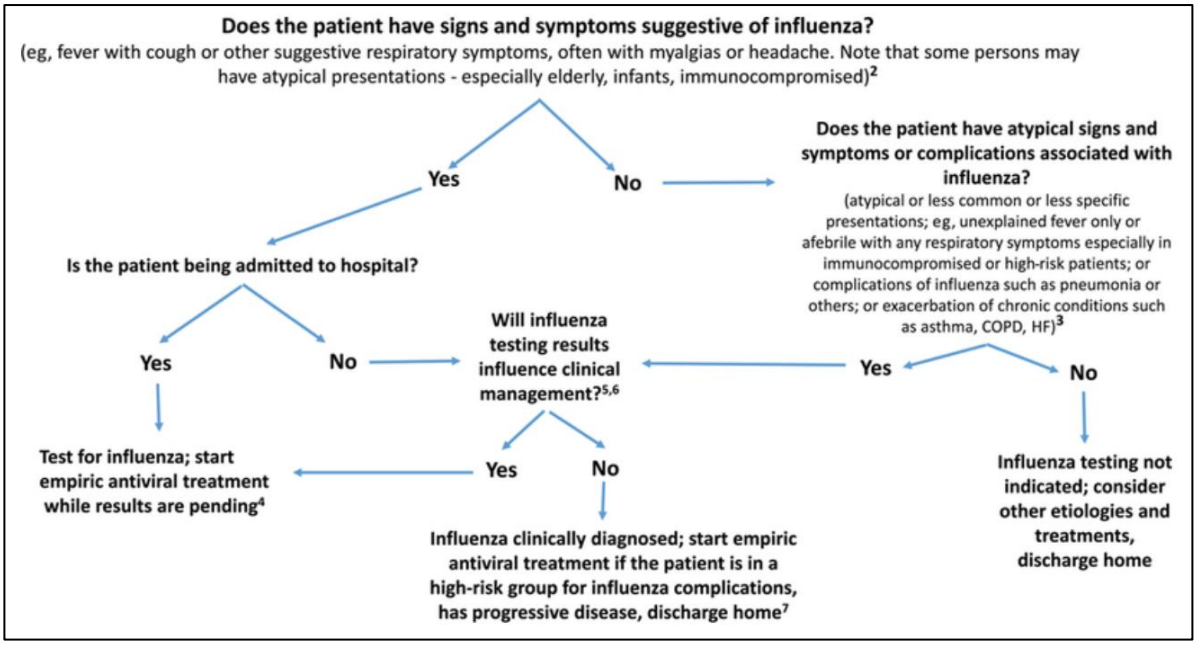

Figure 6. *Infectious Diseases Society of America (IDSA) guide for considering influenza testing when influenza viruses are circulating in the community (regardless of influenza vaccination history). Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6653685/*

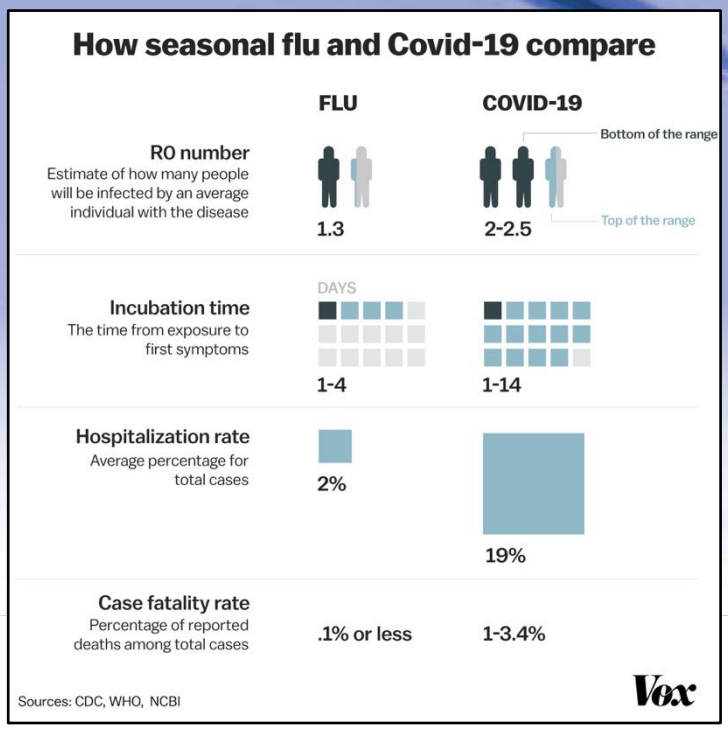

Figure 7. *Infographic comparing seasonal influenza and COVID-19 R0 number, incubation time, hospitalization rate, and fatality rate. Source:* https://www.vox.com/science-and-health/2020/3/18/21184992/coronavirus-covid-19-flu-comparison-chart

The differences between the number of cases, hospitalizations, and deaths reported for COVID-19 and influenza are staggering; however, this is a very difficult question to answer as the data collection for COVID-19 in the U.S. only began with the first reported case on January 20, 2020 and can't be directly compared to an entire influenza season[36].

From the data gathered so far, it appears as if COVID-19 is more contagious, more deadly (particularly in the elderly population), and more overwhelming to our health care system (Figure 7)[37].

Influenza should still remain a priority

Despite the apparent severity of COVID-19 being much worse than influenza, it is still important to keep influenza a health priority. Every year, influenza continues to be associated with high rates of morbidity and mortality. Unfortunately, only about 52% of individuals reported they planned to receive a flu vaccine this season, with the main reason for refusal being that individuals don't believe flu vaccines work very well[25].

Although influenza is a self-limiting disease, it is also important to recognize that it can lead to the development of serious secondary complications which can in turn, if not appropriately controlled, lead to death, especially in high risk groups (Table 2).

Table 2. Patient Populations at High Risk for Complications or Severe Influenza[27]
• Individuals with certain chronic medical conditions (such as asthma, diabetes, or heart disease) or immunosuppression • Women who are pregnant or two weeks postpartum • Individuals younger than 19 years who are receiving chronic aspirin- or salicylate-containing medications • Individuals who are extremely obese (BMI $\geq$ 40 kg/m^2) • Residents of nursing homes and other long-term care facilities • Children younger than 5 years, especially those younger than 2 years old

In particular, individuals greater than 65 years and younger than 2 years are at the highest risk for severe illness, hospitalization, and death. To date, 68 children have died from the flu and the number continues to rise at a faster rate compared to last

year's numbers. For comparison, 116 children died from the flu during the 2018-2019 flu season and 183 from the 2017-2018 flu season[26]. Thus, it's important to be able to recognize the following emergency warning signs of flu in children so that medical interventions may be immediately implemented (Table 3).

Table 3. Emergency Warning Signs of Flu in Children[23]

- Fast or troubled breathing
- Bluish lips or face
- Ribs pulling in with each breath
- Chest pain
- Severe muscle pain (child refuses to walk)
- Dehydration (Anuria for 8 hours, dry mouth, no tears when crying)
- Not alert or interacting when awake
- Seizures
- Fever above 104°F
- Any fever in children less than 12 weeks
- Fever or cough that improves but returns or worsens
- Worsening of chronic medical conditions

CDC Influenza Vaccine Recommendations and Other Preventive Measures

As the most accessible healthcare professionals, the role of pharmacists, pharmacist interns, and pharmacy technicians in preventing the spread of influenza is absolutely critical. As a reminder, the CDC recommends everyone 6 months of age and older receive the influenza vaccine every flu season. Children 6 months through 8 years may need 2 doses during a single flu season. The injectable influenza vaccine (IIV) is administered as an intramuscular injection and is approved for use in individuals 6 months and older. The live inactivated influenza vaccine (LAIV) is administered intranasally and is approved for use in individuals 2 through 49 years old; however, certain individuals with underlying medical conditions (such as pregnancy, history of severe hypersensitivity to any component of LAIV, and immunosuppression) may not qualify for this dosage form[30]. For children less than 8 years old who are receiving the flu vaccine for the first time or have only previously received one dose of vaccine, a total of two doses are required. The first dose should be administered as early in the season (early October) as possible, and the second dose should be administered at least 4 weeks later. It's important to note that it will usually take two weeks after the second dose for immunity against the influenza virus to take effect. Lastly, pharmacists should provide counseling on daily preventive actions such as properly covering coughs, practicing good hand hygiene, and avoiding others who are sick[27].

The ability to recognize the clinical signs and symptoms of influenza, promote annual influenza vaccination and healthy preventive measures, and address barriers associated with receiving the seasonal vaccination are skills that make pharmacists invaluable assets in the seasonal war against influenza. With the introduction of COVID-19, the scope of pharmacy practice has further widened. Unquestionably, the role pharmacists play in helping with the influenza virus will be adopted to COVID-19 as it continues to spread across the world and we discover more information about this novel virus.

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ALTERNATIVES TO CEFOTAXIME IN THE TREATMENT OF NEONATAL SEPSIS

BY: ZAYD AHMAD, PHARM.D. CANDIDATE 2021

Sepsis is a serious complication in neonatal patients. It occurs in up to 8 per 1000 births with the highest rates occurring in low birth weight infants, premature rupture of the membranes, and infants with a low Apgar score[1]. While the incidence of sepsis in both term and preterm infants is low, it remains an important cause of mortality and morbidity in this population. Sepsis is defined as life threatening organ damage in response to systemic infection, with or without a positive blood culture[2]. In neonates, signs and symptoms of systemic infection include temperature irregularities, respiratory distress, tachycardia, lethargy, and hypotension. Asymptomatic sepsis also occurs, although less likely. International guidelines published by the Society of Critical Care Medicine (SCCM) recommend initiation of antimicrobial therapy as soon as possible. Empiric antibiotic therapy should include coverage against pathogens that are likely to be seen in septic shock. In previously healthy neonates without risk factors for multidrug resistant bacteria, these are group B streptococci and *Escherichia coli*[1]. To target these pathogens, treatment of neonatal sepsis often includes a third-generation cephalosporin, commonly cefotaxime. Unfortunately, nationwide drug shortages have severely crippled its availability. Because of this, viable alternatives to cefotaxime are warranted in order to continue providing safe and effective therapy.

Cefotaxime is third-generation cephalosporin that is routinely recommended in neonatal patients due to its antimicrobial spectrum of activity, favorable distribution, and side effect profile. Covering *Streptococcus pneumoniae,* Group A *streptococcus,* and *Haemophilus influenza,* it is recommended by the Infectious Disease Society of America (IDSA) to treat pneumonia in neonates that are not fully immunized. Its high penetration into the central nervous system and activity against gram-negative bacilli such as *E. coli* and *Klebsiella* makes

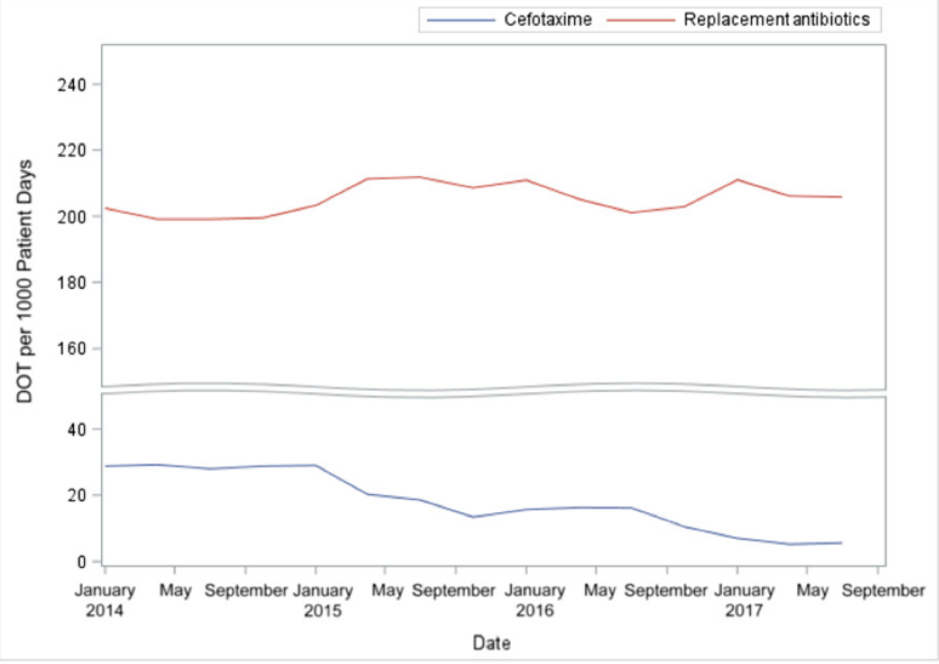

FIGURE 1
Trends in use of cefotaxime and replacement antibiotics (ampicillin, ceftriaxone, ceftazidime, cefepime, gentamicin, meropenem) among children hospitalized at 45 Pediatric Hospital Information System (PHIS) hospitals, 2014 through 2017. DOT, days of therapy (unpublished data).

https://www.aappublications.org/content/early/2015/02/25/aapnews.20150225-1

it the one of the drugs of choice for the treatment of bacterial meningitis as well[3,4]. These two conditions are the most common secondary infections that lead to sepsis in neonates[1]. Because of this, cefotaxime is one of the few antimicrobials recommended by the SCCM for the treatment of neonatal sepsis. Despite its clinical utility, it has been on the American Society of Health-System Pharmacists (ASHP) shortage list since 2013. Drug manufacturers Sanofi-Aventis, Hospira, and Baxter have all discontinued cefotaxime due to an increased cost of raw materials. The sole current manufacturer, Hikma, has been unable to meet demand for the cephalosporin leading to the national drug shortage[5]. Currently, the Food and Drug Association (FDA) has allowed Apollo Pharmaceuticals and Canadian company SteriMax to temporarily import cefotaxime vials from Canada in order to combat the shortage[6]. This shortage has disproportionally affected neonatal patient populations due to limited therapeutic alternatives. Because of international shortages, pharmacists should be aware of what alternatives are available without compromising the safety of their patients.

One substitution for cefotaxime is ceftriaxone. As another third-generation cephalosporin, ceftriaxone shares broad spectrum coverage as cefotaxime. The IDSA often mentions ceftriaxone for a plethora of pediatric infections for the same reasons as cefotaxime. Unlike cefotaxime, however, ceftriaxone is highly bound to serum albumin. It competes with bilirubin for the binding site of albumin and has been shown to increase the proportion of free bilirubin circulating in plasma. In neonates, this can lead to a condition called kernicterus, which is characterized as bilirubin induced encephalopathy[7]. Kernicterus can progress to seizures, coma, and death. Because of the concern for neurological damage, the American Academy of Pediatrics (AAP) cautions against the use of ceftriaxone in infants under two months old.

Another empiric treatment is ampicillin and the aminoglycoside gentamicin. Because aminoglycosides do not intrinsically cover gram-positive organisms, and one of the most common pathogens in neonatal sepsis is Group B *streptococcus*, the use of both antimicrobials at the same time is necessary until the offending organism is determined. Gentamicin does not cross the blood brain barrier in high concentrations like cefotaxime. Consequently, if bacterial meningitis is suspected as the secondary cause of sepsis, cefotaxime should be added to the regimen. Aminoglycoside blood levels should also be monitored in all patient groups, as both efficacy and toxicity are dependent upon the serum concentration. Adverse effects of aminoglycosides include kidney dysfunction and hearing loss[1].

Due to the extensive cefotaxime shortages in the United States, the AAP currently recommends using ceftazidime in place of cefotaxime for all indications. Ceftazidime has similar CNS penetration as cefotaxime making it an option in meningitis. It is also not highly albumin bound and does not displace bilirubin like ceftriaxone[7]. Ceftazidime also has a near identical spectrum of activity to cefotaxime with the exception of its *Pseudomonas aeruginosa* coverage. This is notable because *P. aeruginosa* is an organism responsible for many multi-drug resistant nosocomial infections. It is unclear how widespread use in neonatal patients will affect *Pseudomonas* susceptibility or resistance to ceftazidime.

Because of global shortages, pharmacists must be aware of what alternatives are available without compromising the safety of their patients. Unfortunately, these alternatives are greatly limited. As of now, the AAP only recommends one drug, ceftazidime, as a viable replacement to cefotaxime in neonates. However, there are possible repercussions with regard to its use. To combat this, some institutions have decided to reserve cefotaxime for their neonatal patients[8]. Although the FDA is currently working for a solution, it is unknown how or when the cefotaxime shortage will resolve. Pediatric pharmacists should utilize ceftazidime in clinical practice and continue to monitor for any shortage updates.

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NEW FDA APPROVED DRUGS FOR PEDIATRIC TYPE 2 DIABETES MELLITUS

BY: LATIA JONES, PHARM.D. CANDIDATE 2022

Type 2 diabetes is a long-standing condition that affects the way the body metabolizes glucose and uses it for energy. The body either resists the effects of insulin, which regulates the transport of glucose into your cells, or fails to meet insulin demand to allow the body to maintain a normal blood glucose level. Type 2 diabetes was formerly known as adult-onset diabetes, as it typically occurs later in life, but today, more children are being diagnosed with the disorder as the rates of childhood obesity continue to rise[1]. Unfortunately, there is no cure for type 2 diabetes. Treatment options typically begin with lifestyle modifications such as losing weight, eating well, and daily exercise to avoid the development of lifelong complications. If not adequately managed with lifestyle interventions, physicians may look to the limited, FDA-approved medication options for adolescents, which include metformin and insulin therapy. In 2019, the FDA had approved two products for use in diabetes management in pediatric patients. The first of the two is the first non-insulin drug to be approved for diabetic pediatric patients since metformin, and the second is an emergency hypoglycemia treatment that can be administered without an injection[2].

Victoza®, also known as liraglutide, is a subcutaneous injection given once daily that was previously approved for adults in 2010. With the increase in prevalence of obesity and T2DM among children, this GLP-1 receptor agonist has shown to be a beneficial adjunct to diet, exercise, and metformin monotherapy to help improve glycemic control 2. The approval of Victoza® was based on a 26-week, double-blind study published in the New England Journal of Medicine titled “Liraglutide in Children and Adolescents with Type 2 Diabetes Mellitus.” In this study, 135 patients aged 10 to 17 years of age were given either liraglutide or placebo and monitored over the course of 26 or more weeks. Eligible patients participating in the study had a body mass index in the 85th percentile for their age group, with A1c levels between 6.5 and 11%. Their histories varied with previous treatment being either exercise and diet modification or solely metformin monotherapy. The primary endpoint was the change from baseline in the glycated hemoglobin level after 26 weeks. The study looked at other secondary endpoints, including the change in fasting plasma glucose level and BMI[3]. These endpoints demonstrate the benefits associated with liraglutide in gaining glycemic control in pediatric patients, and they were significant information used in the FDA approval process.

Figure 2 illustrates the outcomes of multiple endpoings when comparing liraglutide ro placebo, including glycated hemoglobin level, fasting plasma glucose, and BMI z-score. Liraglutide was superior to placebo at both week 26 and 52 in reducing fasting plasma glucose levels. Moreover, 63.7% of the patients in the liraglutide group, as compared with 36.5% in the placebo group, attained glycated hemoglobin levels of less than 7.0%[3]. These results show the efficacy of the treatment in pediatric patients and exhibited promising evidence that liraglutide could be used to improve glycemic

control in younger individuals as well as adults. Liraglutide's approval for pediatric use shows promise in the future of medication options for pediatric patients.

Secondly, the FDA approved Baqsimi®, which is a formulated glucagon powder that is administered intranasally for severe hypoglycemic events. It is the first product indicated for use in this setting that does not need to be given by injection. One study revealed that among 58 patients 4 years or older, who received either intramuscular glucagon or Baqsimi®, both groups experienced an increase in glucose within 20 minutes of insulin-induced hypoglycemia[2]. Based on the results of this study, investigators concluded that Baqsimi® is non-inferior to other glucagon products on the market, and also offers the advantage of a non-invasive dosage form. Ease of administration is beneficial to both the patient and the caregiver in a hypoglycemic emergency.

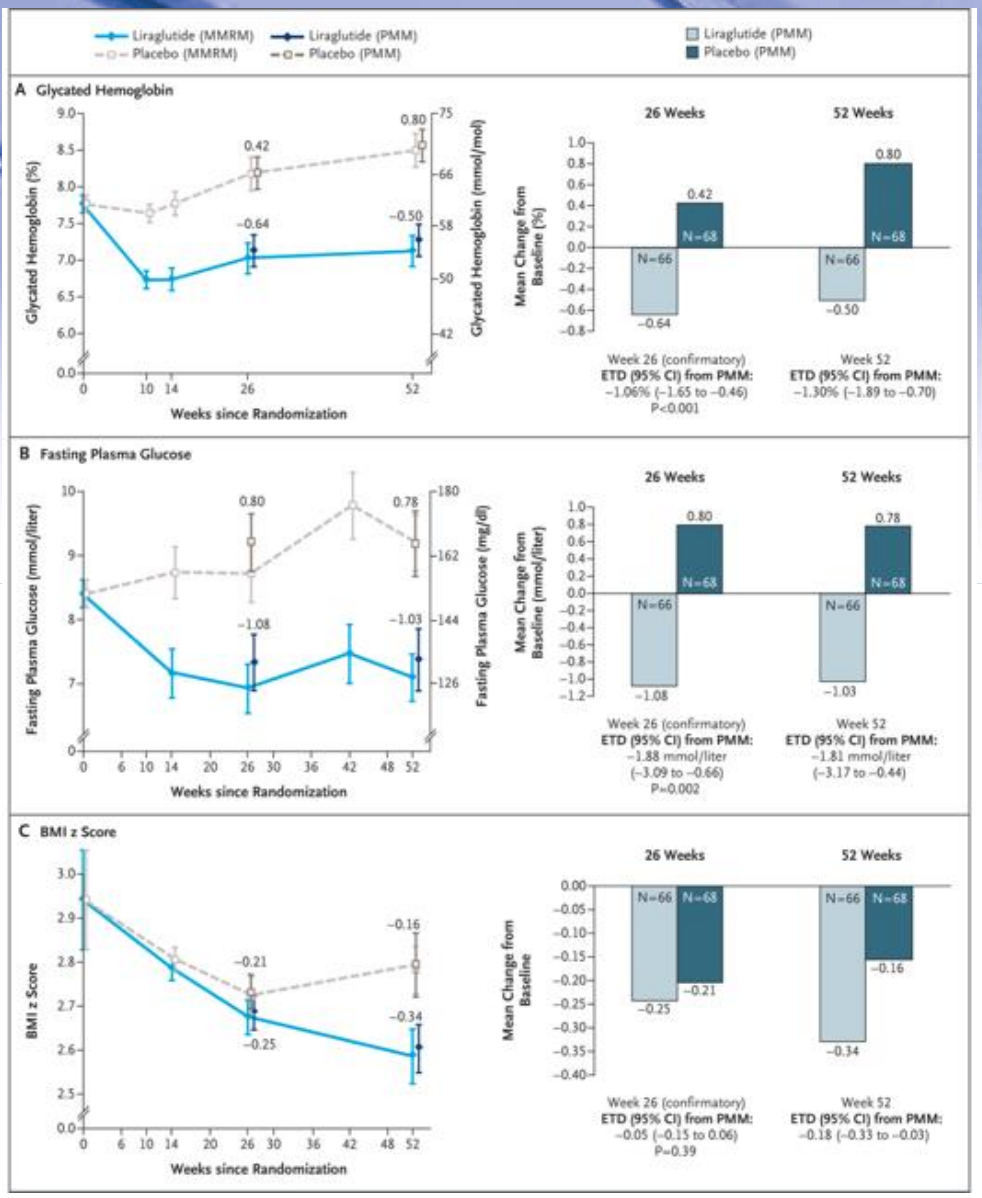

Figure 2[3]

The pharmaceutical industry is making great advances in modern medicine to ensure that we are finding new forms of treatments to better understand and care for all of the patients that are living with type 2 diabetes. As new studies emerge in the pipeline, the ultimate goal remains that new therapies will be safe and effective in managing type 2 diabetes, as the pediatric population remains vulnerable due to a lack of ideal dosage forms along with pharmacodynamic and pharmacokinetic differences.

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OMEGA-3 SUPPLEMENTATION IN CHILDREN WITH ADHD

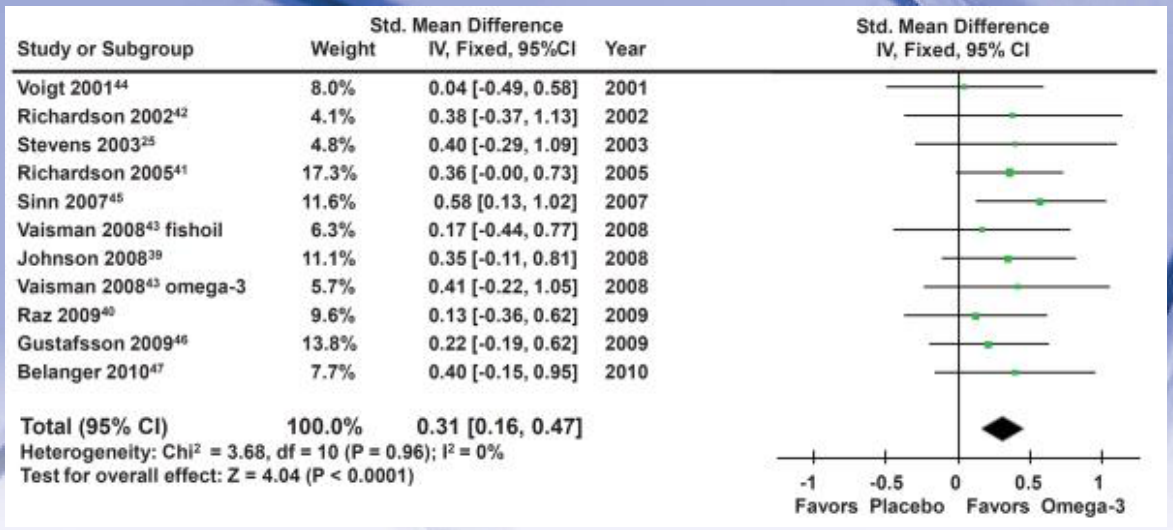
BY: GRISHMA PATEL, PHARM.D. CANDIDATE 2022

Attention deficit hyperactivity disorder (ADHD) is a common persistent neurodevelopmental disorder that commences during early childhood and often spans through adulthood. Symptoms of ADHD can include hyperactivity, impulsivity, and/or inattention, which can be associated with significant impairment academically, behaviorally, emotionally, and socially[6]. Based on the parent-based report data from the National Survey of Children's Health (NSCH), the prevalence of children aged 4-17 years diagnosed with ADHD increased by 42% between 2003 (7.8%) and 2011 (11.0%), and the median age of onset for children with current ADHD was 6 years. In 2011, 63.9% of children with a current diagnosis of ADHD received medication for it[1]. While first line treatment is pharmacotherapy and psychosocial therapy, some individuals are exploring alternative options to these traditional therapies.

While the pathogenesis of ADHD is not fully known, a genetic imbalance of catecholamine metabolism in the cerebral cortex plays a primary role. However, environmental factors may also play a role in the pathogenesis of ADHD. While the influence of diet on ADHD is controversial, a small subset of children may display behavioral symptoms with a diet consisting of food additives, artificial colors, excess sugar, or reduced intake of essential fatty acids and minerals. Specifically, some studies have noted decreased fatty acid concentrations in the serum of children with ADHD and/or lower ratios of Omega-3 Fatty acids to Omega-6 fatty acids[6]. A high Omega-6 to Omega-3 ratio can alter cell membranes and result in the release of inflammatory mediators due to Omega-6 fatty acids being involved in the production of pro-inflammatory mediators. Omega-3 fatty acids have more anti-inflammatory properties and are essential for brain development and neurofunction. Omega-3 fatty acids are components of phospholipids and may alter the structure and function of proteins embedded in the phospholipid membrane. The presence of more Omega-3 fatty acids in the structures of the cell membrane have been found to alter dopaminergic and serotonergic neurotransmission in specific regions of the brain, signifying that Omega-3 fatty acids may play a role in the management of ADHD[3]. Several classifications of Omega 3 fatty acids exist, but the majority of literature focuses on alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). EPA and DHA are considered long chain Omega-3 fatty acids. ALA can be converted into EPA and DHA, but the conversions are very limited with reported rates of <15%. Therefore, EPA and DHA from food and dietary supplements are the most practical way to increase fatty acids levels in the body[7].

A meta-analysis involving 10 trials and 699 children with ADHD demonstrated a benefit from polyunsaturated fatty acid supplementation (PUFA) compared to placebo. The benefits from PUFA supplementation were small compared to pharmacological treatment but still statistically significant as depicted by Figure 1 with a standardized mean difference (SMD): 0.31, 95% Confidence Interval (CI) of 0.16–0.47, z=4.04, and p~0.0001[4].

Figure 1:



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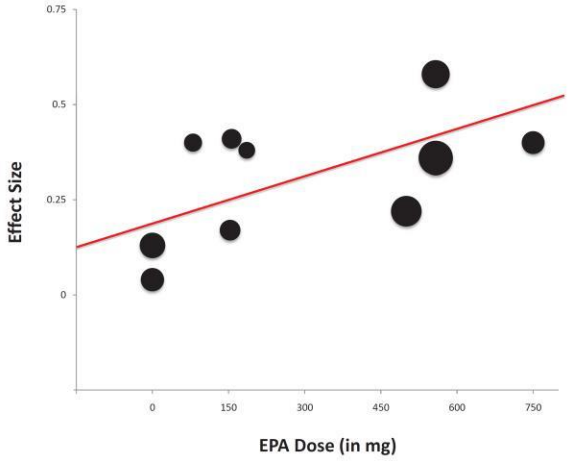
In addition, a higher dose of EPA was also associated with increasing efficacy in treatment of ADHD symptoms (β=0.36 (95% CI: 0.01–0.72), t=2.34, p=0.04, R2=0.38)[4].

Figure 2:



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According to a meta-analysis performed by Bloch and Mulqueen, evidence from multiple randomized control trials suggest efficacy of Omega-3 fatty acids with a dose of 1 to 2 grams daily and a higher EPA content for the treatment of ADHD. However, evidence for children with ADHD and other primary disorders such as dyslexia and developmental coordination disorders with reading impairments is inconclusive[3]. A meta-analysis by Chang et al. (2018) examined interventions and plasma levels of Omega 3 fatty acids in youth with ADHD. Based on their analysis, PUFA supplementation improved ADHD symptoms when compared with placebo, and those with ADHD had lower levels of DHA and EPA. However, there was no effect of PUFAs on teacher reported ADHD severity, and supplementation of PUFA did not help with memory and information processing. The dosages of Omega 3 fatty acids supplementation in this meta-analysis ranged from 2.7mg to 640mg of DHA and 80mg to 650mg of EPA. Overall, the meta-analysis showed that there was an improvement in

inattention and total ADHD symptom scores regardless of the EPA dosage. However, EPA dosages of 500mg and greater were needed to improve hyperactivity symptoms. Chang and colleagues (2018) stated that there is significant evidence supporting a role of Omega-3 fatty acids deficiency in ADHD and supplementation of Omega-3 fatty acids in this group with a biomarker based personalization approach[5].

Although pharmacotherapy and psychosocial therapy are first line treatments for ADHD, an increasing interest has grown in the use of PUFA supplementation in ADHD. Individuals who want to delay the need for pharmacological treatment or those who have not tolerated traditional pharmacological treatments may be interested in the use of PUFA for ADHD. PUFA supplementation, specifically Omega-3 fatty acids, may reduce ADHD symptoms and are generally well tolerated to an extent. While most studies focus on EPA and DHA dosing in children with ADHD, the Food and Nutrition Board of the Institute of Medicine has not established recommended intake values for EPA and DHA in ages 1 year and older[7]. In addition, not all PUFA supplement formulations are the same due to variations in EPA and DHA proportions. Several formulations such as gummies and liquids are available for purchase, but these formulations may not contain sufficient doses of EPA and DHA to be beneficial. Also, safety is a concern for these supplements due to not having to prove safety and efficacy prior to marketing. Finding a safe formulation with the adequate doses of EPA and DHA can be challenging and costly. Although there has been a small benefit from PUFA supplementation in children with ADHD, patients and caregivers should be aware that PUFAs may not be as effective as stimulants in the treatment of ADHD, and patients should be evaluated on an individual basis, taking into account the severity of ADHD symptoms, patient preference, and treatment history, before discussing PUFA supplementation. Due to variations in results from multiple studies and lack of larger studies, further research on PUFA supplementation in the management of ADHD is needed to provide more definitive evidence for PUFA's place in ADHD therapy[2].

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