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"Review on : H3N2"

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Abstract : The influenza virus is classified into four types A,B,C and D but type A and B major illness in people with influenza A only virus responsible for flu pandemic presence of two surface proteins called as hemagglutinin (H) and neuraminidase (N) on the virus .

Annual seasonal influenza vaccines are composed of two influenza A strains. Representing H1N1 and H_3N_2 subtypes and two influenza B strains representing the Victoria and Yamagata lineages. Strains from influenza A and influenza B viruses currently co-circulate in humans. During the 2016/2017 flu season the H_3N_2 component of influenza vaccine poor protective efficiency (~28-42%) against preventing infection of co-circulating strains. To the human population in 1986,H_3N_2 infection viruses have envolved genetically and antigenetically .To evaluate the clinical , laboratory , radiological and demographic data of H_3N_2 pneumonia cases hospitalized to the pulmonology department during H_3N_2 pandemics and compare with non H_3N_2 community-acquired pneumonia (CAP) cases. Influenza A (H_3N_2) have caused significant deaths as per WHO report . Amongst the molecular methods, real-time polymerase chain reaction (RT-PCR) is considered a gold standard test due to its many advantages. Most of the people with influenza abrupt onset of respiratory system and myalgia with or without fever and recover within 1 week but some can experience sever and fetal complications . Sporadic zoonotic infections with novel influenza A viruses avian or swine origin continue to pose pandemic threats. The WHO estimates that annual epidemics of influenza result in 1billion infections, 3-5 million cases of severe illness and 300,000-500,000 deaths.

Key words: Influenza A,H_3N_2, hemagglutinin , Real-time PCR , influenza pandemic , pneumonia, ETC.

1.INTRODUCTION

influenza is an infectious respiratory disease ;in humans , it is caused by influenza A (genus influenza virus A)and influenza B (Genus B) viruses (influenza virus C and influenza virus D genera are also known).[1]

The influenza virus is classified into four types;

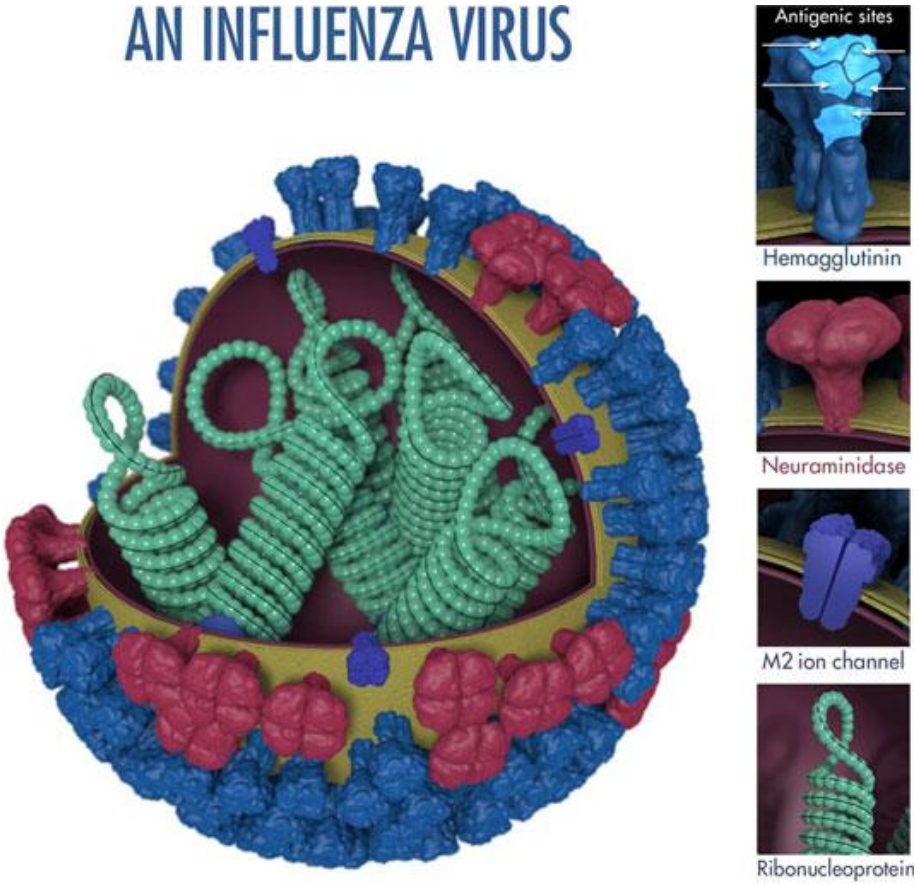
Type A
Type B
Type C
Type D

- Type A: influenza A viruses infect humans and many different animal .They have ability infect peoples and sustained human

to human transmission, can cause influenza pandemic.

- Type B :influenza B virus circulates among humans and cause seasonal epidemics .Also can be infected seals (showed recently)
- Type C: influenza C virus can infect both pigs and humans
- Type D: Influenza D virus affects cattle and cause illness in people .[2]

Influenza A is classified into different subtypes (based on hemagglutinin and neuraminidase with surface antigen) CDC report 18 different subtypes of hemagglutinin (H) and 11 different neuraminidase (N).H_1N_1 and H_3N_2 due to its rapid antigenic and genetic changes.[3] In our country the 1st flu in 2013-2014 was detected in 43rd week (October 22, 2013). In our study planned results of treatment and demographic clinical , laboratory ,radiological features .A diagnosis of H_3N_2 pneumonia in 2013-2014 flu season and during H_3N_2 pandemic.[4] Most people with influenza have self –limited upper respiratory tract symptoms with or without systemic signs and symptoms temporarily affect activity on daily, also missing work or school and some might access medical care.[5] H_1N_1 & H_3N_2 viruses have many differences at the gene sequence level, which are also inherited at amino acid level . In another study, they tested immunized rabbit sera H_1 antigen not show any activity against Influenza A (H_3N_2)virus. Similarly rabbit immunized with H_3 antigen, no significant HI titer was found against Influenza A (H_1N_1) virus.[6]Influenza virus , which enveloped single–stranded RNA virus from orthomyxoviridae family is divided into three types A,B,C according to nucleocapsid and matrix proteins. Type A influenza viruses are pathogens for birds, pigs , horses and specially for humans 5 to 20 % of population is infected with type A influenza virus about 360000 people die from disease associated with influenza A . Influenza A , respiratory syncytial virus , adenovirus ,parainfluenza type 1, 2, 3 and influenza B are common viral agents cause viral pneumonia.[7]In 2009 , the first influenza virus pandemic of this country was caused by novel H_1N_1 influenza A virus reassortant circulating in pigs.[8]According to study of genome from analysis of 286 influenza A(H_3N_2) virus, the rate of mutation is more for surface antigens (hemagglutinin, neuraminidase) and PB1-F2 proteins.[9]In 1968 (H_3N_2) influenza virus have genetic and antigenic evaluation leading to numerous seasonal epidemics exemplified by WHO recommended 28 vaccines strains changes our period of time H_3N_2 influenza viruses their receptor binding properties A reduced affinities for oligosaccharide analogues of cell surfaces receptors. Recent H_3N_2 influenza viruses vaccine study in US and in Europe from 2016/2017 .[10]



1.1.Animal Influenza:

Infection of waterfowl with low pathogenic avian influenza A (LPAI) viruses, called as such owing to their lack of lethality in poultry, produces little or no clinical symptoms.[11] However on transmission to poultry ,LPAI can cause substantial disease symptoms; in addition , viruses with H5 and H7 subtypes can become highly pathogenic (i.e. lethal) in poultry. Outbreaks of highly pathogenic influenza A(HPAI) throughout Euresia and northern Africa are the major influenza disease burden in animals ,with>400 million birds killed and economic losses totaling US$20 billion in the first 10 years of the 21stcentury.[12]Influenza A virus can also cause mild to severe respiratory infection in a variety of mammals , including swine ,horses and dogs ; additionally , and outbreak of an influenza A virus of avian origin was detected in cats in New York , as first reported in December 2016. From its first report until February 2017, the influenza A H7N2 feline influenza A virus infected ~ 500shelter cats and a veterinarian who treated one of the infected cats .[13]the management of influenza in pigs or horses is dependent on the use of vaccine. In pigs, influenza is a major disease causing problem for which biosecurity is paramount, and vaccination uses primarily whole inactivated virus in oil emulsion .In horses, the problem with vaccination is the short –term protection offered, but antigenically matched adjuvanted inactivated vaccine and LAIVs are efficacious.[14]

2. Signs and symptoms:

2.1. Avian, swain and other zoonotic influenza infections in humans may cause disease ranging from mild upper respiratory infection(fever and cough) rapid progression to severe pneumonia,

acute respiratory distress syndrome, shock and even death Gastrointestinal symptoms such as nausea , vomiting and diarrhea has been reported more frequently in A (H5N1) infection .Conjunctivitis has also been reported in influenza A (H7) .

2.2. Disease features such as the incubation period severity of symptoms and clinical outcomes varies by the virus causing infection but mainly manifest with respiratory symptoms.

2.3. In many patients infected by A(H5) or A(H7N9) avian influenza viruses, the disease has aggressive clinical course. Common initial symptoms are high fever (greater than or equal to 38^0c) and cough followed by symptoms of lower respiratory track involvement including dysponea or difficulty breathing. Upper respiratory tract symptoms such as sore throat or coryza are less common.

2.4. Other symptoms such as diarrhea, vomiting, and abdominal pain, bleeding from the nose or gums encephalitis, and chest pain have also been reported in the clinical course of some patients.

2.5. Complications of infection include sever pneumonia, hypoxemic respiratory failure, multi-organ dysfunction, septic shock and secondary bacterial and fungal infections. The case fatality rate for A (H5) and A (H7N9)subtype virus infections among humans is much higher than that of seasonal influenza infections .

2.6. For human infections with avian influenza A (H7N7) and A (H9N2) viruses, disease is typically mild or subclinical.

2.7. Only one fatal A (H7N7)human infection with swine influenza viruses, most cases have been mild with a few cases hospitalized and very few report of deaths resulting from infection .[15]

3. Epidemiology:

In terms of transmission, human infections with avian & other zoonotic influenza viruses, through rare, have been reported sporadically. Human infection are primarily acquired through direct contact with infected animals or contaminated environments but do not result in efficient transmission of these viruses between people.[16]Transmission of seasonal influenza A virus in humans have proposed that population in southeast Asia, eastern Asia and/or the tropics act as permanent sources for seeding seasonal epidermis, whereas other studies indicate that multiple geographical regions might act as seed population for virus migration.[17]seasonal influenza virus outbreaks typically occurs in the winter months, when low humidity and low temperatures favors transmission; two 'influenza seasons ' occur per year: one in Northern Hemisphere and one in the southern Hemisphere. Climate factors, including minimum temperature, hours of sunshine and maximum rainfall, seem to be strongest predictors of influenza seasonality.[18]Seasonal influenza B viruses co-circulate in humans with influenza A viruses and follow the same patterns of transmission.[19]

In 2013, human infections with A (H7N9) virus were reported for the first time in china. Since then, the virus has spread in the poultry population across the country and resulted in over 1500 reported human cases and many human dead[20].In the USA, annual, including incidence of symptomatic influenza is USA, annual incidence of symptomatic influenza is estimated to vary from 3% to 11%.[21] Household - based and community- based studies in different countries have shown that influenza virus infections and illness rates are higher in children and decrease with increasing age, approximately 20-40% of symptomatic people can manifest influenza like illness (fever and cough or some throat), whereas up to half of people with symptomatic illness can experience acute upper respiratory tract symptoms without fever, and the symptomatic proportion can range from 14% to more than 50%.[22]

3.1.In terms of risk factors for human infections :

For avian influenza virus ,the primary risk factor for human infection appears to be direct or indirect exposure to infected live or dead poultry or contaminated environments , such as live bird markets .Slaughtering ,for feathering ,handling carcasses of infected poultry ,and preparing poultry for consumption ,especially in household setting are also likely to be risk factor .There is no evidence to suggest that the A(H5),A(H7N8) or other avian influenza viruses can be transmitted to human through properly prepared poultry or eggs . A few influenza A (H5N1) human cases have been linked to consumption of dishes made with raw, contaminated poultry blood. Controlling the circulation of avian influenza viruses in poultry is essential to reducing the risk of human infection. Given the persistence of the A(H5)&A(H7N9) viruses in same poultry populations, control will required & strong co-ordination between animal &public health authorities.[23]

4. Pathophysiology:

Influenza and other members of the orthomyxoviridae are enveloped viruses characterized by having eight segmented, negative-sense RNA genomes.[24]HA is a trimeric glycoprotein that is typically classified in two groups: group 1 contains H1,H2, H5,H6,H8,H9,H11,H12,H13,and H16 while group 2 includes H3,H4,H7,H10,H14,H15. Two more HA subtypes, H17 and H18,have been discovered in bats.NA tetrameric glycoprotein that is divided into three groups: group 1 (N1,N4,N5,and N8),group 2(N2,N3,N6,N7,N9),and group 3, which contains NA from B influenza viruses.N10 and N11 have only recently been discovered and primarily circulate in bats[25].For avian influenza A (H5N1) virus infections in humans, current data indicates an incubation period averaging 2 to 5 days and ranging up to 17 days. For human infections with the A (H7N9) virus, incubation period ranges from 1 to 10 days. With an average of 5 days. For both viruses, the average incubation period is longer than that for seasonal influenza (2 days) for human infections with swine influenza viruses, an incubation period of 2-7 days has been reported.[26]Human influenza viruses are transmitted through the respiratory route, whereas avian influenza viruses in wild bird are

transmitted through the faecal- faecal, faecal-oral and faecal- respiratory routes .

In addition, some avian influenza A viruses, especially those of the H7 subtype, have been associated with human infections of the eye and conjunctivitis (inflammation of the conjunctiva).[27]

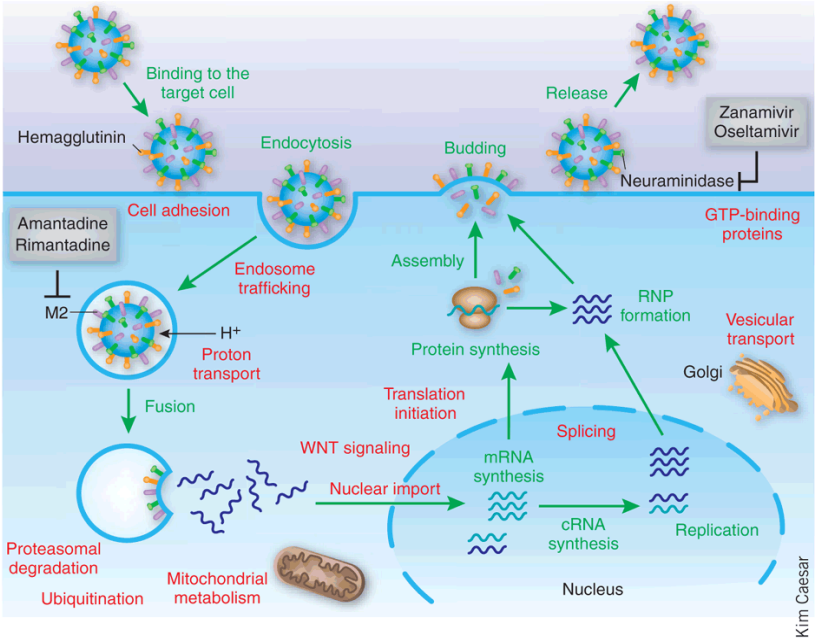


Fig 2

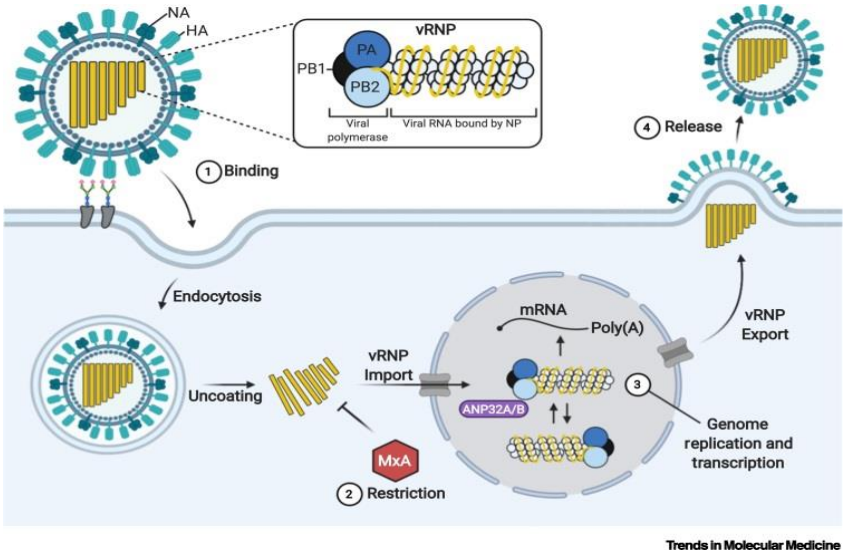


Fig 3

5. Treatment

Evidence suggest some antiviral drugs notably neuraminidase inhibitors (oseltamivir, zanamivir),can reduce the duration of viral replication.

-Treatment is recommended for minimum of 5 days but can be extended until satisfactory clinical improvement.

-Most recent A(H5) and A(H7N9) viruses are resist to admantane antiviral drugs.(e.g.

amantadine and rimantadine) therefore not recommended for monotheraty.[28]In December 2013-February 2014 flu season, total 83 patients who hospitalized in chest clinic. Treatment on appropriate antibiotic started in accordance with TTS-CAP-RR.[29]

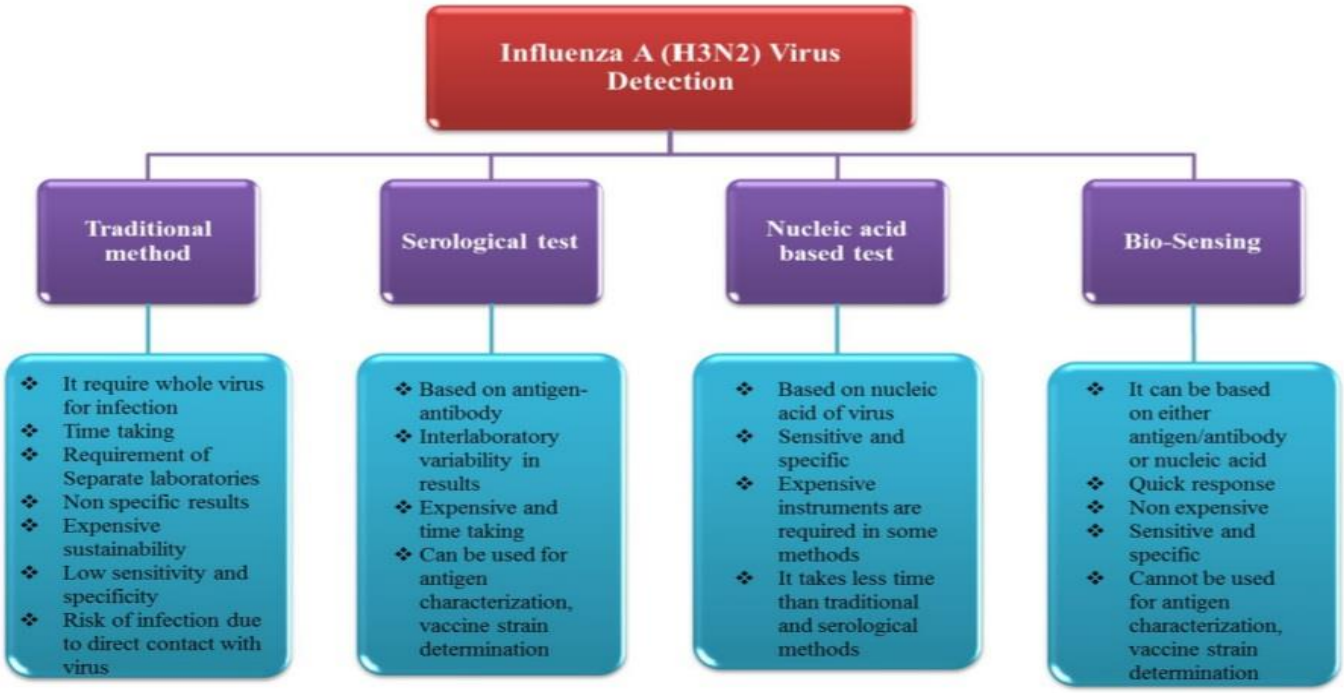
6. Diagnostic testing:-

Several Diagnostic tests detect influenza viruses in respiratory specimens. Point -of- care (POC) rapid antigen detection tests influenza viral proteins in upper-respiratory specimens are simple and can produce quick results, but lower sensitivity lower negative predictive values than RT-PCR[30].

7. Clinical treatment

Clinical management of influenza in patients who are hospitalized includes supportive care of complications (e.g. antibiotics for bacterial co-infection or low flow supplemental oxygen) and extracerbation of chronic medical conditions, providing critical care and advanced O2 support (e.g. high flow supplemental oxygen, non-invasive or invasive mechanical ventilation, renal replacement therapy, vasopressors and extracorporeal membrane oxygenation for refractory hypoxaemia[31]

Detection techniques of Influenza A (H3N2) virus



1) Serological method :

These assays are generally used to diagnose antibiotics response against the influenza virus. The serological tests include hemagglutinin inhibition assay (HAI), virus neutralization assay (VN)or micro neutralization, single radial hemolysis (SRH),complement fixation assay, enzyme linked immunosorbent assay (E1ISA) and

western blotting[32].Due to the sample collection complexity such as paired serum samples, these should be, test are not recommended routinely, the first swab must be taken 2-4 weeks post infection, however this test is cheap and simple, but assay is not satisfactory [33].

2) Nucleic acid based test:

These methods takes 2-4 hrs.to complete the detection and representing the higher specificity and sensitivity as compared to the serological test[34].

3) RT -PCR Test :

RT-PCR method shows 10^6 and 10^3 times higher sensitivity to ELISA and cell culture methods he process of merging several primer sets in multiplex RT-PCR techniques permits the detection of numerous respiratory viruses in a single reactions. RT -PCR is a most expensive and requires 1_8h along reactions time[35]. In a study multiplex RT-PCR was used for differential of Influenza H3N2 viruses of avian origin from human origin H3N2also with equine -origin H3N8 and H1N1 2009 using four primer set for HA gene amplification[36].

8. Prevention:

8.1 Health-care settings

Engineering and environment both controls can reduce chances of infectious respiratory contaminated surfaces and inanimate objects to health-care personnel(HCP) and patients .

A minimum room ventilation recommended as the centers for Diseases Control and preventation (CDC), rate of six air changes per hour in an existing facility and higher ventilation of 12 air changes per hour for new or renovated construction are required to prevent room contamination ,especially when managing patients receiving mechanical ventilation & during aerosol-generating procedures.[37]

8.2 When health-care associated influenza is suspected or confirmed, particularly in congrete setting such as long term care facilities, implementation of bundle of NPIS is recommended, as is influenza vaccination of unvaccinated people, antiviral treatment of people who are symptomic and antiviral treatment of chemoprophylaxis of exposed individuals .[38]

Both oseltamivir and baloxavir can be used for prophylaxis after exposure, but should not be administered within 1-2 days of exposure to a close contact with influenza.[39]

8.3 Non pharmaceutical prevention stratergies

1 In addition to vaccine and antiviral drugs, non-pharmaceutical interventions can help to slow the spread of influenza illness.

2 this interventions include personal measures, such as hand washing and using alcohol based hand sanitizer, covering cough and the nose and mouth when sick and staying at home when sick.

3 Additionally , social distancing by clousers of school and places od gathering ,quarantine measures and frequent cleaning of potential virus contaminated surfaces ,such as door knobs ,can also slow the spread.

4 Mathematically modelling studies suggest than non-pharmaceutical interventions have a substantial effect on lowering the attack rate of pandemic influenza before vaccine are available .[40]

9. Conclusion:

Influenza A (H3N2)virus in human introduced since in 1986, as a result this virus have including the additional of numerus N linked glycans increases to net charge of HA molecules, changes to receptor binding from α 2,3 to α 2,6-linked SA receptors and the ability of NA to agglutinate RBCs prior to host entry. In a study, phylodynamic simulations were used to predict in advance the future virus strains that will dominate on earth .So diagnostic methods have modified according to mutated virus for detection.

Adopting changes to the standard methods to analise H3N2 virus would allow researchers to continue to study and better understand this ever changing subtype of influenza viruses. The management of both animal and human influenza by vaccination is less than optimal. The development of highly efficacious universal vaccine and genetically resistant animals (that have been engineered or that have evolved to be so) are future options.

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