Journal of Biology, Agriculture and Healthcare
ISSN 2224-3208 (Paper) ISSN 2225-093X (Online)
Vol.11, No.4, 2021

Investigating Covid- 19 and Prophylactive Measures to Contain Spread of the Disease

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Abstract
Covid-19 disease is a highly infectious and contagious disease and the outbreak has caused high mortality and morbidity with rates of about 5% and 0.9% it is a global pandemic requiring immediate attention,some of the symptoms include Anemia ,dehydration,Emaciation,weakness ,pneumonitis and Death. The etiology is covid-19 ,the problem at the moment is the lack of cure for the disease.In this study five continents where of interest and they include North and South America,Europe,Africa and Asia.Data was obtained from the internet from worldometer.info/coronavirus/country and cases from February to 15 december 2020 were considered and analysed statistically using analysis of variants to determine monthly incidence and prevalence,case fatality,morbidity ,mortality and population at risk.The reason for this survey is to establish ways to decrease the high morbidity and mortality rates , reduce the devastating economic impact of this disease and increase daily socialization among Humans and curb hunger and boredom that covid-19 has caused.More so the it is a global pandemic needing urgent attention.In conclusion the morbidity and mortality where highest in the months of July and October and the population at risk are 95%-98%.Prophylactic measure to help alleviate the incidence of this disease include daily administration of blood tonic and ascorbic acid in their daily recommended dosages pre-infection to enhance growth of tissues and cellular epithelization and boost energy generation and build .
Keywords: Anemia ,Mortality, Morbidity, Prophylaxis, Griscelli syndrome, Genome,Replicase-trypticase,MHC I and II, Lupus erythmatosus M and E proteins
DOI: 10.7176/JBAH/11-4-05
Publication date: February 28th 2021

1.0 INTRODUCTON

Statement of research problem
i. High Morbidity and Mortality Rates
ii. Devastating effect on economic development and recovery
iii. Restricted movement and Social distancing among Human beings with a resultant boredom and subsequent hunger.
iv. Zoonotic

Coronavirus is highly infectious and contagious disease and mode of transmission are through direct and indirect routes such as inhalation of contaminated aerosol and ingestion of contaminated food other modes are through formites.Covid -19 high mordity and mortality rates through out the world .This rates are so alarming that existence of the Human race is in jeopardy.

It is so acclaimed that “a Tree cannot make an Island” we need interaction between and among ourselves for survival.It is therefore pertinent that businesses cannot be at a still between and among countries in order for economies not to go into recession, but with decrease interaction among Humans due to the Covid-19 pandemic most countries in the world have gone into recession with some finding it very difficult to navigate their way out. Boredom and it”s intricacies makes life not worth living ,what is the use of making money without been able to utilize it for goods and services, more so, covid 19 can be transmitted from man to animals and like-wise, hence zoonotic .Most African countries are hungry and are lagging behind in availability of animal protein and with the subsequent occurrence of this disease living in Africa becomes more difficult in the area of food scarcity and daily animal protein requirement.

1.1.1 Significance of the study

In order for the Human race not to be annihilated from the surface of Earth by Coronavirus because what started as an epidermic in one country has gradually turned into a pandemic with a lot relying on various ways and means of survival. It is therefore evident that Palliative and prophylactive ways need to be abruptly designed to curb the menace of Coronavirus.

1.1.2 Objectives of the study

The objective of the study are:
1 To decrease the high morbidity and mortality rates
2 To decrease the devastating economic effects of this disease
3 To increase the daily socialization among Humans and curb hunger and boredom

2.0 LITERATURE REVIEW

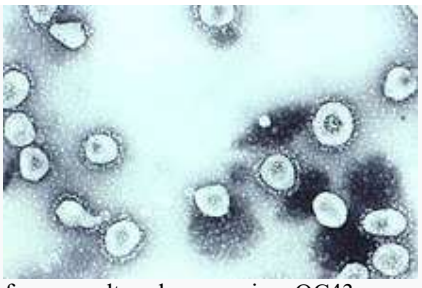
2.1.1 History of Coronavirus

The name "coronavirus" is derived from Latin *corona*, meaning "crown" or "wreath", .[9][10] The name was coined by June Almeida and David Tyrrell who first observed and studied human coronaviruses.[11] The word was first used in print in 1968 by an informal group of virologists in the journal *Nature* to designate the new family of viruses.[8] The name refers to the characteristic appearance of virions (the infective form of the virus) by electron microscopy, which have a fringe of large, bulbous surface projections creating an image reminiscent of the solar corona or halo.[8][11] This morphology is created by the viral spike peplomers, which are proteins on the surface of the virus.[12]

The scientific name *Coronavirus* was accepted as a genus name by the International Committee for the Nomenclature of Viruses (later renamed International Committee on Taxonomy of Viruses) in 1971.[13] As the number of new species increased, the genus was split into four genera, namely *Alphacoronavirus*, *Betacoronavirus*, *Deltacoronavirus*, and *Gammacoronavirus* in 2009.[14] The common name coronavirus is used to refer to any member of the subfamily *Orthocoronavirinae*.[5] As of 2020, 45 species are officially recognise[15

The earliest reports of a coronavirus infection in animals occurred in the late 1920s, when an acute respiratory infection of domesticated chickens emerged in North America.[16] Arthur Schalk and M.C. Hawn in 1931 made the first detailed report which described a new respiratory infection of chickens in North Dakota. The infection of new-born chicks was characterized by gasping and listlessness with high mortality rates of 40–90%.[17] Leland David Bushnell and Carl Alfred Brandly isolated the virus that caused the infection in 1933.[18] The virus was then known as infectious bronchitis virus (IBV). Charles D. Hudson and Fred Robert Beaudette cultivated the virus for the first time in 1937.[19] The specimen came to be known as the Beaudette strain. In the late 1940s, two more animal coronaviruses, JHM that causes brain disease (murine encephalitis) and mouse hepatitis virus (MHV) that causes hepatitis in mice were discovered.[20] It was not realized at the time that these three different viruses were related.[21][13]

Human coronaviruses were discovered in the 1960s[22][23] using two different methods in the United Kingdom and the United States.[24] E.C. Kendall, Malcolm Bynoe, and David Tyrrell working at the Common Cold Unit of the British Medical Research Council collected a unique common cold virus designated B814 in 1961.[25][26][27] The virus could not be cultivated using standard techniques which had successfully cultivated rhinoviruses, adenoviruses and other known common cold viruses. In 1965, Tyrrell and Bynoe successfully cultivated the novel virus by serially passing it through organ culture of human embryonic trachea.[28] The new cultivating method was introduced to the lab by Bertil Hoorn.[29] The isolated virus when intranasally inoculated into volunteers caused a cold and was inactivated by ether which indicated it had a lipid envelope.[25][30] Dorothy Hamre[31] and John Procknow at the University of Chicago isolated a novel cold from medical students in 1962. They isolated and grew the virus in kidney tissue culture, assigning it as 229E. The novel virus caused a cold in volunteers and was inactivated by ether similarly as B814.[32]



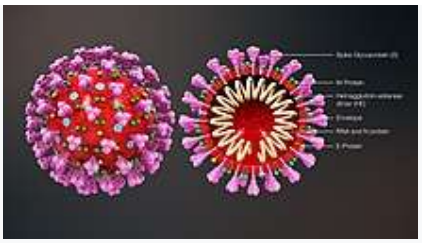
Transmission electron micrograph of organ cultured coronavirus OC43

Scottish virologist June Almeida at St. Thomas Hospital in London, collaborating with Tyrrell, compared the structures of IBV, B814 and 229E in 1967.[33][34] Using electron microscopy the three viruses were shown to be morphologically related by their general shape and distinctive club-like spikes.[35] A research group at the National Institute of Health the same year was able to isolate another member of this new group of viruses using organ culture and named one of the samples OC43 (OC for organ culture).[36] Like B814, 229E, and IBV, the novel cold virus OC43 had distinctive club-like spikes when observed with the electron microscope.[37][38]

The IBV-like novel cold viruses were soon shown to be also morphologically related to the mouse hepatitis virus.[20] This new group of viruses were named coronaviruses after their distinctive morphological appearance.[8] Human coronavirus 229E and human coronavirus OC43 continued to be studied in subsequent decades.[39][40] The coronavirus strain B814 was lost. It is not known which present human coronavirus it was.[41] Other human coronaviruses have since been identified, including SARS-CoV in 2003, HCoV NL63 in 2003, HCoV HKU1 in 2004, MERS-CoV in 2013, and SARS-CoV-2 in 2020.[42] There have also been a large number of animal coronaviruses identified since the 1960s.[43]

2.1.2 Microbiology

Structure



Cross-sectional model of a coronavirus

Coronaviruses are large, roughly spherical particles with unique surface projections.[44] Their size is highly variable and generally is an average diameter of 120 nm. Extreme sizes are known from 50 to 200 nm in diameter.[45] The total molecular weight is on average 40,000 kDa. They are enclosed in an envelope embedded with a number of protein molecules.[46] The lipid bilayer envelope, membrane proteins, and nucleocapsid protect the virus when it is outside the host cell.[47]

The viral envelope is made up of a lipid bilayer, in which the membrane (M), envelope (E) and spike (S) structural proteins are anchored.[48] The ratio of E:S:M in the lipid bilayer is approximately 1:20:300.[49] The E and M protein are the structural proteins that combined with the lipid bilayer shape the viral envelope and maintain its size.[50] S proteins are needed for interaction with the host cells. But human coronavirus NL63 is peculiar in that its M protein has the binding site for the host cell, and not its S protein.[51] The diameter of the envelope is 85 nm. The envelope of the virus in electron micrographs appears as a distinct pair of electron-dense shells (shells that are relatively opaque to the electron beam used to scan the virus particle).[52][50]

The M protein is the main structural protein of the envelope that provides the overall shape and is a type III membrane protein. It consists of 218 to 263 amino acid residues and forms a layer of 7.8 nm thickness.[46] It has three domains such as a short N-terminal ectodomain, a triple-spanning transmembrane domain, and a C-terminal endodomain. The C-terminal domain forms a matrix-like lattice that adds to the extra-thickness of the envelope. Different species can have either *N*- or *O*-linked glycans in their protein amino-terminal domain. The M protein is crucial in the life cycle of the virus such as during assembly, budding, envelope formation, and pathogenesis.[53]

The E proteins are minor structural proteins and highly variable in different species. There are only about 20 E proteins in a coronavirus. They are 8.4 to 12 kDa in size and are composed of 76 to 109 amino acids.[45] They are integral proteins (i.e. embedded in the lipid layer) and have two domains namely transmembrane domain and extramembrane C-terminal domain. They are almost fully α-helical, with a single α-helical transmembrane domain, and form pentameric (five-molecular) ion channels in the lipid bilayer. They are responsible for virion assembly, intracellular trafficking and morphogenesis (budding).[46]

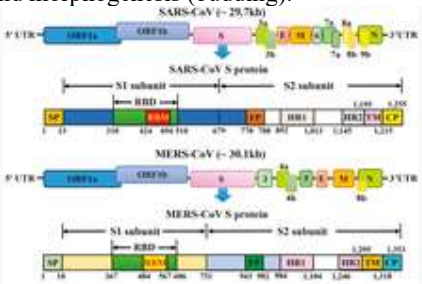


Diagram of the genome and functional domains of the S protein for SARS-CoV and MERS-CoV

The spikes are the most distinguishing feature of coronaviruses, and are responsible for the corona- or halo-like surface. On average a coronavirus particle has 74 surface spikes.[54] Each spike is about 20 nm long and is composed of a trimer of the S protein. The S protein is in turn composed of an S1 and S2 subunit. The homotrimeric S protein is a class I fusion protein which mediates the receptor binding and membrane fusion between the virus and host cell. The S1 subunit forms the head of the spike and has the receptor binding domain (RBD). The S2 subunit forms the stem which anchors the spike in the viral envelope and on protease activation enables fusion. The two subunits remain noncovalently linked as they are exposed on the viral surface, until they attach on the host cell membrane.[46] In a functionally active state, three S1 are attached to two S2 subunits. The subunit complex is split to individual subunits when the virus binds and fuses with the host cell under the action of proteases such as cathepsin family and transmembrane protease serine 2 (TMPRSS2) of the host cell.[55]

S1 proteins are the most critical components in terms of infection. They are also the most variable components as they are responsible for host cell specificity. They possess two major domains named N-terminal domain (S1-NTD) and C-terminal domain (S1-CTD), both of which serve as the receptor-binding domains. The NTDs

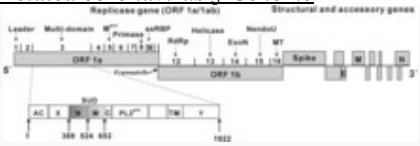
recognise and bind sugars on the surface of the host cell. An exception is the MHV NTD that binds to a protein receptor carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1). S1-CTDs are responsible for recognizing different protein receptors such as angiotensin-converting enzyme 2 (ACE2), aminopeptidase N (APN), and dipeptidyl peptidase 4 (DPP4).[46]

A subset of coronaviruses (specifically the members of betacoronavirus subgroup A) also have a shorter spike-like surface protein called hemagglutinin esterase (HE).[43] The HE proteins occur as homodimers composed of about 400 amino acid residues and are 40 to 50 kDa in size. They appear as tiny surface projections of 5 to 7 nm long embedded in between the spikes. They help in attachment to and detachment from the host cell.[56]

Inside the envelope, there is the nucleocapsid, which is formed from multiple copies of the nucleocapsid (N) protein, which are bound to the positive-sense single-stranded RNA genome in a continuous beads-on-a-string type conformation.[50][57] N protein is a phosphoprotein of 43 to 50 kDa in size, and is divided into three conserved domains. The majority of the protein is made up of domains 1 and 2, which are typically rich in arginines and lysines. Domain 3 has a short carboxy terminal end and has a net negative charge due to excess of acidic over basic amino acid residues.[45]

2.1.3 Genome

Severe acute respiratory syndrome-related coronavirus § Genome



SARS-CoV genome and proteins

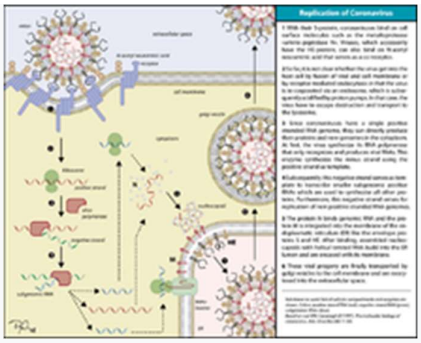
Coronaviruses contain a positive-sense, single-stranded RNA genome. The genome size for coronaviruses ranges from 26.4 to 31.7 kilobases.[7] The genome size is one of the largest among RNA viruses. The genome has a 5′ methylated cap and a 3′ polyadenylated tail.[50]

The genome organization for a coronavirus is 5′-leader-UTR-replicase (ORF1ab)-spike (S)-envelope (E)-membrane (M)-nucleocapsid (N)-3′UTR-poly (A) tail. The open reading frames 1a and 1b, which occupy the first two-thirds of the genome, encode the replicase polyprotein (pp1ab). The replicase polyprotein self cleaves to form 16 nonstructural proteins (nsp1–nsp16).[50]

The later reading frames encode the four major structural proteins: spike, envelope, membrane, and nucleocapsid.[58] Interspersed between these reading frames are the reading frames for the accessory proteins. The number of accessory proteins and their function is unique depending on the specific coronavirus.[50]

Replication cycle

Cell entry



The life cycle of a coronavirus

Infection begins when the viral spike protein attaches to its complementary host cell receptor. After attachment, a protease of the host cell cleaves and activates the receptor-attached spike protein. Depending on the host cell protease available, cleavage and activation allows the virus to enter the host cell by endocytosis or direct fusion of the viral envelope with the host membrane.[59]

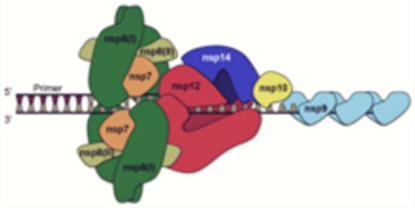
2.1.4 Genome translation

On entry into the host cell, the virus particle is uncoated, and its genome enters the cell cytoplasm. The coronavirus RNA genome has a 5′ methylated cap and a 3′ polyadenylated tail, which allows it to act like a messenger RNA and be directly translated by the host cell's ribosomes. The host ribosomes translate the initial overlapping open reading frames ORF1a and ORF1b of the virus genome into two large overlapping polyproteins, pp1a and pp1ab.[50]

The larger polyprotein pp1ab is a result of a -1 ribosomal frameshift caused by a slippery sequence (UUUAAAC) and a downstream RNA pseudoknot at the end of open reading frame ORF1a.[60] The ribosomal frameshift allows for the continuous translation of ORF1a followed by ORF1b.[50]

The polyproteins have their own proteases, PLpro (nsp3) and 3CLpro (nsp5), which cleave the polyproteins at different specific sites. The cleavage of polyprotein pp1ab yields 16 nonstructural proteins (nsp1 to nsp16). Product proteins include various replication proteins such as RNA-dependent RNA polymerase (nsp12), RNA helicase (nsp13), and exoribonuclease (nsp14).[50]

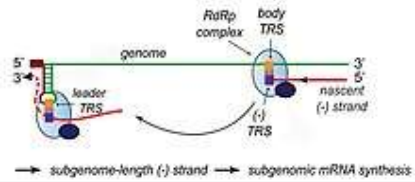
Replicase-transcriptase



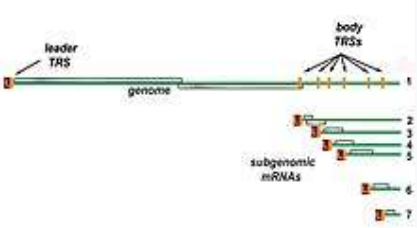
Replicase-transcriptase complex

A number of the nonstructural proteins coalesce to form a multi-protein replicase-transcriptase complex. The main replicase-transcriptase protein is the RNA-dependent RNA polymerase (RdRp). It is directly involved in the replication and transcription of RNA from an RNA strand. The other nonstructural proteins in the complex assist in the replication and transcription process. The exoribonuclease nonstructural protein, for instance, provides extra fidelity to replication by providing a proofreading function which the RNA-dependent RNA polymerase lacks.[61]

Replication – One of the main functions of the complex is to replicate the viral genome. RdRp directly mediates the synthesis of negative-sense genomic RNA from the positive-sense genomic RNA. This is followed by the replication of positive-sense genomic RNA from the negative-sense genomic RNA.[50]



Transcription of nested mRNAs



Nested set of subgenomic mRNAs

Transcription – The other important function of the complex is to transcribe the viral genome. RdRp directly mediates the synthesis of negative-sense subgenomic RNA molecules from the positive-sense genomic RNA. This process is followed by the transcription of these negative-sense subgenomic RNA molecules to their corresponding positive-sense mRNAs.[50] The subgenomic mRNAs form a "nested set" which have a common 5'-head and partially duplicate 3'-end.[62]

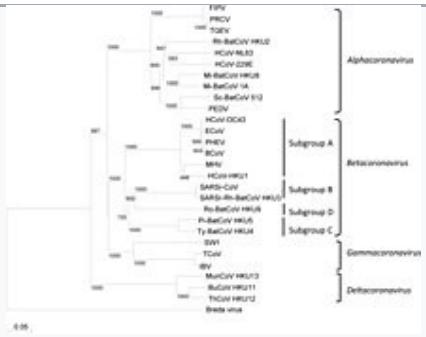
Recombination – The replicase-transcriptase complex is also capable of genetic recombination when at least two viral genomes are present in the same infected cell.[62] RNA recombination appears to be a major driving force in determining genetic variability within a coronavirus species, the capability of a coronavirus species to jump from one host to another and, infrequently, in determining the emergence of novel coronaviruses.[63] The exact mechanism of recombination in coronaviruses is unclear, but likely involves template switching during genome replication.[63]

2.1.5 Assembly and release

The replicated positive-sense genomic RNA becomes the genome of the progeny viruses. The mRNAs are gene transcripts of the last third of the virus genome after the initial overlapping reading frame. These mRNAs are translated by the host's ribosomes into the structural proteins and a number of accessory proteins.[50] RNA translation occurs inside the endoplasmic reticulum. The viral structural proteins S, E, and M move along the secretory pathway into the Golgi intermediate compartment. There, the M proteins direct most protein-protein interactions required for assembly of viruses following its binding to the nucleocapsid. Progeny viruses are then released from the host cell by exocytosis through secretory vesicles. Once released the viruses can infect other host cells.[64]

2.1.6 Transmission

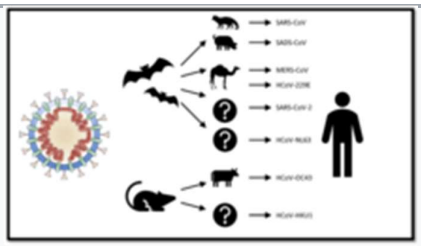
Infected carriers are able to shed viruses into the environment. The interaction of the coronavirus spike protein with its complementary cell receptor is central in determining the tissue tropism, infectivity, and species range of the released virus.[65][66] Coronaviruses mainly target epithelial cells.[43] They are transmitted from one host to another host, depending on the coronavirus species, by either an aerosol, fomite, or fecal-oral route.[67]
Human coronaviruses infect the epithelial cells of the respiratory tract, while animal coronaviruses generally infect the epithelial cells of the digestive tract.[43] SARS coronavirus, for example, infects via an aerosol route,[68] the human epithelial cells of the lungs by binding to the angiotensin-converting enzyme 2 (ACE2) receptor.[69] Transmissible gastroenteritis coronavirus (TGEV) infects, via a fecal-oral route,[67] the pig epithelial cells of the digestive tract by binding to the alanine aminopeptidase (APN) receptor.[50]
Classification
Coronaviridae.



Phylogenetic tree of coronaviruses
Coronaviruses form the subfamily *Orthocoronavirinae,*[3][4][5] which is one of two sub-families in the family *Coronaviridae,* order *Nidovirales,* and realm *Riboviria*.[43][70] They are divided into the four genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus* and *Deltacoronavirus*. Alphacoronaviruses and betacoronaviruses infect mammals, while gammacoronaviruses and deltacoronaviruses primarily infect birds.[71][72]

- Genus: ***Alphacoronavirus***;[67] type species: *Alphacoronavirus 1* (TGEV)
  - Species: *Alphacoronavirus 1, Human coronavirus 229E*, *Human coronavirus NL63*, *Miniopterus bat coronavirus 1*, *Miniopterus bat coronavirus HKU8*, *Porcine epidemic diarrhea virus*, *Rhinolophus bat coronavirus HKU2*, *Scotophilus bat coronavirus 512*
- Genus ***Betacoronavirus***;[68] type species: *Murine coronavirus* (MHV)
  - Species: *Betacoronavirus 1* (*Bovine Coronavirus*, *Human coronavirus OC43*), *Hedgehog coronavirus 1, Human coronavirus HKU1*, *Middle East respiratory syndrome-related coronavirus, Murine coronavirus*, *Pipistrellus bat coronavirus HKU5*, *Rousettus bat coronavirus HKU9*, *Severe acute respiratory syndrome-related coronavirus* (*SARS-CoV*, *SARS-CoV-2*), *Tylonycteris bat coronavirus HKU4*
- Genus ***Gammacoronavirus***;[19] type species: *Avian coronavirus* (IBV)
  - Species: *Avian coronavirus, Beluga whale coronavirus SW1*
- Genus ***Deltacoronavirus***; type species: *Bulbul coronavirus HKU11*
  - Species: *Bulbul coronavirus HKU11*, *Porcine coronavirus HKU15*

Origin



Origins of human coronaviruses with possible intermediate hosts
The most recent common ancestor (MRCA) of all coronaviruses is estimated to have existed as recently as 8000 BCE, although some models place the common ancestor as far back as 55 million years or more, implying long term coevolution with bat and avian species.[73] The most recent common ancestor of the alphacoronavirus line has been placed at about 2400 BCE, of the betacoronavirus line at 3300 BCE, of the gammacoronavirus line

at 2800 BCE, and of the deltacoronavirus line at about 3000 BCE. Bats and birds, as warm-blooded flying vertebrates, are an ideal natural reservoir for the coronavirus gene pool (with bats the reservoir for alphacoronaviruses and betacoronavirus – and birds the reservoir for gammacoronaviruses and deltacoronaviruses). The large number and global range of bat and avian species that host viruses has enabled extensive evolution and dissemination of coronaviruses.[74]

Many human coronaviruses have their origin in bats.[75] The human coronavirus NL63 shared a common ancestor with a bat coronavirus (ARCoV.2) between 1190 and 1449 CE.[76] The human coronavirus 229E shared a common ancestor with a bat coronavirus (GhanaGrp1 Bt CoV) between 1686 and 1800 CE.[77] More recently, alpaca coronavirus and human coronavirus 229E diverged sometime before 1960.[78] MERS-CoV emerged in humans from bats through the intermediate host of camels.[79] MERS-CoV, although related to several bat coronavirus species, appears to have diverged from these several centuries ago.[80] The most closely related bat coronavirus and SARS-CoV diverged in 1986.[81] A possible path of evolution of SARS coronavirus and keen bat coronaviruses is that SARS-related coronaviruses coevolved in bats for a long time. The ancestors of SARS-CoV first infected leaf-nose bats of the genus *Hipposideridae*; subsequently, they spread to horseshoe bats in the species *Rhinolophidae*, then to Asian palm civets, and finally to humans.[82][83]

Unlike other betacoronaviruses, bovine coronavirus of the species *Betacoronavirus 1* and subgenus *Embecovirus* is thought to have originated in rodents and not in bats.[75][84] In the 1790s, equine coronavirus diverged from the bovine coronavirus after a cross-species jump.[85] Later in the 1890s, human coronavirus OC43 diverged from bovine coronavirus after another cross-species spillover event.[86][85] It is speculated that the flu pandemic of 1890 may have been caused by this spillover event, and not by the influenza virus, because of the related timing, neurological symptoms, and unknown causative agent of the pandemic.[87] Besides causing respiratory infections, human coronavirus OC43 is also suspected of playing a role in neurological diseases.[88] In the 1950s, the human coronavirus OC43 began to diverge into its present genotypes.[89] Phylogentically, mouse hepatitis virus (*Murine coronavirus*), which infects the mouse's liver and central nervous system,[90] is related to human coronavirus OC43 and bovine coronavirus. Human coronavirus HKU1, like the aforementioned viruses, also has its origins in rodents.[75]

Infection in humans

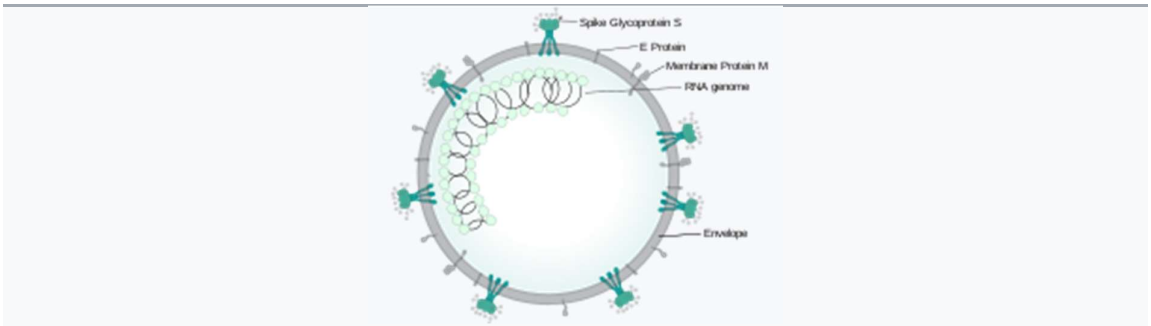


Illustration of SARSr-CoV virion

Coronaviruses vary significantly in risk factor. Some can kill more than 30% of those infected, such as MERS-CoV, and some are relatively harmless, such as the common cold.[50] Coronaviruses can cause colds with major symptoms, such as fever, and a sore throat from swollen adenoids.[91] Coronaviruses can cause pneumonia (either direct viral pneumonia or secondary bacterial pneumonia) and bronchitis (either direct viral bronchitis or secondary bacterial bronchitis).[92] The human coronavirus discovered in 2003, SARS-CoV, which causes severe acute respiratory syndrome (SARS), has a unique pathogenesis because it causes both upper and lower respiratory tract infections.[92]

Six species of human coronaviruses are known, with one species subdivided into two different strains, making seven strains of human coronaviruses altogether.

Four human coronaviruses produce symptoms that are generally mild:

1. Human coronavirus OC43 (HCoV-OC43), β-CoV
2. Human coronavirus HKU1 (HCoV-HKU1), β-CoV
3. Human coronavirus 229E (HCoV-229E), α-CoV
4. Human coronavirus NL63 (HCoV-NL63), α-CoV

Three human coronaviruses produce symptoms that are potentially severe:

1. Middle East respiratory syndrome-related coronavirus (MERS-CoV), β-CoV
2. Severe acute respiratory syndrome coronavirus (SARS-CoV), β-CoV
3. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), β-CoV

Common cold

The human coronaviruses HCoV-OC43, HCoV-HKU1, HCoV-229E, and HCoV-NL63 continually circulate in the human population and produce the generally mild symptoms of the common cold in adults and children worldwide.[93] These coronaviruses cause about 15% of common colds,[94] while 40 to 50% of colds are caused by rhinoviruses.[95]

Severe acute respiratory syndrome

Characteristics of zoonotic coronavirus strains MERS-CoV, SARS-CoV, SARS-CoV-2, and related diseases

	MERS-CoV	SARS-CoV	SARS-CoV-2
Disease	MERS	SARS	COVID-19
Outbreaks	2012, 2015, 2018	2002–2004	2019–2020 pandemic
Epidemiology			
Date of first identified case	June 2012	November 2002	December 2019[99]
Location of first identified case	Jeddah, Saudi Arabia	Shunde, China	Wuhan, China
Age average	56	44[100][a]	56[101]
Sex ratio (M:F)	3.3:1	0.8:1[102]	1.6:1[101]
Confirmed cases	2494	8096[103]	67,618,431[104][b]
Deaths	858	774[103]	1,544,985[104][b]
Case fatality rate	37%	9.2%	2.3%[104]
Symptoms			
Fever	98%	99–100%	87.9%[105]
Dry cough	47%	29–75%	67.7%[105]
Dyspnea	72%	40–42%	18.6%[105]
Diarrhea	26%	20–25%	3.7%[105]
Sore throat	21%	13–25%	13.9%[105]
Ventilatory use	24.5%[106]	14–20%	4.1%[107]

In 2003, following the outbreak of severe acute respiratory syndrome (SARS) which had begun the prior year in Asia, and secondary cases elsewhere in the world, the World Health Organization (WHO) issued a press release stating that a novel coronavirus identified by a number of laboratories was the causative agent for SARS. The virus was officially named the SARS coronavirus (SARS-CoV). More than 8,000 people from 29 different countries and territories were infected, and at least 774 died.[108][69]

Middle East respiratory syndrome (MERS)

Middle East respiratory syndrome

In September 2012, a new type of coronavirus was identified, initially called Novel Coronavirus 2012, and now officially named Middle East respiratory syndrome coronavirus (MERS-CoV).[109][110] The World Health Organization issued a global alert soon after.[111] The WHO update on 28 September 2012 said the virus did not seem to pass easily from person to person.[112] However, on 12 May 2013, a case of human-to-human transmission in France was confirmed by the French Ministry of Social Affairs and Health.[113] In addition, cases of human-to-human transmission were reported by the Ministry of Health in Tunisia. Two confirmed cases involved people who seemed to have caught the disease from their late father, who became ill after a visit to Qatar and Saudi Arabia. Despite this, it appears the virus had trouble spreading from human to human, as most individuals who are infected do not transmit the virus.[114] By 30 October 2013, there were 124 cases and 52 deaths in Saudi Arabia.[115]

After the Dutch Erasmus Medical Centre sequenced the virus, the virus was given a new name, Human Coronavirus—Erasmus Medical Centre (HCoV-EMC). The final name for the virus is Middle East respiratory syndrome coronavirus (MERS-CoV). The only U.S. cases (both survived) were recorded in May 2014.[116]

In May 2015, an outbreak of MERS-CoV occurred in the Republic of Korea, when a man who had traveled

to the Middle East, visited four hospitals in the Seoul area to treat his illness. This caused one of the largest outbreaks of MERS-CoV outside the Middle East.[117] As of December 2019, 2,468 cases of MERS-CoV infection had been confirmed by laboratory tests, 851 of which were fatal, a mortality rate of approximately 34.5%.[118]

2.1.8 Coronavirus disease 2019 (COVID-19)

Coronavirus disease 2019

In December 2019, a pneumonia outbreak was reported in Wuhan, China.[119] On 31 December 2019, the outbreak was traced to a novel strain of coronavirus,[120] which was given the interim name 2019-nCoV by the World Health Organization (WHO),[121][122][123] later renamed SARS-CoV-2 by the International Committee on Taxonomy of Viruses.

As of 8 December 2020, there have been at least 1,544,985[104] confirmed deaths and more than 67,618,431[104] confirmed cases in the COVID-19 pandemic. The Wuhan strain has been identified as a new strain of Betacoronavirus from group 2B with approximately 70% genetic similarity to the SARS-CoV.[124] The virus has a 96% similarity to a bat coronavirus, so it is widely suspected to originate from bats as well.[125][126] The pandemic has resulted in travel restrictions and nationwide lockdowns in many countries.

Infection in animals

Coronaviruses have been recognized as causing pathological conditions in veterinary medicine since the 1930s.[20] They infect a range of animals including swine, cattle, horses, camels, cats, dogs, rodents, birds and bats.[127] The majority of animal related coronaviruses infect the intestinal tract and are transmitted by a fecal-oral route.[128] Significant research efforts have been focused on elucidating the viral pathogenesis of these animal coronaviruses, especially by virologists interested in veterinary and zoonotic diseases.[129]

Farm animals

Coronaviruses infect domesticated birds.[130] Infectious bronchitis virus (IBV), a type of coronavirus, causes avian infectious bronchitis.[131] The virus is of concern to the poultry industry because of the high mortality from infection, its rapid spread, and its effect on production.[127] The virus affects both meat production and egg production and causes substantial economic loss.[132] In chickens, infectious bronchitis virus targets not only the respiratory tract but also the urogenital tract. The virus can spread to different organs throughout the chicken.[131] The virus is transmitted by aerosol and food contaminated by feces. Different vaccines against IBV exist and have helped to limit the spread of the virus and its variants.[127] Infectious bronchitis virus is one of a number of strains of the species *Avian coronavirus*.[133] Another strain of avian coronavirus is turkey coronavirus (TCV) which causes enteritis in turkeys.[127]

Coronaviruses also affect other branches of animal husbandry such as pig farming and the cattle raising.[127] Swine acute diarrhea syndrome coronavirus (SADS-CoV), which is related to bat coronavirus HKU2, causes diarrhea in pigs.[134] Porcine epidemic diarrhea virus (PEDV) is a coronavirus that has recently emerged and similarly causes diarrhea in pigs.[135] Transmissible gastroenteritis virus (TGEV), which is a member of the species *Alphacoronavirus 1*,[136] is another coronavirus that causes diarrhea in young pigs.[137][138] In the cattle industry bovine coronavirus (BCV), which is a member of the species *Betacoronavirus 1* and related to HCoV-OC43,[139] is responsible for severe profuse enteritis in young calves.[127]

Domestic pets

Coronaviruses infect domestic pets such as cats, dogs, and ferrets.[130] There are two forms of feline coronavirus which are both members of the species *Alphacoronavirus 1*.[136] Feline enteric coronavirus is a pathogen of minor clinical significance, but spontaneous mutation of this virus can result in feline infectious peritonitis (FIP), a disease with high mortality.[127] There are two different coronaviruses that infect dogs. Canine coronavirus (CCoV), which is a member of the species *Alphacoronavirus 1*,[136] causes mild gastrointestinal disease.[127] Canine respiratory coronavirus (CRCoV), which is a member of the species *Betacoronavirus 1* and related to HCoV-OC43,[139] cause respiratory disease.[127] Similarly, there are two types of coronavirus that infect ferrets.[140] Ferret enteric coronavirus causes a gastrointestinal syndrome known as epizootic catarrhal enteritis (ECE), and a more lethal systemic version of the virus (like FIP in cats) known as ferret systemic coronavirus (FSC).[141][142]

Laboratory animals

Coronaviruses infect laboratory animals.[127] Mouse hepatitis virus (MHV), which is a member of the species *Murine coronavirus*,[143] causes an epidemic murine illness with high mortality, especially among colonies of laboratory mice.[144] Prior to the discovery of SARS-CoV, MHV was the best-studied coronavirus both *in vivo* and *in vitro* as well as at the molecular level. Some strains of MHV cause a progressive demyelinating encephalitis in mice which has been used as a murine model for multiple sclerosis.[129] Sialodacryoadenitis virus (SDAV), which is a strain of the species *Murine coronavirus*,[143] is highly infectious coronavirus of laboratory rats, which can be transmitted between individuals by direct contact and indirectly by aerosol. Rabbit enteric coronavirus causes acute gastrointestinal disease and diarrhea in young European rabbits.[127] Mortality rates are high.[145]

Prevention and treatment

No vaccines existed against coronaviruses until 2020 in the midst of the COVID-19 pandemic, during which substantial resources were deployed to develop vaccine candidates.[146][147] Several antiviral drugs were also

identified during that period which are theraputic against coronavirus.[148] Previously, a number of antiviral targets were identified such as viral proteases, polymerases, and entry proteins. Drugs are in development which target these proteins and the different steps of viral replication. A number of vaccines using different methods are also under development for different human coronaviruses[50]

Vaccines are available for IBV, TGEV, and Canine CoV, although their effectiveness is limited. In the case of outbreaks of highly contagious animal coronaviruses, such as PEDV, measures such as destruction of entire herds of pigs may be used to prevent transmission to other herds.

2.1.9 Anemia

Anemia is defined as a low number of red blood cells. In a routine blood test, anemia is reported as a low hemoglobin or hematocrit. Hemoglobin is the main protein in your red blood cells. It carries oxygen, and delivers it throughout your body. If you have anemia, your hemoglobin level will be low too. If it is low enough, your tissues or organs may not get enough oxygen. Symptoms of anemia -- like fatigue or shortness of breath -- happen because your organs aren't getting what they need to work the way they should.

Anemia is the most common blood condition in the U.S. It affects almost 6% of the population. Women, young children, and people with long-term diseases are more likely to have anemia. Important things to remember are:

- Certain forms of anemia are passed down through your genes, and infants may have it from birth.
- Women are at risk of iron-deficiency anemia because of blood loss from their periods and higher blood supply demands during pregnancy.
- Older adults have a greater risk of anemia because they are more likely to have kidney disease or other chronic medical conditions.

There are many types of anemia. All have different causes and treatments. Some forms -- like the mild anemia that happens during pregnancy -- aren't a major concern. But some types of anemia maymay reflect a serious underlying medical condition

2.2.1 Anemia Symptoms

The signs of anemia can be so mild that you might not even notice them. At a certain point, as your blood cells decrease, symptoms often develop. Depending on the cause of the anemia, symptoms may include:

- Dizziness, lightheadness, or feeling like you are about to pass out
- Fast or unusual heartbeat
- Headache
- Pain, including in your bones, chest, belly, and joints
- Problems with growth, for children and teens
- Shortness of breath
- Skin that's pale or yellow
- Cold hands and feet
- Tiredness or weakness

2.2.2 Anemia Types and Causes

There are more than 400 types of anemia, and they're divided into three groups:

- Anemia caused by blood loss
- Anemia caused by decreased or faulty red blood cell production
- Anemia caused by destruction of red blood cells

2.2.3 Lupus Erythmatosus

This is inflammatory disease where the immune system attack the body tissues of it,s own. there are four types, namely:

- Systemic lupus erythmatosus
- Immunologic lupus erythmatosus
- Lupus dermatitis
- Congenital lupus erythmatosus

2.2.4 Histiocytosis

In medicine, **histiocytosis** is an excessive number of histiocytes[1] (tissue macrophages), and the term is also often used to refer to a group of rare diseases which share this sign as a characteristic. Occasionally and confusingly, the term "histiocytosis" is sometimes used to refer to individual diseases.

According to the Histiocytosis Association of America, 1 in 200,000 children in the United States are born with histiocytosis each year.[2] HAA also states that most of the people diagnosed with histiocytosis are children under the age of 10, although the disease can afflict adults. The disease usually occurs from birth to age 15.[3]

Histiocytosis (and malignant histiocytosis) are both important in veterinary as well as human pathology.

Types

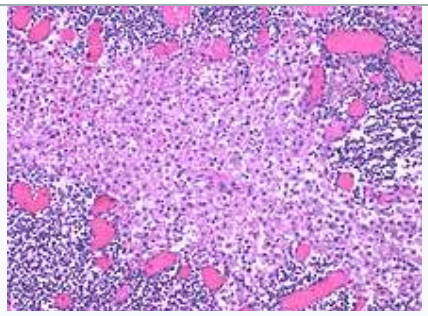
Types of LCH have also been known as "eosinophilic granuloma", "Hand-Schuller-Christian disease", "Letterer-Siwe disease", and "histiocytosis.

Alternatively, histiocytoses may be divided into the following groups:[4]:714–724

- X-type histiocytoses
- Non-X histiocytoses

Lymphohistiocytosis is "a widespread infiltrate of non-malignant lymphocytes and macrophages, involving principally the liver, spleen and central nervous system and associated with a severe lymphoid atrophy."[5]

Diagnosis



Sinus histiocytosis, a common feature in lymph node biopsies, is characterized by dilated sinuses containing variable numbers of histiocytes.[6]

2.2.3 Classification

There are competing systems for classifying histiocytoses. According to the 1999 classification proposed by the World Health Organization, they can be divided into three categories.[7][8] However, the classifications in ICD10 and MeSH are slightly different, as shown below:

Name	**WHO**	**ICD10**	**MeSH**
Langerhans cell histiocytosis (LCH)	I	D76.0	Langerhans-cell histiocytosis
Juvenile xanthogranuloma (JXG)	II	D76.3	non-Langerhans-cell histiocytosis
Hemophagocytic lymphohistiocytosis (HLH)	II	D76.1	non-Langerhans-cell histiocytosis
Niemann–Pick disease	II	E75.2	non-Langerhans-cell histiocytosis
Sea-blue histiocytosis	II	-	non-Langerhans-cell histiocytosis
Acute monocytic leukemia	III	C93.0	malignant histiocytic disorders
Malignant histiocytosis	III	C96.1	malignant histiocytic disorders
Erdheim–Chester disease	II	C96.1	malignant histiocytic disorders

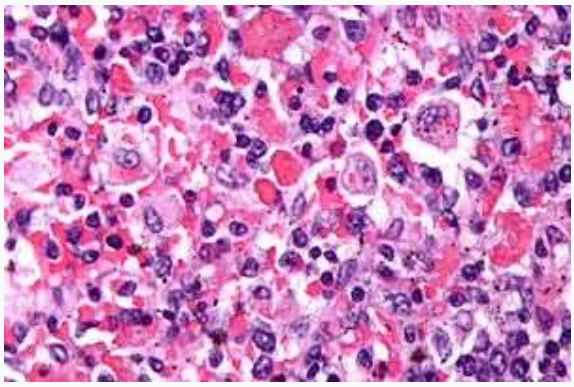
Treatment

- Chemotherapy
  - Cladribine (also known as 2CDA or Leustatin)
  - Etoposide
  - Vinblastine (Velban)

2.2.4 Hemophagocytic lymphohistiocytosis

Hemophagocytic lymphohistiocytosis

Other names **HLH**



Micrograph showing red blood cells within macrophages. H&E stain.

Hemophagocytic lymphohistiocytosis (**HLH**), also known as **haemophagocytic lymphohistiocytosis** (British spelling), and **hemophagocytic** or **haemophagocytic syndrome**,[1] is an uncommon hematologic disorder seen more often in children than in adults. It is a life-threatening disease of severe hyperinflammation caused by uncontrolled proliferation of activated lymphocytes and macrophages, characterised by proliferation of morphologically benign lymphocytes and macrophages that secrete high amounts of inflammatory cytokines. It is classified as one of the cytokine storm syndromes. There are inherited and non-inherited (acquired) causes of hemophagocytic lymphohistiocytosis (HLH).

Signs and symptoms

The onset of HLH occurs under the age of one year in approximately 70 percent of cases. Familial HLH should be suspected if siblings are diagnosed with HLH or if symptoms recur when therapy has been stopped. Each full sibling of a child with familial HLH has a twenty-five–percent chance of developing the disease, a fifty-percent chance of carrying the defective gene (which is very rarely associated with any risk of disease), and a twenty-five–percent chance of not being affected and not carrying the gene defect.[*citation needed*]

Patients with HLH, especially when untreated, may need intensive therapy. Therefore, HLH should be included in the differential diagnosis of intensive care unit patients with cytopenia and hyperferritinemia.[2] Patients in the earlier stages of HLH are frequently hospitalized at internal medicine wards.[3]

HLH clinically manifests with fever, enlargement of the liver and spleen, enlarged lymph nodes, yellow discoloration of the skin and eyes, and a rash.[4] Laboratory findings may include elevated triglyceride levels, low fibrinogen levels, transaminitis, and elevated ferritin levels (among others).[4]

Causes

Primary HLH is caused by loss of function, (i.e. inactivating) mutations in genes that code for proteins cytotoxic T cells and NK cells use to kill targeted cells, such as those infected with pathogens like the Epstein-Barr virus (EBV) or the Dengue virus.[5] These mutations include those in the following genes: *UNC13D, STX11, RAB27A, STXBP2, LYST, PRF1 1, SH2D1A, BIRC4, ITK, CD27,* and *MAGT1*.[6]

Secondary HLH (sHLH) is associated with, and thought to be promoted, by malignant and non-malignant diseases that likewise weaken the ability of the immune system ability to attack EBV-infected cells. Malignant disorders associated with secondary HLH include T-cell lymphoma, B-cell lymphoma, acute lymphocytic leukemia, acute myeloid leukemia, and myelodysplastic syndrome. Non-malignant disorders associated with secondary HLH include: autoimmune disorders such as juvenile idiopathic arthritis, juvenile Kawasaki disease, systemic lupus erythematosus, the juvenile onset and adult onset forms of Still's disease, and rheumatoid arthritis;[6] immunodeficiency disorders such as severe combined immunodeficiency, DiGeorge syndrome, Wiskott–Aldrich syndrome, ataxia–telangiectasia, and dyskeratosis congenita);[7] and infections caused by EBV, cytomegalovirus, HIV/AIDS, bacteria, protozoa, fungi and possibly SARS-CoV-2.[8] Secondary HLH may also result from iatrogenic causes such as bone marrow or other organ transplantations; chemotherapy; or therapy with immunosuppressing agents;[9]

About 33% of all HLH cases, ~75% of Asian HLH cases, and nearly 100% of HLH cases caused by mutations in

SH2D1A (see X-linked lymphoproliferative disease type 1) are associated with, and thought triggered or promoted by, EBV infection. These cases of HLH are classified as belonging to the class of Epstein–Barr virus-associated lymphoproliferative diseases and termed EBV+ HLH.[10]

Pathophysiology

The underlying causes, either inherited or acquired, lead to an unchecked immune response when exposed to triggers. Impaired NK-cell cytotoxicity is the hallmark of HLH. All genetic defects for familial HLH are related to granule-dependent cytotoxicity. This inability to remove infected and antigen-presenting cells and terminate the immune response leads to uncontrolled proliferation and activation of the immune system with release of excessive cytokines. These cells then infiltrate organs, releasing more cytokines, which gives the clinical picture. The fever is caused by IL-1, IL-6 and TNF-alpha; the cytopenia is due to the suppressive effect on hematopoiesis by TNF-alpha and TNF-gamma. TNF-alpha and TNF-gamma may also lead to inhibition of lipoprotein lipase or stimulate triglyceride synthesis. Activated macrophages secrete ferritin and plasminogen activator leading to hyperfibrinolysis.[11]

Genetics

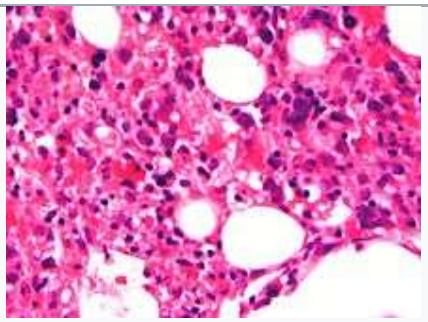
Five genetic subtypes (FHL1, FHL2, FHL3, FHL4, and FHL5) are described, with an estimated overall prevalence of one in 50,000 and equal gender distribution. Molecular genetic testing for four of the causative genes, PRF1 (FHL2), UNC13D (FHL3), STX11 (FHL4), and STXBP2 (FHL5), is available on a clinical basis. Symptoms of FHL are usually evident within the first few months of life and may even develop *in utero*.

The five subtypes of FHL[12] are each associated with a specific gene:

- FHL1: *HPLH1*
- FHL2: *PRF1* (Perforin)
- FHL3: *UNC13D* (Munc13-4)
- FHL4: *STX11* (Syntaxin 11)
- FHL5: *STXBP2* (Syntaxin binding protein 2)/UNC18-2

Nearly half of the cases of type 2 familial hemophagocytic lymphohistiocytosis are due to bi-allelic PRF1 mutations.[13]

Diagnosis



Light microscopic image of bone marrow showing stromal macrophages containing numerous red blood cells in their cytoplasm

The blood count typically shows decreased numbers of blood cells—including a decreased number of circulating red blood cells, white blood cells, and platelets. The bone marrow may show hemophagocytosis. The liver function tests are usually elevated. A low level of the protein albumin in the blood is common.[*citation needed*]

The serum C reactive protein, erythrocyte sedimentation rate, and ferritin level are markedly elevated. In children, a ferritin above 10000 is very sensitive and specific for the diagnosis of HLH,[14] however, the diagnostic utility for ferritin is less for adult HLH patients.[15]

The serum fibrinogen level is usually low and the D-dimer level is elevated.

The sphingomyelinase is elevated.[16]

Bone marrow biopsy shows histiocytosis.[17]

2.2.5 Classification

Primary HLH, also known as **familial haemophagocytic lymphohistiocytosis** (FHL) or familial erythrophagocytic lymphohistiocytosis, is a heterogeneous autosomal recessive disorder found to be more prevalent with parental consanguinity.[*citation needed*]

Secondary haemophagocytic lymphohistiocytosis (acquired haemophagocytic lymphohistiocytosis) occurs after strong immunologic activation, such as that which can occur with systemic infection, immunodeficiency, or underlying malignancy.[*citation needed*]

Both forms are characterized by the overwhelming activation of normal T lymphocytes and macrophages,

invariably leading to clinical and haematologic alterations and death in the absence of treatment.[*citation needed*]

A subtype of primary HLH where the inflammation is limited to the central nervous system has been described.[18]

2.2.6 Diagnostic criteria

The current (2008) diagnostic criteria for HLH are[19]

1. A molecular diagnosis consistent with HLH. These include the identification of pathologic mutations of PRF1, UNC13D, or STX11.

OR

2. Fulfillment of five out of the eight criteria below:

- Fever (defined as a temperature >100.3 °F, >38 °C)
- Enlargement of the spleen
- Decreased blood cell counts affecting at least two of three lineages in the peripheral blood:
  - Haemoglobin <9 g/100 ml (in infants <4 weeks: haemoglobin <10 g/100 ml) (anemia)
  - Platelets $<100\times10^9$/L (thrombocytopenia)
  - Neutrophils $<1\times10^9$/L (neutropenia)
- High blood levels of triglycerides (fasting, greater than or equal to 265 mg/100 ml) and/or decreased amounts of fibrinogen in the blood (≤ 150 mg/100 ml)
- Ferritin ≥ 500 ng/ml
- Haemophagocytosis in the bone marrow, spleen or lymph nodes
- Low or absent natural killer cell activity
- Soluble CD25 (soluble IL-2 receptor) >2400 U/ml (or per local reference laboratory)

In addition, in the case of familial HLH, no evidence of malignancy should be apparent.

Not all five out of eight criteria are required for diagnosis of HLH in adults, and a high index of suspicion is required for diagnosis as delays results in increased mortality. The diagnostic criteria were developed in pediatric populations and have not been validated for adult HLH patients.[20] Attempts to improve diagnosis of HLH have included use of the HScore, which can be used to estimate an individual's risk of HLH.[21] In adults, soluble IL-2 receptor has been found to be a very sensitive marker for HLH, demonstrating 100% sensitivity for ruling out HLH below a cutoff of 2400 U/mL and optimal cutoff for ruling in at 2515 U/mL (sensitivity, 100%; specificity, 72.5%), with 93% specificity at >10 000 U/mL.[22]

Differential diagnosis

The differential diagnosis of HLH includes secondary HLH and macrophage-activation syndrome or other primary immunodeficiencies that present with hemophagocytic lymphohistiocytosis, such as X-linked lymphoproliferative disease.[*citation needed*]

Other conditions that may be confused with this condition include autoimmune lymphoproliferative syndrome.[23] As a syndrome of intense inflammation it needs to be differentiated from sepsis, what may be extremely challenging.[24]

The diagnosis of acquired, or secondary, HLH is usually made in association with infection by viruses, bacteria, fungi, or parasites or in association with lymphoma, autoimmune disease, or metabolic disease. Acquired HLH may have decreased, normal, or increased NK cell activity.[*citation needed*]

2.2.7 Griscelli syndrome

A major differential diagnosis of HLH is Griscelli syndrome (type 2). This is a rare autosomal recessive disorder characterized by partial albinism, hepatosplenomegaly, pancytopenia, hepatitis, immunologic abnormalities, and lymphohistiocytosis. Most cases have been diagnosed between 4 months and 7 years of age, with a mean age of about 17 months.[*citation needed*]

Three types of Griscelli syndrome are recognised: type 1 has neurologic symptoms and mutations in MYO5A. Prognosis depends on the severity of neurologic manifestations. Type 2 has mutations in RAB27A and haemophagocytic syndrome, with abnormal T-cell and macrophage activation. This type has a grave prognosis if untreated. Type 3 has mutations in melanophilin and is characterized by partial albinism. This type does not pose a threat to those so affected.[*citation needed*]

Treatment

In secondary cases, treatment of the cause, where possible, is indicated. Additionally, treatment for HLH itself is usually required.

While optimal treatment of HLH is still being debated, current treatment regimes usually involve high dose corticosteroids, etoposide and cyclosporin.[*citation needed*] Intravenous immunoglobulin is also used. Methotrexate and

vincristine have also been used. Other medications include cytokine targeted therapy.
On 20 November 2018, the FDA approved the anti-IFN-gamma monoclonal antibody emapalumab (proprietary name Gamifant) for the treatment of pediatric and adult primary HLH.[25]

Prognosis

The prognosis is guarded with an overall mortality of 50%. Poor prognostic factors included HLH associated with malignancy, with half the patients dying by 1.4 months compared to 22.8 months for non-tumour associated HLH patients.[26]
Secondary HLH in some individuals may be self-limited because patients are able to fully recover after having received only supportive medical treatment (i.e., IV immunoglobulin only). However, long-term remission without the use of cytotoxic and immune-suppressive therapies is unlikely in the majority of adults with HLH and in those with involvement of the central nervous system (brain and/or spinal cord).[12]

2.2.8 The major histocompatibility complex (MHC)

MHC is a large locus on vertebrate DNA containing a set of closely linked polymorphic genes that code for cell surface proteins essential for the adaptive immune system. This locus got its name because it was discovered in the study of tissue compatibility upon transplantation.[1] Later studies revealed that tissue rejection due to incompatibility is an experimental artifact masking the real function of MHC molecules - binding an antigen derived from self-proteins or from pathogen and the antigen presentation on the cell surface for recognition by the appropriate T-cells.[2] MHC molecules mediate interactions of leukocytes, also called white blood cells (WBCs), which are immune cells, with other leukocytes or with body cells. The MHC determines compatibility of donors for organ transplant, as well as one's susceptibility to an autoimmune disease via cross-reacting immunization.
In a cell, protein molecules of the host's own phenotype or of other biologic entities are continually synthesized and degraded. Each MHC molecule on the cell surface displays a small peptide, molecular fraction of a protein, called an epitope.[3] The presented self-antigens prevent an organism's immune system targeting its own cells. Presentation of pathogen-derived proteins results in the elimination of the infected cell by the immune system.
Diversity of antigen presentation, mediated by MHC antigens, is attained in at least three ways: (1) an organism's MHC repertoire is polygenic (via multiple, interacting genes); (2) MHC expression is codominant (from both sets of inherited alleles); (3) MHC gene variants are highly polymorphic (diversely varying from organism to organism within a species).[4] Sexual selection has been observed in male mice making mate choices of females with different MHCs and thus demonstrating sexual selection.[5] Also, at least for MHC I presentation, there has been evidence of antigenic peptide splicing which can combine peptides from different proteins, vastly increasing antigen diversity.[6]

Discovery

The first descriptions of the MHC were made by British immunologist Peter Gorer in 1936.[7] MHC genes were first identified in inbred mice strains. Clarence Little transplanted tumors across differing strains and found rejection of transplanted tumors according to strains of host versus donor.[8] George Snell selectively bred two mouse strains, attained a new strain nearly identical to one of the progenitor strains, but differing crucially in histocompatibility—that is, tissue compatibility upon transplantation—and thereupon identified an MHC locus.[9] Later Jean Dausset demonstrated the existence of MHC genes in humans and described the first human leucocyte antigen, the protein which we call now HLA-A2. Some years later Baruj Benacerraf showed that polymorphic MHC genes not only determine an individual's unique constitution of antigens but also regulate the interaction among the various cells of the immunological system. These three scientists have been awarded the 1980 Nobel Prize in Physiology or Medicine[10] for their discoveries concerning "genetically determined structures on the cell surface that regulate immunological reactions".
The first fully sequenced and annotated MHC was published for humans in 1999 by a consortium of sequencing centers from the UK, USA and Japan in *Nature*.[11] It was a "virtual MHC" since it was a mosaic from different individuals. A much shorter MHC locus from chickens was published in the same issue of *Nature*.[12] Many other species have been sequenced and the evolution of the MHC was studied, e.g. in the gray short-tailed opossum (Monodelphis domestica), a marsupial, MHC spans 3.95 Mb, yielding 114 genes, 87 shared with humans.[13] Marsupial MHC genotypic variation lies between eutherian mammals and birds, taken as the minimal MHC encoding, but is closer in organization to that of nonmammals. The IPD-MHC Database[14] was created which provides a centralised repository for sequences of the Major Histocompatibility Complex (MHC) from a number of different species. The database contains 77 species for the release from 2019-12-19.

2.2.9 Genes

The MHC locus is present in all jawed vertebrates, it is assumed to have arisen about 450 million years ago.[15] Despite the difference in the number of genes included in the MHC of different species, the overall organization of the locus is rather similar. Usual MHC contains about a hundred genes and pseudogenes, not all of them are involved in immunity. In humans, the MHC region occurs on chromosome 6, between the flanking genetic markers *MOG* and *COL11A2* (from 6p22.1 to 6p21.3 about 29Mb to 33Mb on the hg38 assembly), and contains 224 genes spanning 3.6 megabase pairs (3 600 000 bases).[11] About half have known immune functions. The human MHC

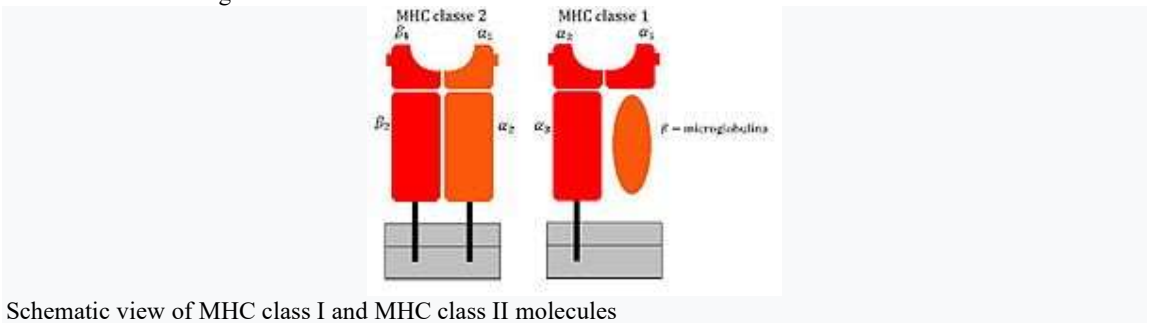
is also called the HLA (human leukocyte antigen) complex (often just the HLA). Similarly, there is SLA (Swine leukocyte antigens), BoLA (Bovine leukocyte antigens), DLA for dogs, etc. However, historically, the MHC in mice is called the Histocompatibility system 2 or just the H-2, in rats - RT1, and in chicken - B-locus.
The MHC gene family is divided into three subgroups: MHC class I, MHC class II, and MHC class III. Among all those genes present in MHC, there are two types of genes coding for the proteins MHC class I molecules and MHC class II molecules that directly involved in the antigen presentation. These genes are highly polymorphic, 19031 alleles of class I HLA, and 7183 of class II HLA are deposited for human in the IMGT database.[16]

Class	Encoding	Expression
I	(1) peptide-binding proteins, which select short sequences of amino acids for antigen presentation, as well as (2) molecules aiding antigen-processing (such as TAP and tapasin).	One chain, called α, whose ligands are the CD8 receptor—borne notably by cytotoxic T cells—and inhibitory receptors borne by NK cells
II	(1) peptide-binding proteins and (2) proteins assisting antigen loading onto MHC class II's peptide-binding proteins (such as MHC II DM, MHC II DQ, MHC II DR, and MHC II DP).	Two chains, called α & β, whose ligands are the CD4 receptors borne by helper T cells.
III	Other immune proteins, outside antigen processing and presentation, such as components of the complement cascade (e.g., C2, C4, factor B), the cytokines of immune signaling (e.g., TNF-α), and heat shock proteins buffering cells from stresses	Various

2.3.1 Proteins

MHC class I

MHC class I molecules are expressed in all nucleated cells and also in platelets—in essence all cells but red blood cells. It presents epitopes to killer T cells, also called cytotoxic T lymphocytes (CTLs). A CTL expresses CD8 receptors, in addition to T-cell receptors (TCR)s. When a CTL's CD8 receptor docks to a MHC class I molecule, if the CTL's TCR fits the epitope within the MHC class I molecule, the CTL triggers the cell to undergo programmed cell death by apoptosis. Thus, MHC class I helps mediate cellular immunity, a primary means to address intracellular pathogens, such as viruses and some bacteria, including bacterial L forms, bacterial genus Mycoplasma, and bacterial genus Rickettsia. In humans, MHC class I comprises HLA-A, HLA-B, and HLA-C molecules.
The first crystal structure of Class I MHC molecule, human HLA-A2, was published in 1989.[17] The structure revealed that MHC-I molecules are heterodimers, they have polymorphic heavy α-subunit whose gene occurs inside the MHC locus and small invariant β_2 microglobulin subunit whose gene is located usually outside of it. Polymorphic heavy chain of MHC-I molecule contains N-terminal extra-cellular region composed by three domains, α1, α2, and α3, transmembrane helix to hold MHC-I molecule on the cell surface and short cytoplasmic tail. Two domains, α1 and α2 form deep peptide-binding groove between two long α-helices and the floor of the groove formed by eight β-strands. Immunoglobulin-like domain α3 involved in the interaction with CD8 co-receptor. β_2 microglobulin provides stability of the complex and participates in the recognition of peptide-MHC class I complex by CD8 co-receptor.[18] The peptide is non-covalently bound to MHC-I, it is held by the several pockets on the floor of the peptide-binding groove. Amino acid side-chains that are most polymorphic in human alleles fill up the central and widest portion of the binding groove, while conserved side-chains are clustered at the narrower ends of the groove.



Schematic view of MHC class I and MHC class II molecules

Classical MHC molecules present epitopes to the TCRs of CD8+ T lymphocytes. **Nonclassical molecules** (MHC class IB) exhibit limited polymorphism, expression patterns, and presented antigens; this group is subdivided into a group encoded within MHC loci (e.g., HLA-E, -F, -G), as well as those not (e.g., stress ligands such as ULBPs, Rae1, and H60); the antigen/ligand for many of these molecules remain unknown, but they can interact with each

of CD8+ T cells, NKT cells, and NK cells. The evolutionary oldest nonclassical MHC class I lineage in human was deduced to be the lineage that includes the CD1 and PROCR (alias EPCR) molecules, and this lineage may have been established before the origin of tetrapod species [19]. However, the only nonclassical MHC class I lineage for which evidence exists that it was established before the evolutionary separation of Actinopterygii (ray-finned fish) and Sarcopterygii (lobe-finned fish plus tetrapods) is lineage Z of which members are found, together in each species with classical MHC class I, in lungfish and throughout ray-finned fishes [20]; why the Z lineage was well conserved in ray-finned fish but lost in tetrapods is not understood.

2.3.2 MHC class II

MHC class II can be conditionally expressed by all cell types, but normally occurs only on "professional" antigen-presenting cells (APCs): macrophages, B cells, and especially dendritic cells (DCs). An APC takes up an antigenic protein, performs antigen processing, and returns a molecular fraction of it—a fraction termed the epitope—and displays it on the APC's surface coupled within an MHC class II molecule (antigen presentation). On the cell's surface, the epitope can be recognized by immunologic structures like T-cell receptors (TCRs). The molecular region which binds to the epitope is the paratope.

On surfaces of helper T cells are CD4 receptors, as well as TCRs. When a naive helper T cell's CD4 molecule docks to an APC's MHC class II molecule, its TCR can meet and bind the epitope coupled within the MHC class II. This event primes the naive T cell. According to the local milieu, that is, the balance of cytokines secreted by APCs in the microenvironment, the naive helper T cell (Th_0) polarizes into either a memory Th cell or an effector Th cell of phenotype either type 1 (Th_1), type 2 (Th_2), type 17 (Th_{17}), or regulatory/suppressor (T_{reg}), as so far identified, the Th cell's terminal differentiation.

MHC class II thus mediates immunization to—or, if APCs polarize Th_0 cells principally to T_{reg} cells, immune tolerance of—an antigen. The polarization during primary exposure to an antigen is key in determining a number of chronic diseases, such as inflammatory bowel diseases and asthma, by skewing the immune response that memory Th cells coordinate when their memory recall is triggered upon secondary exposure to similar antigens. B cells express MHC class II to present antigens to Th_0, but when their B cell receptors bind matching epitopes, interactions which are not mediated by MHC, these activated B cells secrete soluble immunoglobulins: antibody molecules mediating humoral immunity.

Class II MHC molecules are also heterodimers, genes for both α and β subunits are polymorphic and located within MHC class II subregion. Peptide-binding groove of MHC-II molecules is forms by N-terminal domains of both subunits of the heterodimer, α1 and β1, unlike MHC-I molecules, where two domains of the same chain are involved. In addition, both subunits of MHC-II contain transmembrane helix and immunoglobulin domains α2 or β2 that can be recognized by CD4 co-receptors.[21] In this way MHC molecules chaperone which type of lymphocytes may bind to the given antigen with high affinity, since different lymphocytes express different T-Cell Receptor (TCR) co-receptors.

MHC class II molecules in humans have five to six isotypes. **Classical molecules** present peptides to CD4+ lymphocytes. **Nonclassical molecules**, accessories, with intracellular functions, are not exposed on cell membranes, but in internal membranes, assisting with the loading of antigenic peptides onto classic MHC class II molecules. The important nonclassical MHC class II molecule DM is only found from the evolutionary level of lungfish [22], although also in more primitive fishes both classical and nonclassical MHC class II are found [23][24].

Sr.No	Feature[25]	Class I MHC	Class II MHC
1	Constituting polypeptide chains	α chain (45KDa in humans) β_2 chain (12 KDa in humans)	α chain (30-34 KDa in humans) β chain (26-29 KDa in humans)
2	Antigen binding domain	α1and α2 domains	α_1 and β_1 domains
3	Binds protein antigens of	8-10 amino acids residues	13-18 amino acids residues
4	Peptide bending cleft	Floor formed by β sheets and sides by a helices, blocked at both the ends	Floor formed by β sheets and sides by a helices, opened at both the ends
5	Antigenic peptide motifs involved in binding	Anchor residues located at amino and carbon terminal ends	Anchor residues located almost uniformly along the peptide
6	Presents antigenic peptide to	CD8+ T cells	CD4+ T cells

2.3.3 MHC class III

Class III molecules have physiologic roles unlike classes I and II, but are encoded between them in the short arm of human chromosome 6. Class III molecules include several secreted proteins with immune functions:

components of the complement system (such as C2, C4, and B factor), cytokines (such as TNF-α, LTA, and LTB), and heat shock proteins.

Function

MHC is the tissue-antigen that allows the immune system (more specifically T cells) to bind to, recognize, and tolerate itself (autorecognition). MHC is also the chaperone for intracellular peptides that are complexed with MHCs and presented to T cell receptors (TCRs) as potential foreign antigens. MHC interacts with TCR and its co-receptors to optimize binding conditions for the TCR-antigen interaction, in terms of antigen binding affinity and specificity, and signal transduction effectiveness.

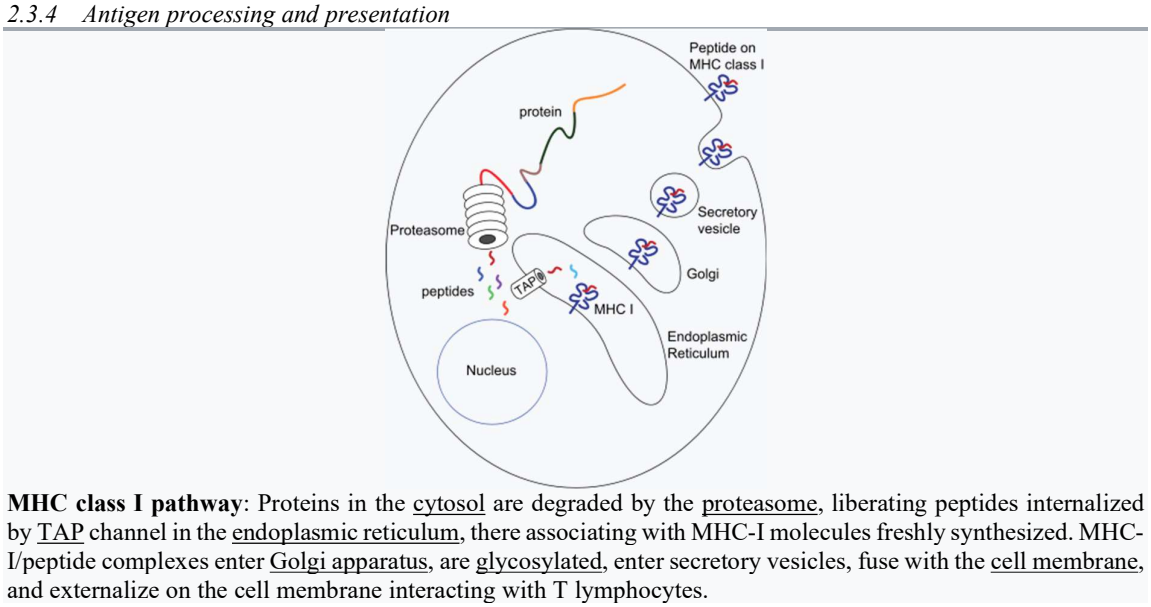
Essentially, the MHC-peptide complex is a complex of auto-antigen/allo-antigen. Upon binding, T cells should in principle tolerate the auto-antigen, but activate when exposed to the allo-antigen. Disease states occur when this principle is disrupted.

Antigen presentation: MHC molecules bind to both T cell receptor and CD4/CD8 co-receptors on T lymphocytes, and the antigen epitope held in the peptide-binding groove of the MHC molecule interacts with the variable Ig-Like domain of the TCR to trigger T-cell activation[26]

Autoimmune reaction: Having some MHC molecules increases the risk of autoimmune diseases more than having others. HLA-B27 is an example. It is unclear how exactly having the HLA-B27 tissue type increases the risk of ankylosing spondylitis and other associated inflammatory diseases, but mechanisms involving aberrant antigen presentation or T cell activation have been hypothesized.

Tissue allorecognition: MHC molecules in complex with peptide epitopes are essentially ligands for TCRs. T cells become activated by binding to the peptide-binding grooves of any MHC molecule that they were not trained to recognize during positive selection in the thymus.

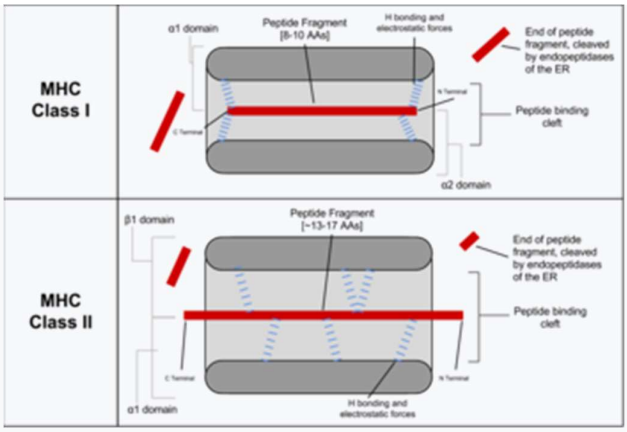
2.3.4 Antigen processing and presentation



MHC class I pathway: Proteins in the cytosol are degraded by the proteasome, liberating peptides internalized by TAP channel in the endoplasmic reticulum, there associating with MHC-I molecules freshly synthesized. MHC-I/peptide complexes enter Golgi apparatus, are glycosylated, enter secretory vesicles, fuse with the cell membrane, and externalize on the cell membrane interacting with T lymphocytes.

Peptides are processed and presented by two classical pathways:

- In **MHC class II**, phagocytes such as macrophages and immature dendritic cells take up entities by phagocytosis into phagosomes—though B cells exhibit the more general endocytosis into endosomes—which fuse with lysosomes whose acidic enzymes cleave the uptaken protein into many different peptides. Via physicochemical dynamics in molecular interaction with the particular MHC class II variants borne by the host, encoded in the host's genome, a particular peptide exhibits immunodominance and loads onto MHC class II molecules. These are trafficked to and externalized on the cell surface.[27]
- In **MHC class I**, any nucleated cell normally presents cytosolic peptides, mostly self peptides derived from protein turnover and defective ribosomal products. During viral infection, intracellular microorganism infection, or cancerous transformation, such proteins degraded in the proteosome are as well loaded onto MHC class I molecules and displayed on the cell surface. T lymphocytes can detect a peptide displayed at 0.1%-1% of the MHC molecules.



Peptide binding for Class I and Class II MHC molecules, showing the binding of peptides between the alpha-helix walls, upon a beta-sheet base. The difference in binding positions is shown. Class I primarily makes contact with backbone residues at the Carboxy and amino terminal regions, while Class II primarily makes contacts along the length of the residue backbone. The precise location of binding residues is determined by the MHC allele.[28]

Table 2. Characteristics of the antigen processing pathways

Characteristic	MHC-I pathway	MHC-II pathway
Composition of the stable peptide-MHC complex	Polymorphic chain α and β_2 microglobulin, peptide bound to α chain	Polymorphic chains α and β, peptide binds to both
Types of antigen-presenting cells (APC)	All nucleated cells	Dendritic cells, mononuclear phagocytes, B lymphocytes, some endothelial cells, epithelium of thymus
T lymphocytes able to respond	Cytotoxic T lymphocytes (CD8+)	Helper T lymphocytes (CD4+)
Origin of antigenic proteins	cytosolic proteins (mostly synthetized by the cell; may also enter from the extracellular medium via phagosomes)	Proteins present in endosomes or lysosomes (mostly internalized from extracellular medium)
Enzymes responsible for peptide generation	Cytosolic proteasome	Proteases from endosomes and lysosomes (for instance, cathepsin)
Location of loading the peptide on the MHC molecule	Endoplasmic reticulum	Specialized vesicular compartment
Molecules implicated in transporting the peptides and loading them on the MHC molecules	TAP (transporter associated with antigen processing)	DM, invariant chain

2.3.5 T lymphocyte recognition restrictions

MHC restriction

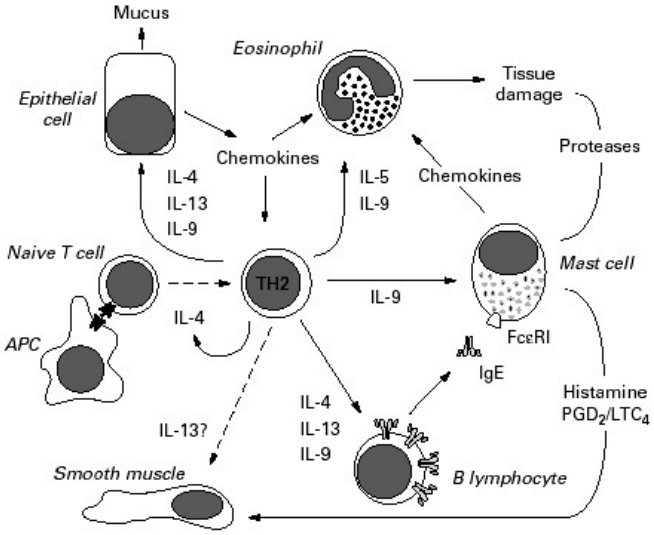
In their development in the thymus, T lymphocytes are selected to recognize MHC molecules of the host, but not recognize other self antigens. Following selection, each T lymphocyte shows dual specificity: The TCR recognizes self MHC, but only non-self antigens.

MHC restriction occurs during lymphocyte development in the thymus through a process known as positive selection. T cells that do not receive a positive survival signal — mediated mainly by thymic epithelial cells presenting self peptides bound to MHC molecules — to their TCR undergo apoptosis. Positive selection ensures that mature T cells can functionally recognize MHC molecules in the periphery (i.e. elsewhere in the body).

The TCRs of T lymphocytes recognise only sequential epitopes, also called linear epitopes, of only peptides and only if coupled within an MHC molecule. (Antibody molecules secreted by activated B cells, though, recognize diverse epitopes—peptide, lipid, carbohydrate, and nucleic acid—and recognize conformational epitopes, which have three-dimensional structure.)

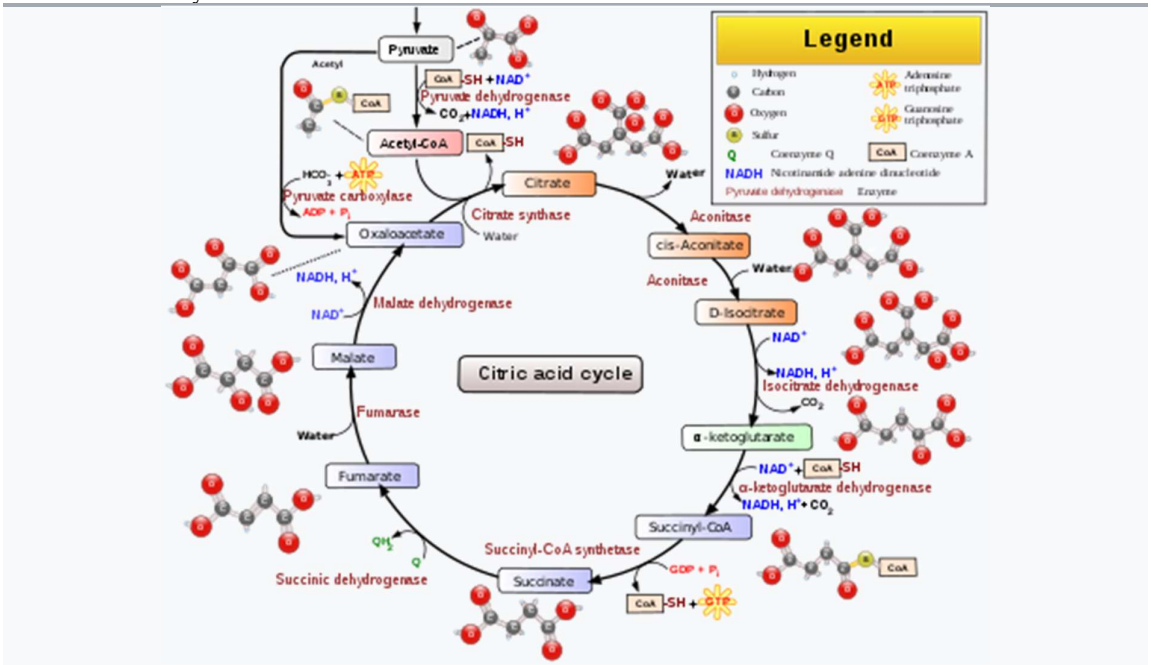
2.3.6 Role of Leucotrienes in airway inflammation

IL-4 Eosinophil growth ,increase and decrease T helper cells type 2 and 1 respectively and increase IgE.
IL-5 Eosinophil maturation,decrease cellular apoptosis,increase IgE and t helper cells 2
IL-10 Decrease survival of eosiniphils and TH2 and TH1 and activation of monocytes.
IL-13 Activate Eosinophils,decrease apoptosis and increase IgE.
IL15 Growth and differenciation of T- cells
1L-16 Eosinophil migration and growth factor and chemotaxis of T-cells
IL-17 T-cell proliferation,activation of fibroblast and epithelial and endothelium cells
IL-18 Interferon$-\gamma$ release from TH1 cells , activation of Natural killer cells and monocytes and decrease IgE
INF-γ Decrease in TH2 cells and Eosinophil influx after allegen,activation of endothelium and epithelium and also macrophages and monocytes ,decrease IgE



Pleiotropic activities of T helper type 2 (Th2) cytokines in allergic asthma. Upon recognition of the antigen and activation by antigen presenting cells (APC), naive T-cells differentiate into Th2 cells, a process that is promoted by interleukin 4 (IL-4). Activated Th2 cells stimulate B cells to produce IgE antibodies in response to IL-4, and to a lower extend to IL-13 or IL-9. IgE binds the high affinity IgE receptor at the surface of mast cells, the proliferation and differentiation of which is promoted by IL-9, in synergy with other factors such as fibroblast derived mast cell growth factor. At contact with antigen, mast cells release the contents of their granules, including histamine, which will induce a bronchospasm, together with newly synthesized prostaglandins and leukotrienes (PGD2 and LTC4). Mast cells also release chemotactic factors that contribute to the recruitment of inflammatory cells, particularly eosinophils, whose proliferation and differentiation from bone marrow progenitors is promoted by IL-5 and IL-9. Finally, epithelial cells up regulate their production of mucus and chemokines in responses to Th2 cytokines such as Il-4, IL-13, and IL-9. The presence of the IL-13 receptor at the surface of smooth muscle cell suggests that this factor can also directly affect smooth muscle contractility, but this remains to be demonstrated.

2.3.7 Citric acid cycle



Overview of the citric acid cycle

The **citric acid cycle** (**CAC**) – also known as the **TCA cycle (tricarboxylic acid cycle)** or the **Krebs cycle**[1][2] – is a series of chemical reactions used by all aerobic organisms to release stored energy through the oxidation of acetyl-CoA derived from carbohydrates, fats, and proteins. In addition, the cycle provides precursors of certain amino acids, as well as the reducing agent NADH, that are used in numerous other reactions. Its central importance to many biochemical pathways suggests that it was one of the earliest components of metabolism and may have originated abiogenically.[3][4] Even though it is branded as a 'cycle', it is not necessary for metabolites to follow only one specific route; at least three segments of the citric acid cycle have been recognized.[5]

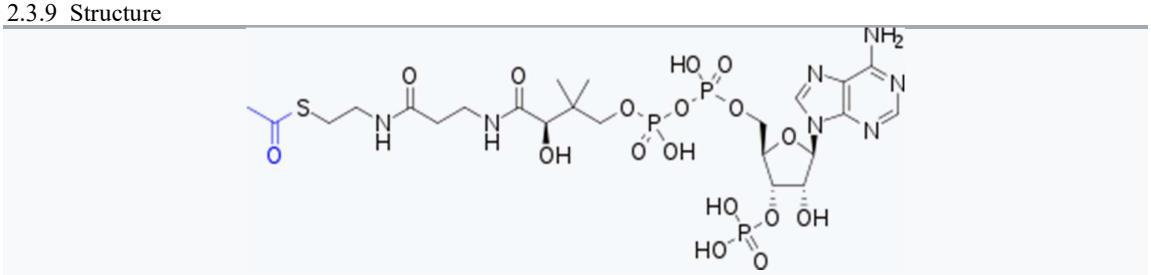
The name of this metabolic pathway is derived from the citric acid (a tricarboxylic acid, often called citrate, as the ionized form predominates at biological pH[6]) that is consumed and then regenerated by this sequence of reactions to complete the cycle. The cycle consumes acetate (in the form of acetyl-CoA) and water, reduces NAD^+ to NADH, releasing carbon dioxide. The NADH generated by the citric acid cycle is fed into the oxidative phosphorylation (electron transport) pathway. The net result of these two closely linked pathways is the oxidation of nutrients to produce usable chemical energy in the form of ATP.

In eukaryotic cells, the citric acid cycle occurs in the matrix of the mitochondrion. In prokaryotic cells, such as bacteria, which lack mitochondria, the citric acid cycle reaction sequence is performed in the cytosol with the proton gradient for ATP production being across the cell's surface (plasma membrane) rather than the inner membrane of the mitochondrion. The overall yield of energy-containing compounds from the TCA cycle is three NADH, one $FADH_2$, and one GTP.[7]

2.3.8 Discovery

Several of the components and reactions of the citric acid cycle were established in the 1930s by the research of Albert Szent-Györgyi, who received the Nobel Prize in Physiology or Medicine in 1937 specifically for his discoveries pertaining to fumaric acid, a key component of the cycle.[8] He made this discovery by studying pigeon breast muscle. Because this tissue maintains its oxidative capacity well after breaking down in the "Latapie" mill and releasing in aqueous solutions, breast muscle of the pigeon was very well qualified for the study of oxidative reactions.[9] The citric acid cycle itself was finally identified in 1937 by Hans Adolf Krebs and William Arthur Johnson while at the University of Sheffield,[10] for which the former received the Nobel Prize for Physiology or Medicine in 1953, and for whom the cycle is sometimes named (Krebs cycle).[11]

2.3.9 Structure



Structural diagram of acetyl-CoA: The portion in blue, on the left, is the acetyl group; the portion in black is coenzyme A.

The citric acid cycle is a key metabolic pathway that connects carbohydrate, fat, and protein metabolism. The reactions of the cycle are carried out by eight enzymes that completely oxidize acetate (a two carbon molecule), in the form of acetyl-CoA, into two molecules each of carbon dioxide and water. Through catabolism of sugars, fats, and proteins, the two-carbon organic product acetyl-CoA (a form of acetate) is produced which enters the citric acid cycle. The reactions of the cycle also convert three equivalents of nicotinamide adenine dinucleotide (NAD^+) into three equivalents of reduced NAD^+ (NADH), one equivalent of flavin adenine dinucleotide (FAD) into one equivalent of $FADH_2$, and one equivalent each of guanosine diphosphate (GDP) and inorganic phosphate (P_i) into one equivalent of guanosine triphosphate (GTP). The NADH and $FADH_2$ generated by the citric acid cycle are, in turn, used by the oxidative phosphorylation pathway to generate energy-rich ATP.

One of the primary sources of acetyl-CoA is from the breakdown of sugars by glycolysis which yield pyruvate that in turn is decarboxylated by the pyruvate dehydrogenase complex generating acetyl-CoA according to the following reaction scheme:

$$CH_3C(=O)C(=O)O^-\text{pyruvate} + \underline{HSCoA} + \underline{NAD^+} \rightarrow CH_3C(=O)SCoA\text{acetyl-CoA} + NADH + CO_2$$

The product of this reaction, acetyl-CoA, is the starting point for the citric acid cycle. Acetyl-CoA may also be obtained from the oxidation of fatty acids. Below is a schematic outline of the cycle:

- The citric acid cycle begins with the transfer of a two-carbon acetyl group from acetyl-CoA to the four-carbon acceptor compound (oxaloacetate) to form a six-carbon compound (citrate).
- The citrate then goes through a series of chemical transformations, losing two carboxyl groups as CO_2. The carbons lost as CO_2 originate from what was oxaloacetate, not directly from acetyl-CoA. The carbons donated by acetyl-CoA become part of the oxaloacetate carbon backbone after the first turn of the citric acid cycle. Loss of the acetyl-CoA-donated carbons as CO_2 requires several turns of the citric acid cycle. However, because of the role of the citric acid cycle in anabolism, they might not be lost, since many citric acid cycle intermediates are also used as precursors for the biosynthesis of other molecules.[12]
- Most of the electrons made available by the oxidative steps of the cycle are transferred to NAD^+, forming NADH. For each acetyl group that enters the citric acid cycle, three molecules of NADH are produced. The citric acid cycle includes a series of oxidation reduction reaction in mitochondria .[*clarification needed*][13]
- In addition, electrons from the succinate oxidation step are transferred first to the FAD cofactor of succinate dehydrogenase, reducing it to $FADH_2$, and eventually to ubiquinone (Q) in the mitochondrial membrane, reducing it to ubiquinol (QH_2) which is a substrate of the electron transfer chain at the level of Complex III.
- For every NADH and $FADH_2$ that are produced in the citric acid cycle, 2.5 and 1.5 ATP molecules are generated in oxidative phosphorylation, respectively.
- At the end of each cycle, the four-carbon oxaloacetate has been regenerated, and the cycle continues.[14]

The theoretical maximum yield of ATP through oxidation of one molecule of glucose in glycolysis, citric acid cycle, and oxidative phosphorylation is 38 (assuming 3 molar equivalents of ATP per equivalent NADH and 2 ATP per UQH_2). In eukaryotes, two equivalents of NADH and four equivalents of ATP are generated in glycolysis, which takes place in the cytoplasm. Transport of two of these equivalents of NADH into the mitochondria consumes two equivalents of ATP, thus reducing the net production of ATP to 36. Furthermore, inefficiencies in oxidative phosphorylation due to leakage of protons across the mitochondrial membrane and slippage of the ATP synthase/proton pump commonly reduces the ATP yield from NADH and UQH_2 to less than the theoretical maximum yield.[18] The observed yields are, therefore, closer to ~2.5 ATP per NADH and ~1.5 ATP per UQH_2, further reducing the total net production of ATP to approximately 30.[19] An assessment of provides an estimate of 29.85 ATP per glucose molecule.[20]

2.4.1 Roles of Iron, copper and Zinc in Nutrition.

2.4.2 Iron in Diet

Iron is pervasive, but particularly rich sources of dietary iron include red meat, oysters, lentils, beans, poultry, fish, leaf vegetables, watercress, tofu, chickpeas, black-eyed peas, and blackstrap molasses.[5] Bread and breakfast

cereals are sometimes specifically fortified with iron.[5]
Iron provided by dietary supplements is often found as iron(II) fumarate, although iron(II) sulfate is cheaper and is absorbed equally well.[135] Elemental iron, or reduced iron, despite being absorbed at only one-third to two-thirds the efficiency (relative to iron sulfate),[153] is often added to foods such as breakfast cereals or enriched wheat flour. Iron is most available to the body when chelated to amino acids[154] and is also available for use as a common iron supplement. Glycine, the least expensive amino acid, is most often used to produce iron glycinate supplements.[155]

Dietary recommendations

The U.S. Institute of Medicine (IOM) updated Estimated Average Requirements (EARs) and Recommended Dietary Allowances (RDAs) for iron in 2001.[5] The current EAR for iron for women ages 14–18 is 7.9 mg/day, 8.1 for ages 19–50 and 5.0 thereafter (post menopause). For men the EAR is 6.0 mg/day for ages 19 and up. The RDA is 15.0 mg/day for women ages 15–18, 18.0 for 19–50 and 8.0 thereafter. For men, 8.0 mg/day for ages 19 and up. RDAs are higher than EARs so as to identify amounts that will cover people with higher than average requirements. RDA for pregnancy is 27 mg/day and, for lactation, 9 mg/day.[5] For children ages 1–3 years 7 mg/day, 10 for ages 4–8 and 8 for ages 9–13. As for safety, the IOM also sets Tolerable upper intake levels (ULs) for vitamins and minerals when evidence is sufficient. In the case of iron the UL is set at 45 mg/day. Collectively the EARs, RDAs and ULs are referred to as Dietary Reference Intakes.[156]

The European Food Safety Authority (EFSA) refers to the collective set of information as Dietary Reference Values, with Population Reference Intake (PRI) instead of RDA, and Average Requirement instead of EAR. AI and UL defined the same as in United States. For women the PRI is 13 mg/day ages 15–17 years, 16 mg/day for women ages 18 and up who are premenopausal and 11 mg/day postmenopausal. For pregnancy and lactation, 16 mg/day. For men the PRI is 11 mg/day ages 15 and older. For children ages 1 to 14 the PRI increases from 7 to 11 mg/day. The PRIs are higher than the U.S. RDAs, with the exception of pregnancy.[157] The EFSA reviewed the same safety question did not establish a UL.[158]

Infants may require iron supplements if they are bottle-fed cow's milk.[159] Frequent blood donors are at risk of low iron levels and are often advised to supplement their iron intake.[160]

For U.S. food and dietary supplement labeling purposes the amount in a serving is expressed as a percent of Daily Value (%DV). For iron labeling purposes 100% of the Daily Value was 18 mg, and as of May 27, 2016 remained unchanged at 18 mg.[161][162] Compliance with the updated labeling regulations was required by 1 January 2020, for manufacturers with $10 million or more in annual food sales, and by 1 January 2021, for manufacturers with less than $10 million in annual food sales.[163][164][165] During the first six months following the 1 January 2020 compliance date, the FDA plans to work cooperatively with manufacturers to meet the new Nutrition Facts label requirements and will not focus on enforcement actions regarding these requirements during that time.[163] A table of the old and new adult Daily Values is provided at Reference Daily Intake.

Deficiency

Iron deficiency

Iron deficiency is the most common nutritional deficiency in the world.[5][166][167][168] When loss of iron is not adequately compensated by adequate dietary iron intake, a state of latent iron deficiency occurs, which over time leads to iron-deficiency anemia if left untreated, which is characterised by an insufficient number of red blood cells and an insufficient amount of hemoglobin.[169] Children, pre-menopausal women (women of child-bearing age), and people with poor diet are most susceptible to the disease. Most cases of iron-deficiency anemia are mild, but if not treated can cause problems like fast or irregular heartbeat, complications during pregnancy, and delayed growth in infants and children.[170]

Excess

Iron overload

Iron uptake is tightly regulated by the human body, which has no regulated physiological means of excreting iron. Only small amounts of iron are lost daily due to mucosal and skin epithelial cell sloughing, so control of iron levels is primarily accomplished by regulating uptake.[171] Regulation of iron uptake is impaired in some people as a result of a genetic defect that maps to the HLA-H gene region on chromosome 6 and leads to abnormally low levels of hepcidin, a key regulator of the entry of iron into the circulatory system in mammals.[172] In these people, excessive iron intake can result in iron overload disorders, known medically as hemochromatosis.[5] Many people have an undiagnosed genetic susceptibility to iron overload, and are not aware of a family history of the problem. Overdoses of ingested iron can cause excessive levels of free iron in the blood. High blood levels of free ferrous iron react with peroxides to produce highly reactive free radicals that can damage DNA, proteins, lipids, and other cellular components. Iron toxicity occurs when the cell contains free iron, which generally occurs when iron levels exceed the availability of transferrin to bind the iron. Damage to the cells of the gastrointestinal tract can also prevent them from regulating iron absorption, leading to further increases in blood levels. Iron typically damages cells in the heart, liver and elsewhere, causing adverse effects that include coma, metabolic acidosis, shock, liver failure, coagulopathy, adult respiratory distress syndrome, long-term organ damage, and even death.[174] Humans experience iron toxicity when the iron exceeds 20 milligrams for every kilogram of body mass; 60 milligrams per

kilogram is considered a lethal dose.[175] Overconsumption of iron, often the result of children eating large quantities of ferrous sulfate tablets intended for adult consumption, is one of the most common toxicological causes of death in children under six.[175] The Dietary Reference Intake (DRI) sets the Tolerable Upper Intake Level (UL) for adults at 45 mg/day. For children under fourteen years old the UL is 40 mg/day.[176]
The medical management of iron toxicity is complicated, and can include use of a specific chelating agent called deferoxamine to bind and expel excess iron from the body.[174][177][178]

COPPER

Copper is an essential trace element in plants and animals, but not all microorganisms. The human body contains copper at a level of about 1.4 to 2.1 mg per kg of body mass.[149]

Absorption

Copper is absorbed in the gut, then transported to the liver bound to albumin.[150] After processing in the liver, copper is distributed to other tissues in a second phase, which involves the protein ceruloplasmin, carrying the majority of copper in blood. Ceruloplasmin also carries the copper that is excreted in milk, and is particularly well-absorbed as a copper source.[151] Copper in the body normally undergoes enterohepatic circulation (about 5 mg a day, vs. about 1 mg per day absorbed in the diet and excreted from the body), and the body is able to excrete some excess copper, if needed, via bile, which carries some copper out of the liver that is not then reabsorbed by the intestine.[152][153]

Dietary recommendations

The U.S. Institute of Medicine (IOM) updated the estimated average requirements (EARs) and recommended dietary allowances (RDAs) for copper in 2001. If there is not sufficient information to establish EARs and RDAs, an estimate designated Adequate Intake (AI) is used instead. The AIs for copper are: 200 µg of copper for 0–6-month-old males and females, and 220 µg of copper for 7–12-month-old males and females. For both sexes, the RDAs for copper are: 340 µg of copper for 1–3 years old, 440 µg of copper for 4–8 years old, 700 µg of copper for 9–13 years old, 890 µg of copper for 14–18 years old and 900 µg of copper for ages 19 years and older. For pregnancy, 1,000 µg. For lactation, 1,300 µg.[154] As for safety, the IOM also sets Tolerable upper intake levels (ULs) for vitamins and minerals when evidence is sufficient. In the case of copper the UL is set at 10 mg/day. Collectively the EARs, RDAs, AIs and ULs are referred to as Dietary Reference Intakes.[155]

The European Food Safety Authority (EFSA) refers to the collective set of information as Dietary Reference Values, with Population Reference Intake (PRI) instead of RDA, and Average Requirement instead of EAR. AI and UL defined the same as in United States. For women and men ages 18 and older the AIs are set at 1.3 and 1.6 mg/day, respectively. AIs for pregnancy and lactation is 1.5 mg/day. For children ages 1–17 years the AIs increase with age from 0.7 to 1.3 mg/day. These AIs are higher than the U.S. RDAs.[156] The European Food Safety Authority reviewed the same safety question and set its UL at 5 mg/day, which is half the U.S. value.[157]

For U.S. food and dietary supplement labeling purposes the amount in a serving is expressed as a percent of Daily Value (%DV). For copper labeling purposes 100% of the Daily Value was 2.0 mg, but as of May 27, 2016 it was revised to 0.9 mg to bring it into agreement with the RDA.[158][159] Compliance with the updated labeling regulations was required by 1 January 2020, for manufacturers with $10 million or more in annual food sales, and by 1 January 2021, for manufacturers with less than $10 million in annual food sales.[160][161][162] During the first six months following the 1 January 2020 compliance date, the FDA plans to work cooperatively with manufacturers to meet the new Nutrition Facts label requirements and will not focus on enforcement actions regarding these requirements during that time.[160] A table of the old and new adult Daily Values is provided at Reference Daily Intake.

Deficiency

Because of its role in facilitating iron uptake, copper deficiency can produce anemia-like symptoms, neutropenia, bone abnormalities, hypopigmentation, impaired growth, increased incidence of infections, osteoporosis, hyperthyroidism, and abnormalities in glucose and cholesterol metabolism. Conversely, Wilson's disease causes an accumulation of copper in body tissues.

Severe deficiency can be found by testing for low plasma or serum copper levels, low ceruloplasmin, and low red blood cell superoxide dismutase levels; these are not sensitive to marginal copper status. The "cytochrome c oxidase activity of leucocytes and platelets" has been stated as another factor in deficiency, but the results have not been confirmed by replication.[163]

Toxicity

Copper toxicity

Gram quantities of various copper salts have been taken in suicide attempts and produced acute copper toxicity in humans, possibly due to redox cycling and the generation of reactive oxygen species that damage DNA.[164][165] Corresponding amounts of copper salts (30 mg/kg) are toxic in animals.[166] A minimum dietary value for healthy growth in rabbits has been reported to be at least 3 ppm in the diet.[167] However, higher concentrations of copper (100 ppm, 200 ppm, or 500 ppm) in the diet of rabbits may favorably influence feed conversion efficiency, growth rates, and carcass dressing percentages.[168]

Chronic copper toxicity does not normally occur in humans because of transport systems that regulate absorption and excretion. Autosomal recessive mutations in copper transport proteins can disable these systems, leading to Wilson's disease with copper accumulation and cirrhosis of the liver in persons who have inherited two defective genes.[149]

Elevated copper levels have also been linked to worsening symptoms of Alzheimer's disease.[169][170]

Human exposure

In the US, the Occupational Safety and Health Administration (OSHA) has designated a permissible exposure limit (PEL) for copper dust and fumes in the workplace as a time-weighted average (TWA) of 1 mg/m^3.[171] The National Institute for Occupational Safety and Health (NIOSH) has set a Recommended exposure limit (REL) of 1 mg/m^3, time-weighted average. The IDLH (immediately dangerous to life and health) value is 100 mg/m^3.[172]

Copper is a constituent of tobacco smoke.[173][174] The tobacco plant readily absorbs and accumulates heavy metals, such as copper from the surrounding soil into its leaves. These are readily absorbed into the user's body following smoke inhalation.[175]

ZINC

Nutrition

Dietary recommendation

The U.S. Institute of Medicine (IOM) updated Estimated Average Requirements (EARs) and Recommended Dietary Allowances (RDAs) for zinc in 2001. The current EARs for zinc for women and men ages 14 and up is 6.8 and 9.4 mg/day, respectively. The RDAs are 8 and 11 mg/day. RDAs are higher than EARs so as to identify amounts that will cover people with higher than average requirements. RDA for pregnancy is 11 mg/day. RDA for lactation is 12 mg/day. For infants up to 12 months the RDA is 3 mg/day. For children ages 1–13 years the RDA increases with age from 3 to 8 mg/day. As for safety, the IOM sets Tolerable upper intake levels (ULs) for vitamins and minerals when evidence is sufficient. In the case of zinc the adult UL is 40 mg/day (lower for children). Collectively the EARs, RDAs, AIs and ULs are referred to as Dietary Reference Intakes (DRIs).[186]

The European Food Safety Authority (EFSA) refers to the collective set of information as Dietary Reference Values, with Population Reference Intake (PRI) instead of RDA, and Average Requirement instead of EAR. AI and UL are defined the same as in the United States. For people ages 18 and older the PRI calculations are complex, as the EFSA has set higher and higher values as the phytate content of the diet increases. For women, PRIs increase from 7.5 to 12.7 mg/day as phytate intake increases from 300 to 1200 mg/day; for men the range is 9.4 to 16.3 mg/day. These PRIs are higher than the U.S. RDAs.[204] The EFSA reviewed the same safety question and set its UL at 25 mg/day, which is much lower than the U.S. value.[205]

For U.S. food and dietary supplement labeling purposes the amount in a serving is expressed as a percent of Daily Value (%DV). For zinc labeling purposes 100% of the Daily Value was 15 mg, but on May 27, 2016 it was revised to 11 mg.[206][207] Compliance with the updated labeling regulations was required by 1 January 2020, for manufacturers with $10 million or more in annual food sales, and by 1 January 2021, for manufacturers with less than $10 million in annual food sales.[208][209][210] During the first six months following the 1 January 2020 compliance date, the FDA plans to work cooperatively with manufacturers to meet the new Nutrition Facts label requirements and will not focus on enforcement actions regarding these requirements during that time.[208] A table of the old and new adult Daily Values is provided at Reference Daily Intake.

Dietary intake

Foods and spices containing zinc

Animal products such as meat, fish, shellfish, fowl, eggs, and dairy contain zinc. The concentration of zinc in plants varies with the level in the soil. With adequate zinc in the soil, the food plants that contain the most zinc are wheat (germ and bran) and various seeds, including sesame, poppy, alfalfa, celery, and mustard.[211] Zinc is also found in beans, nuts, almonds, whole grains, pumpkin seeds, sunflower seeds, and blackcurrant.[212] Plant phytates are particularly found in pulses and cereals and interfere with zinc absorption.

Other sources include fortified food and dietary supplements in various forms. A 1998 review concluded that zinc oxide, one of the most common supplements in the United States, and zinc carbonate are nearly insoluble and poorly absorbed in the body.[213] This review cited studies that found lower plasma zinc concentrations in the subjects who consumed zinc oxide and zinc carbonate than in those who took zinc acetate and sulfate salts.[213] For fortification, however, a 2003 review recommended cereals (containing zinc oxide) as a cheap, stable source that is as easily absorbed as the more expensive forms.[214] A 2005 study found that various compounds of zinc, including oxide and sulfate, did not show statistically significant differences in absorption when added as fortificants to maize tortillas.[215]

Deficiency

Zinc deficiency

Nearly two billion people in the developing world are deficient in zinc. Groups at risk include children in developing countries and elderly with chronic illnesses.[10] In children, it causes an increase in infection and diarrhea and contributes to the death of about 800,000 children worldwide per year.[9] The World Health

Organization advocates zinc supplementation for severe malnutrition and diarrhea.[216] Zinc supplements help prevent disease and reduce mortality, especially among children with low birth weight or stunted growth.[216] However, zinc supplements should not be administered alone, because many in the developing world have several deficiencies, and zinc interacts with other micronutrients.[217] While zinc deficiency is usually due to insufficient dietary intake, it can be associated with malabsorption, acrodermatitis enteropathica, chronic liver disease, chronic renal disease, sickle cell disease, diabetes, malignancy, and other chronic illnesses.[10]

In the United States, a federal survey of food consumption determined that for women and men over the age of 19, average consumption was 9.7 and 14.2 mg/day, respectively. For women, 17% consumed less than the EAR, for men 11%. The percentages below EAR increased with age.[218] The most recent published update of the survey (NHANES 2013–2014) reported lower averages – 9.3 and 13.2 mg/day – again with intake decreasing with age.[219] Symptoms of mild zinc deficiency are diverse.[186] Clinical outcomes include depressed growth, diarrhea, impotence and delayed sexual maturation, alopecia, eye and skin lesions, impaired appetite, altered cognition, impaired immune functions, defects in carbohydrate utilization, and reproductive teratogenesis.[186] Zinc deficiency depresses immunity,[220] but excessive zinc does also.[176]

Despite some concerns,[221] western vegetarians and vegans do not suffer any more from overt zinc deficiency than meat-eaters.[222] Major plant sources of zinc include cooked dried beans, sea vegetables, fortified cereals, soy foods, nuts, peas, and seeds.[221] However, phytates in many whole-grains and fibers may interfere with zinc absorption and marginal zinc intake has poorly understood effects. The zinc chelator phytate, found in seeds and cereal bran, can contribute to zinc malabsorption.[10] Some evidence suggests that more than the US RDA (8 mg/day for adult women; 11 mg/day for adult men) may be needed in those whose diet is high in phytates, such as some vegetarians.[221] The European Food Safety Authority (EFSA) guidelines attempt to compensate for this by recommending higher zinc intake when dietary phytate intake is greater.[204] These considerations must be balanced against the paucity of adequate zinc biomarkers, and the most widely used indicator, plasma zinc, has poor sensitivity and specificity.[223]

Zinc toxicity

Although zinc is an essential requirement for good health, excess zinc can be harmful. Excessive absorption of zinc suppresses copper and iron absorption.[199] The free zinc ion in solution is highly toxic to plants, invertebrates, and even vertebrate fish.[226] The Free Ion Activity Model is well-established in the literature, and shows that just micromolar amounts of the free ion kills some organisms. A recent example showed 6 micromolar killing 93% of all *Daphnia* in water.[227]

The free zinc ion is a powerful Lewis acid up to the point of being corrosive. Stomach acid contains hydrochloric acid, in which metallic zinc dissolves readily to give corrosive zinc chloride. Swallowing a post-1982 American one cent piece (97.5% zinc) can cause damage to the stomach lining through the high solubility of the zinc ion in the acidic stomach.[228]

Evidence shows that people taking 100–300 mg of zinc daily may suffer induced copper deficiency. A 2007 trial observed that elderly men taking 80 mg daily were hospitalized for urinary complications more often than those taking a placebo.[229] Levels of 100–300 mg may interfere with the utilization of copper and iron or adversely affect cholesterol.[199] Zinc in excess of 500 ppm in soil interferes with the plant absorption of other essential metals, such as iron and manganese.[100] A condition called the zinc shakes or "zinc chills" can be induced by inhalation of zinc fumes while brazing or welding galvanized materials.[131] Zinc is a common ingredient of denture cream which may contain between 17 and 38 mg of zinc per gram. Disability and even deaths from excessive use of these products have been claimed.[230]

The U.S. Food and Drug Administration (FDA) states that zinc damages nerve receptors in the nose, causing anosmia. Reports of anosmia were also observed in the 1930s when zinc preparations were used in a failed attempt to prevent polio infections.[231] On June 16, 2009, the FDA ordered removal of zinc-based intranasal cold products from store shelves. The FDA said the loss of smell can be life-threatening because people with impaired smell cannot detect leaking gas or smoke, and cannot tell if food has spoiled before they eat it.[232]

Recent research suggests that the topical antimicrobial zinc pyrithione is a potent heat shock response inducer that may impair genomic integrity with induction of PARP-dependent energy crisis in cultured human keratinocytes and melanocytes.[233]

In 1982, the US Mint began minting pennies coated in copper but containing primarily zinc. Zinc pennies pose a risk of zinc toxicosis, which can be fatal. One reported case of chronic ingestion of 425 pennies (over 1 kg of zinc) resulted in death due to gastrointestinal bacterial and fungal sepsis. Another patient who ingested 12 grams of zinc showed only lethargy and ataxia (gross lack of coordination of muscle movements).[234] Several other cases have been reported of humans suffering zinc intoxication by the ingestion of zinc coins.[235][236]

Pennies and other small coins are sometimes ingested by dogs, requiring veterinary removal of the foreign objects. The zinc content of some coins can cause zinc toxicity, commonly fatal in dogs through severe hemolytic anemia and liver or kidney damage; vomiting and diarrhea are possible symptoms.[237] Zinc is highly toxic in parrots and poisoning can often be fatal.[238] The consumption of fruit juices stored in galvanized cans has resulted

in mass parrot poisonings with zinc.[57]

3.0 MATERIALS AND METHOD

3.1.Experimental design

Data on covid 19 disease was collected on the internet Worldometer.info/coronavirus/country and data was obtained from February to December 15 2020 and Five continents were of interest namely North America, South America ,Europe, Asia and Africa and main countries of interest where United states of America, France,United Kingdom, China,Brazil and Nigeria. The countries were chosen as case study because of their gross domestic product(GDP) and World trade with other Countries and also according to how developed or underdeveloped they were.The population per country, incident rates and death associated with each were reviewed.The United state of America had an incident rate of 1,7143942 and France,UK,China,Brazil and Nigeria had 2391447,1888116,8681821,6974258 and 174132 respectively between February and 15 December 2020.Mortality rates were alarming for these countries ,which is the major concern the U.S.A had 311073 and France,UK,China and Nigeria had 59072,64905, 182854,4634 and 1200 respectively.

Data was analysed statistically using Analysis of variants, tables were used to determine percentage monthly incidence, prevalence, morbidity, fatality, mortality rates and population at risk.

4.0 RESULT AND DISCUSSION

4.1 Result

Table I Prevalence rates of Covid 19 in selected countries from February to December 15 2020.

	USA	FRANCE	UK	CHINA	BRAZIL	NIGERIA
FEBRUARY	68	100	23	79824	2	0
MARCH	197844	52128	22792	81554	5717	135
APRIL	1108447	129581	155151	82862	85380	627
MAY	1863739	151753	248925	83001	10162	10162
JUNE	2747901	164801	283253	83531	25694	25694
JULY	4766320	187919	303101	84292	45151	45151
AUGUST	6291051	281025	335873	85048	54008	54008
SEPTEMBER	7513080	563535	465125	85048	58848	58848
OCTOBER	9461184	1367625	1011660	85973	62855	62855
NOVEMBER	13965693	2222488	1629656	85973	67557	67557
DECEMBER	17143942	2391447	1888116	86758	74132	74132

Source: http;/www.Worldometer.info/coronavirus.

Table II Percentage population at risk.

	Total population	Prevalence rate	Mortality rate	Population at Risk
USA	331891557	17143942	31103	95%
FRANCE	65339853	2391447	59072	97%
UK	68049406	1888116	64905	98%
CHINA	1439323776	8681821	4634	96%
BRAZIL	213312046	6974258	182854	98%
NIGERIA	180000000	74132	1200	96%

Table III showing fatality, morbidity and mortality rates in percentages

	Morbidity rate %	Mortality rate %	Fatality rate %
USA	5.17	0.01	0.18
FRANCE	3.66	0.9	2.47
UK	2.77	0.1	3.43
CHINA	0.006	0.0001	0.05
BRAZIL	3.26	0.09	2.62
NIGERIA	0.04	0.0006	1.21

Table IV showing incident rates per month from February to December 15 2020

	USA	France	UK	China	Brazil	Nigeria
February	197776	52028	22769	1730	5715	134
March	910603	77453	132359	1308	79663	492
April	755292	22172	90774	139	429469	1305
May	884162	13048	34328	530	893636	8230
June	2018419	23118	19928	761	1257813	15532
July	1524731	93106	32692	756	1244603	17457
August	1222029	282510	129252	0	902685	10857
September	1948104	804090	546535	925	722019	4840
October	4504509	854863	617996	0	800673	4005
November	3178249	168959	258460	785	637980	4704

4.3 Discussion

Table I shows the beginning of infection in the month of February with China having the highest prevalence due to the fact that the first case of covid 19 was found there but in the month of March the Prevalence of USA became more than that of China.Incidence of this disease has been on the rise till date and it is accompanied by high Mortality.

Table II shows that in the countries in this study ,the population at risk of contacting the disease is 95% to 98%, this is not a good sign and so warrants urgent measures to curb the menace of this disease because the rate of infection is high.

Table III shows that fatality and mortality of the disease may seem low in most countries but the disease is highly infectious and contagious ,it is very risky not to quickly devise measures of tackling this disease . Mortality has been on the increase in USA, France , UK and Brazil with values of 0.01%,0.9% , 0.1% and 0.09% respectively and the fatality rates were on the increase most especially in UK ,France , USA and Brazil with values of 3.43%,2.47%, 0.18% and 2.62% respectively.

Table IV showing the incident rates per month and in the month of February, USA, France , UK

and Brazil had relatively low rates but in the month of July and October the incident rates for the five countries increased significantly. It was an intriguing to find that in the months of August and October China had no incidents. The incident rate in Brazil in the month of June was very high .The data was not truly representative.

Among Clinical signs observed included Anemia,Dyspnea,hypoxia and cellular and tissue degradation which are the major problems .Anemia was megaloblstic, hemolyitic and hemorrhagic and whole blood was lost through petechial hemorrhages as a result of Lupus dermatitis and immunologic lupus erythmatosus due to the host immune responses to the viral attack. Secondarily, signs of anemia such as dyspnea, edema and dehydration were noticed.

Dehydration and Low packed cell volume indicated the inability of tissues to utilize oxygen and hypoxia produces decrease energy resulting in cell membrane depolarization and tissue necrosis,which in effect results in cellular and tissue degradation. Anemia observed was firstly Normocytic normochromic and later in late stages of the infection becoming Macrocytic hypochromic anemia,due to the failure of the bone marrow to produce sufficient viable red blood cells into peripheral circulation and emaciation seen was as a result of dehydration and anorexia.

Pathologic findings in some of the vital organs such as the Lung ,Liver ,spleen and heart include necrosis and degeneration, edema,petechial hemorrhages , hypertrophy .This is so because of the decrease blood volume and cells and a decrease in peripheral circulation due to pooling of blood into the heart resulting in edema of the extremities especially the legs a phenomenon which is associated with Systemic lupus erythmatosus. Degeneration of the organs result in loss of function for example the liver no longer metabolise glucose nor store it and as we know glucose is essential for energy production the splenic pulps do not produce red blood cells anymore, and with depression of the bone marrow oxygen tissue supply is decreased,Lungs are pneumonic and there maybe Bronchopneumonia ,interstitial or embolic pneumonia depending on duration of disease, Patients in most cases suffer cardiogenic , anaphylactic and hypovolemic shock, dyspnea (gasping for oxygen) and/ or hypoxia result in tissue necrosis and degeneration,loss of function of organs and apoptosis(cell death).

4.4 CONCLUSION

Anemia, hypoxia and tissue death and dehydration are the major threat in this disease

Dehydration as a result of fluid and electrolyte loss which makes packed cell volume appear normal but in actual sense there is hemoconcentration leading to a false representation of blood picture.

Whole Blood, electrolyte fluid therapy and administration of oxygen might not help much because they do not tackle the underlying cause which is the disease.

Prophylactically, to prevent covid 19 daily intake of blood tonic and ascorbic acid at required at recommended daily doses are measures which should be tried experimentally pre-infection to encourage tissue growth and re-epithelisation and also to help hasten maturity of the blood cells and improve their immune mechanism ,more so ascorbic acid can help a lot in the area of energy generation and build by maintaining and improving transmembrane permeability and action potential to prevent tissue and cellular degradation by histiocytes.

My sincere gratitude goes to Professors Sani Adamu , M.N Salka and S.Bisalla , and not forgetting M.Y Fatihu, U.S Abdullahi , L.S Makarfi and Dr A.A Abdulkadir all in the department of veterinary pathology and veterinary medicine and surgery,Ahmadu Bello University Zaria.Nigeria.

My children Mariam ,Mulikat and Mustapha Jnr.

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