Lesson 19.

Microbiology diagnosis of herpes viruses, enterovirus infections and rotaviruses.
Introduction

- It’s a kind of enveloped DNA virus.
- **Icosahedral** core surrounded by a lipoprotein **envelope**.
- Linear double-stranded DNA.
- Large (120–200 nm in diameter), second in size only to poxviruses.
- Capsid surrounds DNA core and over the capsid is tegument (a protein-filled region).
- Nuclear membrane derived lipid bilayer containing viral glycoproteins
Classification

- Eight human herpesvirus species are known.
  - Herpes Simplex Virus type 1 (HSV-1)
  - Herpes Simplex Virus type 2 (HSV-2)
  - Varicella-Zoster Virus (VZV)
  - Cytomegalovirus (CMV)
  - Epstein-Barr Virus (EBV)
  - Human Herpes Virus type 6 (HHV-6)
  - Human Herpes Virus type 7 (HHV-7)
  - Human Herpes Virus type 8 (HHV-8)
Classification

- It is also classified on the basis of biological characteristics:
  - Alphaherpesvirinae (herpes simplex virus group)
  - Betaherpesvirinae (cytomegalovirus group)
  - Gammaherpesvirinae (lymphoproliferative group)
Herpes Simplex Viruses

- Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are distinguished by two main criteria
  - Antigenicity
  - Location of lesions.
- HSV-1: **above the waist**, primarily in adults
  - Acute gingivostomatitis,
  - Recurrent herpes labialis (cold sores),
  - Keratoconjunctivitis (keratitis),
  - Encephalitis
- HSV-2: **below the waist**
  - Herpes genitalis (genital herpes),
  - Neonatal encephalitis and other forms of neonatal herpes
  - Aseptic meningitis
- Humans are the natural hosts of both.
HSV - Replication

- DNA released in the cytoplasm
- DNA migrates to the nucleus
- mRNA (transcription) synthesis takes place in the nucleus by using host RNA polymerase
- tRNA transported to the cytoplasm
- New viral proteins made and migrate to nucleus
- Genomic DNA (replication) synthesis takes place in the nucleus by using viral DNA polymerase
HSV - Replication

1) Fusion
2) Entry and Uncoating
3) Enters nucleus
4) DNA Replication
5) Assembly
6) Exit via endoplasmic reticulum and Golgi apparatus
Transmission

- HSV 1: transmitted primarily in saliva.
- HSV 2: transmitted by sexual contact
  - 10–20% of cases
- HSV-2 infections has markedly increase comparatively.
Clinical Findings: HSV-1

- causes several forms of primary and recurrent disease.
- **Gingivostomatitis**
  - Occurs primarily in children and is characterized by fever, irritability, and vesicular lesions in the mouth.
  - The primary disease is more severe and lasts longer than recurrences.
  - The lesions heal spontaneously in 2 to 3 weeks.
  - Many children have asymptomatic primary infections
- **Herpes labialis**
  - Fever blisters or cold sores is the milder, recurrent form
  - Characterized by crops of vesicles, usually at the mucocutaneous junction of the lips or nose
  - Recurrences frequently reappear at the same site.

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Gingivostomatitis
Clinical Findings: HSV-1

- **Keratoconjunctivitis**
  - characterized by corneal ulcers and lesions of the conjunctival epithelium.
  - Recurrences can lead to scarring and blindness

- **Encephalitis**
  - necrotic lesion in one temporal lobe.
  - Fever, headache, vomiting, seizures, and altered mental status
Clinical Findings: HSV-1

- **Herpetic whitlow**
  - pustular lesion of the skin of the finger or hand.
  - It can occur in medical personnel as a result of contact with patient’s lesions.

- **Herpes gladiatorum**
  - wrestlers and others who have close body contact.
  - vesicular lesions on the head, neck, and trunk.

- **Disseminated infections,**
  - such as esophagitis and pneumonia,
  - occur in immunocompromised patients with depressed T-cell function.
Clinical Findings: HSV-1

Herpetic whitlow

Herpes gladiatorum

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Clinical Findings: HSV-2

- Genital herpes
  - painful vesicular lesions of the male and female genitals and anal area
  - The lesions are more severe and protracted in primary disease than in recurrences.
  - Primary infections are associated with fever and inguinal adenopathy.
  - Asymptomatic infections - source of infection of other individuals
    - Men: prostate or urethra
    - Women: cervix
Clinical Findings: HSV-2

- Neonatal herpes
  - originates chiefly from contact with vesicular lesions within the birth canal.
  - varies from severe disease (e.g., disseminated lesions or encephalitis) to milder local lesions (skin, eye, mouth) to asymptomatic infection.
  - prevented by performing cesarean section on women with either active lesions or positive viral cultures.
  - neither HSV-1 nor HSV-2 causes congenital abnormalities to any significant degree.
Neonatal herpes
Laboratory Diagnosis

- Isolation of the virus from the lesion by growth in cell culture
  - typical cytopathic effect occurs in 1 to 3 days,
  - identified by fluorescent antibody staining of the infected cells or ELISAs
- **Tzanck smear**: rapid diagnosis
  - Giemsa stain: Multinucleated Giant Cell presence in vesicles
- Serologic tests such as the neutralization test
Treatment

- **Acyclovir**: treatment of choice
  - shortens the **duration** of the lesions
  - reduces the **extent of shedding** of the virus
- **Penciclovir** (a derivative of acyclovir) or **docosanol**: recurrences of orolabial HSV-1
- **Valacyclovir and famciclovir**: genital herpes and in the suppression of recurrences.
Prevention

• avoiding contact with the vesicular lesion or ulcer.

• Cesarean section is recommended for women who are at term and who have genital lesions or positive viral cultures.
Varicella-Zoster Virus (VZV)

- Clinical chicken pox (primary infection)
- $\geq$ 80% of cases before age 10, peak incidence 2-8 years
- Virus entry through inhalation
- Replicates in respiratory tract and invades lymph nodes.
- Viremia: spreads virus to target organs
- Incubation period 14-18 days
VZV - Chicken Pox

- Rash appears first on head, neck, trunk
- Vesicles contain clear fluid (itch)
- New vesicles appear during first week
- Mild fever, malaise, headache
- Recovery in 2 weeks
- Adult infections more severe (pneumonia)
- Neonatal infection (encephalitis) in immunosuppressed (severe progressive infection)
VZV - Chicken Pox
VZV - Chicken Pox
VZV - Shingles

- Shingles: reactivation of varicella-zoster
- DNA remains latent in ganglia
- Occurrence increases with age (50% over 50 yrs)
- Onset of pain occurs before appearance of vesicles
- Usually unilateral
- Immunosuppressed patients especially vulnerable
VZV - Shingles
VZV - Diagnosis and Treatment

• Diagnosis
  – Clinical picture (almost always)
  – Immunofluorescent antibody staining biopsy

• Treatment
  – Supportive
  – acyclovir for extreme case
Chicken Pox - Prevention

• Prevention
  – immune globulin for patients at risk
  – Vaccine: live vaccine (VARIVAX, Merck & Co.)
  – Recommended dose
    • For susceptible children aged 12 months to 12 years is one 0.5 ml dose subcutaneously
    • For susceptible adolescents aged 13 years and adults is two 0.5 ml doses 4 to 8 weeks apart
Cytomegalovirus (CMV)

- ds DNA virus
- largest genome of the herpes virus group
- similar to HSV but highly regulated by cis-acting elements and regulatory proteins-slow replication and slow disease effects
- Nuclear and cytoplasmic inclusion bodies, induction of giant cells
CMV - Clinical Features

- **Transmission:** close contact, sexually transmitted, virus can be recovered from all body fluids much as saliva, urine, semen, & cervical secretions
- **Clinical features**
  - high infection rates in early childhood and early adulthood
  - usually asymptomatic
  - Systemic CMV infection; pneumonia and hepatitis in immunosuppressed patients (transplant patients)
  - In AIDS patient; diarrhea, retinitis
CMV - Clinical Features

- **Congenital CMV**
  - most infants appear normal at birth
  - may develop hearing loss or some mental retardation often later.
  - Infants with symptomatic illness at birth demonstrate hepatosplenomegaly, jaundice, anemia, low weight, microcephaly, rash, thrombocytopenia
  - Neonatal – asymptomatic
  - Immunosuppressed: CMV pneumonia, disseminated CMV
  - CMV retinitis
Congenital CMV

Approximately 10 percent of congenitally infected newborns will have symptoms at birth:

- Chorioretinitis
- Small size for gestational age
- Petechiae purpura jaundice
- Hepatosplenomegaly

TREATMENT

For neonates with symptomatic infection, treatment with ganciclovir may protect against hearing loss and developmental impairment.
CMV - Diagnosis and Treatment

- **Diagnosis**
  - isolation of virus, electron microscopy, serology,
  - DNA amplification by PCR

- **Treatment**
  - hyperimmune globulin, ganciclovir
Epstein-Barr Virus (EBV)
Epstein-Barr Virus (EBV)

- **Structure:** DNA virus, enveloped
- Etiologic agent of infectious mononucleosis and African Burkitt’s Lymphomas.
- Recent study has linked with Hodgkins lymphoma
- Cultured in only lymphoblastoid cell lines derived from B lymphocytes of humans and higher primates
- Viral genome can be cultivated continuously and are transformed or immortalized.
Epstein-Barr Virus (EBV)

- EBV nuclear antigens (EBNAs) appear in the nucleus prior to virus directed protein synthesis.
- Viral capsid antigen (VCA) is detected in virus producing cell lines.
- EBV can be cultured from saliva and thus infection is acquired by contact.
- **Transmission**
  - contact with infected secretions,
  - low contagiousness,
  - virus can be cultured from throat washings
Main symptoms of Infectious mononucleosis

Central
- Fatigue
- Malaise
- Loss of appetite
- Headache

Visual
- Photophobia

Tonsils
- Reddening
- Swelling
- White patches

Throat
- Soreness
- Reddening

Respiratory
- Cough

Systemic
- Chills
- Fever
- Aches

Lymph nodes
- Swelling

Spleen
- Enlargement
- Abdominal pain

Gastric
- Nausea

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EBV: Clinical Features

- Infectious mononucleosis, usually asymptomatic
- If symptoms persist (young adults)
  - low fever
  - headache,
  - sore throat,
  - fatigue,
  - night chills (sweats),
  - enlarged lymph nodes and spleen,
  - elevated lymphocytes and monocytes and atypical lymphocytes
- **Complications**
  - laryngeal obstruction, meningitis,
  - encephalitis, hemolytic anemia,
  - thrombocytopenia or splenic rupture may occur in 1 to 5% of the patients

BURKITT’S LYMPHOMA

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Hairy leukoplakia: Strong Association with EBV
EBV - Diagnosis

- Clinical picture
- Complete Blood Cell Count – Atypical lymphocytes
- **Serology**
  - Expensive
  - Demonstrate antibody to viral capsid antigen (VCA) which rises quickly and persists for life.
  - Antibodies to EBNAs rise later and decrease in about 1 month
EBV - Diagnosis

• Serology
  – A high titer of VCA and no titer of EBNA suggest recent infection
  – Antibodies to early antigen (EA) may be useful in correlating with nasopharyngeal CA and African Burkitt’s lymphomas

• Culture
  – Usually positive in acute illness,
  – but asymptomatic viral shedding is so common, that culture is seldom helpful.
EBV - Epidemiology and Treatment

• Epidemiology
  – Burkitt’s lymphoma- Central & East Africa
  – Tumor in jaw area: Nasopharyngeal carcinoma: China & Southeast Asia

• Treatment and Prevention
  – Supportive
  – Acyclovir can suppress the replication process
  – No vaccine available
Human Herpes Virus - 6

- HHV-6 detected in patients with lymphoproliferative diseases.
- Genetically distinct but morphologically similar to other herpes virus.
- Replicates in lymphoid tissue preferentially in T lymphocytes.
- Cytopathic for T lymphocytes in cell culture.
- Establishes a latent infection and may be activated by mitogenic stimulation.
Proliferation of T-lymphocyte
HHV-6 - Clinical Features

- Serologic studies indicate that almost all children are infected by age 5.
- Most communicable of all herpes virus.
- Spread by close personal contact or by respiratory route.
- **Disease**: Roseola infantum (rash like disease)
- Reactivated in transplant patients
- **Treatment**: Acyclovir is 15 to 30% absorbed by oral route
Human Herpes Virus -7

- HHV-7 discovered in 1990
- Isolated from activated CD4+ T lymphocytes.
- HHV-7 is distinct from all other known human herpesviruses but closely related to HHV-6.
- Infects most children by age 2 and 97% of adults are seropositive
- Culture restricted to specialized virology lab.
- Diagnosis of acute infection by seroconversion.
Human Herpes Virus - 8

- HHV-8, Kaposi's sarcoma-associated herpesvirus, KSHV
- Discovered as herpesvirus sequences in AIDS related Kaposi’s sarcoma (KS) patients
- HHV-8 DNA sequences found in 95% of KS tissues, both AIDS and non-AIDS related cases
- KSHV DNA has also been detected in cells from lymphoproliferative diseases
Kaposi’s sarcoma

two raised reddish purple lesions on the foot caused by human herpesvirus-8
Kaposi's sarcoma
Human Herpes Virus - 8

- Recently, HHV-8 was isolated in culture and closely related to EBV
- Like EBV, HHV-8 preferentially infects B lymphocytes
- In addition to HHV-8, immunosuppression, genetic predisposition are cofactors for KS
- HHV-8 appears to be sexually transmitted
- Interferon-alpha can be effective
ENTEROVIRUSES

• Enteroviruses are a genus of the picornavirus family which replicate mainly in the gut.

• Single stranded naked RNA virus with icosahedral symmetry.

• Unlike rhinoviruses, they are stable in acid pH.

• Capsid has 60 copies each of 4 proteins, VP1, VP2, VP3 and VP4 arranged with icosahedral symmetry around a positive sense genome.
ENTEROVIRUSES

• At least 71 serotypes are known: divided into 5 groups
  – Polioviruses
  – Coxsackie A viruses
  – Coxsackie B viruses
  – Echoviruses
  – Enteroviruses (more recently, new enteroviruses subtype have been allocated sequential numbers (68-71))
<table>
<thead>
<tr>
<th>VIRUS</th>
<th>SEROTYPES</th>
<th>CLINICAL DISEASES</th>
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<tr>
<td>Polioviruses</td>
<td>3 types</td>
<td>Asymptomatic infection, viral meningitis, paralytic disease, poliomyelitis</td>
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<td>Coxsackie A viruses</td>
<td>23 types (A1-A22, A24)</td>
<td>Viral meningitis plus, rash, ARD, myocarditis, orchitis</td>
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<td>Coxsackie B viruses</td>
<td>6 types (B1-B6)</td>
<td>Viral meningitis, but no orchitis</td>
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<td>Echoviruses</td>
<td>32 types</td>
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<td>Other Enteroviruses</td>
<td>4 types (68-71)</td>
<td>Viral meningitis</td>
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<td>PROPERTY</td>
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<td>Size (nm)</td>
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<td>Density in Cesium chloride (g/m)</td>
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TRANSMISSION OF ENTERO VIRUSES

• Fecal – oral route: poor hygiene, dirty diapers (especially in day-care settings)
• Ingestion via contaminated food and water
• Contact with infected hands
• Inhalation of infectious aerosols
PATHOGENESIS OF ENTEROVIRUSES

ENTEROVIRUS PATHOGENESIS

Entry via aerosol or ingestion

Replication
Oro-pharynx tonsils

Replication
Peyer's patches

Secondary viremia
Target tissue

Primary viremia
circulation

Polio Cox
Brain
Encephalitis Paralysis

Echo, Polio Cox
Meninges
Meningitis

Hep A
Liver
 Hepatitis A

Echo Cox A
Skin
Hand foot mouth disease Rash Herpangina

Echo Cox A B
Muscle
Myocarditis Pericarditis Pleurodynia

Virus in feces
PATHOGENESIS OF ENTEROVIRUSES

Replication in oropharynx

Rhino, echo, coxsackie, polio

Primary viremia

Target Tissue

Secondary viremia

Skin
Muscle
Brain
Meninges
Liver

Echo Coxsackie A
Echo Coxsackie A, B
Polio Coxsackie
Echo Polio Coxsackie
Echo Coxsackie
Poliomyelitis (polio) is a highly infectious viral disease, which mainly affects young children. The virus is transmitted through contaminated food and water, and multiplies in the intestine, from where it can invade the nervous system.
POLIOMYELITIS

- Polio = gray matter, Myelitis = Inflammation of the spinal cord.
- Involves CNS, produces serious Illness.
- Causes Destruction of Motor Neurons in Spinal cord.
- Produces FLACID PARALYSIS.
- India has still has many cases of Poliomyelitis.
Poliovirus, the causative agent of poliomyelitis, is a human enterovirus and member of the family of Picornaviridae. Poliovirus is composed of a RNA genome and a protein capsid. The genome is single-stranded positive-sense RNA genome that is about 7500 nucleotides long. The viral particle is about 300 Angstrom in diameter with icosahedral symmetry.
CLASSIFICATION OF POLIOVIRUS

- Size is 27 nm
- Contains 4 viral protein VP1 to VP 4
- VP1 Carries the major antigenic site, and combines with type specific neutralizing antibodies
- Endemic
- Epidemic
- Hygiene plays in spread of diseases.
- Children < 5 in Developing countries.
PROPERTIES OF POLIOVIRUS

- Typical Entero virus.
- Inactivated at 55° c for 30 mt.
- Chlorine at 0.1 ppm
- Ether is not effective.
- Animal susceptibility.
  - Monkey brain
  - Requires Primate specific membranes.
  - Contains 3 Antigenic types 1, 2, 3
Can be differentiated by ELISA and CF methods.
POLIO INFECTION

• Incubation 3 – 21 days
• On average 14 days
• Predisposing factors.
  Severe muscular activity can lead to paralysis, as it increases the blood flow
  May produce paralysis in the limb or bulbar region
  Injecting vaccines with adjuvant can predispose to paralysis
  Patients who underwent tonsillectomy have higher incidence as Ig G secretion is reduced
  Rarely oral Polio vaccine produces poliomyelitis.
PATHOLOGY & PATHOGENESIS

- Destroy the Anterior horn cells of the Spinal Cord

- Do not Multiply in Muscles only muscles manifest with weakness and flaccid paralysis result is secondary.

- Occasionally produce Myocarditis, Lymphatic hyperplasia.
PATHOLOGY & PATHOGENESIS

- Enter through Mouth,
- Multiplies in Oropharynx tonsils and Intestines,
- Excreted in Stool.
- Enters the CNS from Blood.
- Spread along the Axons of peripheral nerves to CNS.
- Progress along the fibers of the lower motor neurons spinal cord or brain.
The polio virus infects human cells by binding to an immunoglobulin-like receptor called CD155 (poliovirus receptor).

The exact mechanism that poliovirus uses for entering the cell is unknown. However, the interaction of poliovirus and CD155 causes a change in the shape of the viral particle that is needed to enter the cell.

There are two thesis' for the way the viral nucleic acid to enters the cell. The first thesis is that the RNA of poliovirus is injected into the host cell through a pore in the membrane of the host cell. The second, and the one that is most likely and has the most support through research, is that the poliovirus is taken in by the host cell through endocytosis.

Poliovirus has ssRNA. Also known as single-strand RNA.
CLINICAL MANIFESTATIONS

- In apparent, Only 1% manifest with clinical features.
- Can lead to permanent paralysis.
- Incubation 7-14 days, (3-35)
- May be abortive Poliomyelitis,
  Only Fever, Malaise, Drowsiness,
Non paralytic Poliomyelitis,
Aseptic Meningitis.
PARALYTIC POLIOMYELITIS

- Manifest as Flaccid Paralysis. (Caused due to damage to Lower Motor Neurons.)
- Partial recovery within 6 months.
- Patient may continue with lifetime disability
- Can involve Spinal cord, and Bulbo spinal region
- Bulb spinal involvement can paralyze respiratory muscle and lead to Respiratory failure
PARALYTIC POLIOMYELITIS

MUSCLES COMMONLY WEAKENED BY POLIO

- shoulder muscles
- muscles behind arm (weakness straightening arm)
- back muscles (either side of backbone)
- thumb muscles
- muscles that straighten or bend hip, or that spread or close legs
- muscles that straighten knee
- muscles that lift foot

contractures causing tight cords
ASEPTIC MENINGITIS

- Present with Non paralytic form with stiffness and pain in the back and neck region
- Lasts for 2 -10 days
- Recovery rapid and complete
- On rare occasions advance to paralysis
LABORATORY DIAGNOSIS

- Viral isolation from
  - Throat swabs,
  - Rectal swabs,
  - Stool specimens,
- Transported in frozen containers.
- Produce cytopathic effect on Human and Monkey cells
- Produce cytopathic effects.
VIRAL ISOLATION

• From feces - present in 80% of cases in 1st week
• In 50 % till 3rd week
• In 25 % till several weeks
• Collect the fecal sample at the earliest.
• Primary monkey kidney is the ideal cell line for isolation of virus
• Viral isolation must be interpreted with caution and clinical presentation
LABORATORY DIAGNOSIS (SEROLOGY)

- Estimation of Antibodies IgM
- A paired sample is essential.
- ELISA
- CFT
- Neutralisation.
PREVENTION & CONTROL

• Sabin’s Live attenuated vaccine
• Grown in Monkey kidney cells, Human Diploid cells. Preserved at 4°C
• Multiple doses are given
• Given as oral Drops
• At present only vaccine given in our National Programme of Immunization
• Boosts Immunity with Production IgG, IgM
• And also IgA Participate as participant in Prevention.
ORAL POLIO VACCINE (SABIN’S)

- Highly effective in producing immunity to poliovirus
- 50% immune after 1 dose
- >95% immune after 3 doses
- Immunity probably lifelong
ADVANTAGES OF LIVE VACCINE

- Induces long lasting immunity.
- Induces local immunity in the form of IgA production (gut immunity).
- Administered orally, without the need of sterile syringes.
DISADVANTAGES OF LIVE VACCINE

• The only disadvantage of this vaccine is the vaccine strain particular type 3 strain can revert to virulence and cause paralysis in those who just been vaccinated.

• It is estimated that vaccine-induced poliomyelitis is seen in rate of 1 in 3000,000 vaccinations.
INJECTABLE KILLED SALK VACCINE

- Salk Vaccine - A Killed Vaccine. (INACTIVATED)
- Four Injections are administered in a period of two years,
- Administration of periodic booster recommended.
- Most of the Western Nations do use it.
DISEASES ASSOCIATED WITH COXASKIE A VIRUS

- Febrile illness with maculopapular rash.
- Upper respiratory tract infection.
- Paralytic disease.
- Meningitis & encephalitis.
- Peri and myocarditis.
- Herpangina.
- Hand, foot & mouth disease.
- Acute hemorrhagic conjunctivitis.
DISEASES ASSOCIATED WITH COXASKIE A VIRUS

- Caused by group A Coxsackieviruses.
- Characterized by fever, sore throat, pain on swallowing.
- Small vesicles appear on the pharynx, Palate, uvula and tonsils.
- Recovery is usual.
HAND FOOT & MOUTH DISEASE

- Caused by group A coxsackie viruses.
- Small papules & vesicles develop on the buccal mucosa, hands and feet.
- Recovery is usual.
DISEASES ASSOCIATED WITH COXASKIE B VIRUS

- Febrile illness with maculopapular rash.
- Upper respiratory tract infection.
- Paralytic disease.
- Meningitis & encephalitis.
- Peri & myocarditis.
- Pleurodynia.
- Juvenile diabetes/ pancreatitis.
DISEASES ASSOCIATED WITH ECHO VIRUS

- Febrile illness with maculopapular rash.
- Upper respiratory tract infection.
- Paralytic disease.
- Meningitis & encephalitis.
- Peri & myocarditis.
Rotavirus - Structural features

- Reovirus (RNA)
- 60-80nm in size
- Double stranded (ds) RNA
- Non-enveloped virus
- A rotavirus has a characteristic wheel-like appearance when viewed by electron microscopy
  - The name rotavirus is derived from Latin, meaning "wheel"
- Group A is important human pathogen [7 Groups (A to G)]
- 5 predominant strains (G1-G4, G9), account for 90% of isolates
- Strain G1 accounts for 73% of infections
Characters

- The virus is stable in the environment
- Relatively resistant to hand-washing agents
- Susceptible to disinfection
  - 95% ethanol, ‘Lysol’, formalin
- Very stable and may remain viable for weeks or months if not disinfected
Transmission

- Transmission
  - Mainly person to person via fecal-oral route, fomites
  - Poor hygiene
- Food and water-borne spread is possible
- Spread via respiratory route is speculated
Pathogenesis

- Reservoir: Human-GI tract
- Communicability: 2 days before to 10 days after onset

- Entry through mouth
- Replication in epithelium of small intestine
- Viremia uncommon
- Infection leads to isotonic diarrhea
Pathogenicity

- The virus infect the villi of the small intestine
  - Gastric and colonic mucosa are not infected
- Attach with the enterocytes by VP4
- They multiply in the cytoplasm of the enterocytes and damage their transport mechanisms
- Damaged cell may show into lumen of the intestine and release large quantities of virus which appear in the stool
- Viral excretion usually lasts for 2 – 12 days in otherwise healthy patients
Mechanism of diarrhea

- They strip the tips of the villi thus decreasing the surface area and decreasing by more than 50% the specific absorptive capacities of the intestine
- Damaged cells on villi are replaced by non-absorbing immature cells
- Watery diarrhea due to net secretion of intestinal fluid and loss of absorptive surface
- Activation of the enteric nervous system
- Role of NSP4 peptide regions as an enterotoxin
Clinical Features

- Incubation period 1-3 days
- Clinical manifestations depend on whether it is the first infection or reinfection
- Present with
  - Watery diarrhea (no blood or leukocytes)
  - Fever, can be high grade
  - Abdominal pain
  - Vomiting
  - Loss of electrolytes and fluids leading to dehydration
  - May be fatal unless treated
- First infection after age 3 months generally most severe
  - May be asymptomatic or result in severe dehydrating diarrhea with fever and vomiting
- GI symptoms generally resolve in 3 to 7 days
Dehydration - leading cause of morbidity and mortality
Complications

- Severe chronic diarrhea
- Dehydration
- Electrolyte imbalance
- Metabolic acidosis
- Immunodeficient children may have more severe or persistent disease
Immunity

- Antibody against VP7 and VP4, and Secretory IgA probably important for protection
- First infection usually severe
  - First infection usually does not lead to permanent immunity
  - Subsequent infections generally less severe
- Re-infection can occur at any age
- By age 3 years, 90% of the children have serum antibodies to one or more types
- Young children may suffer up to five re-infections by 2 years of age
Diagnosis

- Serology for epidemiologic studies
  - Antigen detection in stool
  - Antibody detection in serum
- Molecular methods
- Electron Microscopy
- Culture
  - Group A Rotaviruses can be cultured in monkey kidney cells
- Histopathology
Serology

- Antigen detection in stool
  - ELISA, LA (Group A Rotavirus), ICT
- Antibody detection
  - ELISA can detect antibodies and establish rise in titers
- Serology for epidemiologic studies
Microscopy (EM)

- Demonstration of Virus in stool helps in early disease
- Electron Microscopy has made the identification simpler
- Non-Group A viruses also
PCR/Genotyping

- Genotyping is most sensitive method for detection of Rotavirus NA from stool specimens
Histopathology

- Mature enterocytes lining the tips of intestinal villi are affected
- Villous atrophy and blunting
- Infiltration of lamina propria with mononuclear cells
- Death of the mature enterocytes
- Repopulation of the villous tips with immature secretory cells
  - Crypt hyperplasia
Treatment

- Treatment of Gastroenteritis is supportive
- Correction of loss of water and electrolytes remain the goal treatment
- Failure for prompt correction of dehydration leads to Acidosis, Shock, Death
- Lesser deaths if effective fluid replacement therapy is timely initiated
Fluid Replacement

- Management consists of replacement of fluids (ORS) and restoration of Electrolyte balance
- Oral rehydration therapy is highly effective in reducing morbidity and mortality
- Severe dehydration needs parental administration of fluids
Prevention and Control

- In view of fecal-oral route of transmission, significant control measures are
  - Waste water management
  - Safe drinking water supplies
  - Sanitation

- Basic measures
  - Keep your hands clean
  - Wash hands often with soap and warm water after using the toilet, diapering and before preparing or eating food

- Vaccine
Vaccine

- A live, oral, pentavalent, human-bovine re-assortant vaccine
- Administered at 2, 4, and 6 months of age
  - RotaTeq™
  - Rotarix™
Thank you!