L12&13 viral pathogenesis 1&2- learning objectives:

1.Routes of entry
2.Mechanisms of viral spread (local and systemic)
3.Viremia and tissue invasion from the blood
4.Neural spread
5.Congenital infections
6.Viral shedding

1.Routes of Entry
Know the different routes of entry, the barriers to entry via each route and examples of viruses that enter through those routes.

-Respiratory tract:
>Can be further be broken down into compartments- don't worry about trying to memorise which viruses can replicate in which compartment.
>Can be further divided into those that are systemic and those that remain localised

-Alimentary tract:
>>Can be further divided into those that cannot pass through the gut; those that remain localised; and those that are systemic

-Genital tract & Transcutaneous have some overlap

-Conjunctiva

2. Mechanisms of viral spread (local and systemic):
-local
-subepithelial invasion
-lymphatic spread
>Understand what the role of the lymph node is in preventing viraemia.

3. Viremia and tissue invasion from the blood:
-The difference between primary and secondary viraemia (what are some ways in which viruses can overcome the barrier to entering tissues?)

-The difference between cell associated viraemia and free-in-plasma

4.Neural spread:
-The infectious cycle of Rabies; when does it become too late to vaccinate? (Don't worry about memorising how many days it takes for something to happen)
-Varicella-zoster virus: how and when does it spread via viremia? How and when does it spread via nerves?

5.Congenital infections:
-Know that viruses need to be able to cross the placenta if they are to infect the foetus.
-Know the likely outcomes to the foetus when it is infected by 1)Cytocidal viruses 2)Non-cytocidal viruses.
-Name viruses that can infect the baby during birth:
>Congenital rubella syndrome. Diagnostic symptoms?
>Zika. Symptoms? Tropism?
>Congenital HCMV. It's the most common congenital infection
-Understand the concept of immunological tolerance in relation to HBV

6.Viral shedding
-I'd not memorise the all different types of bodily fluids and which viruses use them to shed. Just need to know the infectious cycle of the important viruses.
-The entry route is usually the exit route as well.

L14 viral pathogenesis 3- learning objectives:

1.Determinants of tropism
2.Virus induced changes in cells
3.Measuring Virulence
4.Mechanisms of disease
5.Viral damage
6.Immunopathology
7.Autoimmunity
8.Immunosuppression
9.Host resistance and susceptibility

1.Determinants of tropism:
-Susceptibility: but we need to know that having certain glycoproteins that bind to certain receptors doesn't necessary guarantee that the virus can replicate inside that cell. This is especially the case for viruses that gain entry via binding to ubiquitous receptors: why can't they cause systemic infections?

-Permissivity (genome transcription)

-Accessibility (apical vs basal release)

-Local factors (Tryptase clara)

2.Virus induced changes in cells:
-tumour
-lytic
-chronic (slow virion release without killing the cell)

-latent (can revert into lytic at a later time)

3.Measuring Virulence:
Know that pathogenicity is qualitative, but that virulence can be measured:
>mean time to death
>mean time required for symptoms to appear
>loss of immune cells
>degree of fever/weight loss/clinical pathology

4.Mechanisms of disease

Cell death:

-stop cellular protein synthesis (polio, adeno)
-stop cellular nucleic acid synthesis (pox-DNase)
-accumulation of viral proteins within cells causes cytopathic effects: (Ebola-envelope protein in endothelial cells leads to necrosis)
-inclusions: Adeno-nuclear; Reo-cytoplasmic
-measles (cell fusion happens when viral proteins are embedded within the plasma membrane- death occurs as a result of altered membrane permeability

loss of cell function :

-LCMV: specifically reduces mRNA of growth hormone in the cells that make it.
-Rhinovirus: cilial stops beating in respiratory epithelium

Immunopathology

-Antibody-dependent enhancement (Dengue)
-Deposition of immune complexes in the kidney leading to complement activation =glomerulonephritis (Chronic Hep B)
-CD4+ T cell mediated delayed type hypersensitivity (the skin rashes and Koplik spots (measles) and (cytokines that recruit eosinophils which cause bronchiolitis in infants (RSV)
-CD8 + T cell mediated destruction of hepatocytes leading to accumulation of bilirubin in the eyes and skin (Hep B)

Autoimmunity

-molecular mimicry (influenza and myelin basic proteins- Guillain-Barre syndrome)
-Polyclonal B cell activation by EBV (If these non-specific B cells happen to be self-reactive, then it will cause autoimmunity)

Immunosuppression

-HIV replicates in CD4+ T cells, and kills monocytes.
-Measles virus can stop T cell proliferation when the infected DC presents surface proteins that have the potential to send anti-proliferation signals.

Host resistance/susceptibility:

-HLA makeup

-defects in certain classes of antibodies
-interferon-inducible genes
-chemokine receptor genes.
-Having dual infections
-Being pregnant
-Being very old/young
-Having malnutrition

MIIM30014 MST02 Mock Paper

Multiple Choice

Q1)

Which of the following is correct?

A. Upon recognising 5' triphosphate ssRNA, MDA5 will dimerise and interact with MAVS

B. Upon recognising cytosolic DNA, OAS-1 will produce 2' to 5' adenylic acid, which activates an enzyme by causing it to dimerise. This then will cleave the DNA

C. When TLR3 is ligated by ssRNA, it will recruit adaptor proteins such as TRIF, which will subsequently recruit IRF3.

D. When TLR3 is ligated by ssRNA it will recruit adaptor proteins such as NFkB. The nuclear translocation of this leads to the transcription of thousands of antiviral genes.

E. One of the antiviral genes that are produced in response to TLR7 ligation include MxA, which traps nucleocapsids in the cytosol.

Q2)

Which of the following is correct?

A. miRNA can associate with the RISC complex and thus induce the cleavage of the target sequence.

B. Cellular miRNA mi-R122 can promote the replication of HCV by binding to the 5'UTR

C. SV-40 exploits the ability of cellular miRNA to target the early gene transcripts of SV-40 in order to switch to the production of late gene products.

D. HSV-1 LAT encodes a miRNA that downregulates SMAD3 and TGF-beta, but this makes it more susceptible to being killed by CTLs.

E. siRNAs generally cannot associate with the RISC complex, but can nonetheless bind with less than perfect complementarity to the target sequence, to stop it from becoming translated.

Q3)

Which of the following is correct?

A. EBV can undergo productive replication inside resting B cells

B. In type 2 EBV infections, only EBNA-1 is expressed.

C. Most adults are infected with EBV.

D. EBV is the leading infectious cause of stillbirth

E. EBV can immortalise B cells, causing disease such Burkitt's and nasopharyngeal carcinoma

Answers:

1) E is correct.

What is wrong with the other answers:
A: MDA5 recognises long dsRNA and not 5' PPP-ssRNA (this is RIG-I).
B: OAS-1 & RNaseL for viral RNA detection and cleavage.
C: TLR3 ligated by dsRNA.
D: TLR3 ligated by dsRNA. Adaptor protein is IRF3/7.

2) B is correct.

What is wrong with the other answers:
A: miRNA associates with RISC complex, but this leads to the silencing of the target RNA *without* degrading it
C: Not cellular miRNA, SV-40 produces own miRNA.
D: Not more susceptible but more resistant.
E: miRNA imperfectly bind to the target sequence c.f. siRNAs bind perfectly.

3) E is correct.

What is wrong with the other answers:
A: Doesn't undergo productive replication in B cells (in nasopharynx and oropharynx). Remain latent in B cells
B: EBNA-1 expression in type 3
C: No. Carriers (are carriers not infected? Could argue semantics of this)
D: NO. CMV is the leading infectious cause of stillbirth.