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Diagnosis and treatment of viral infections in patients with CKD

Jens Van Praet
17/03/2018

Introduction to viral infections

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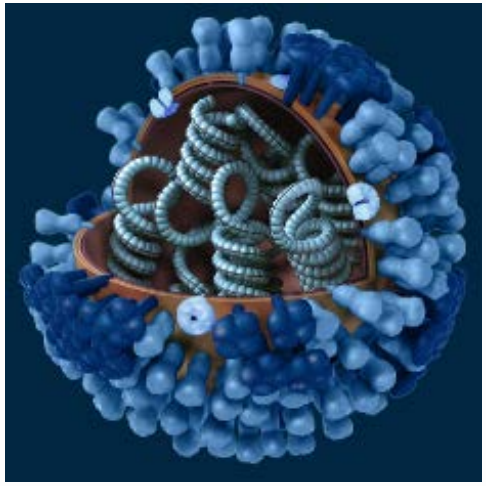
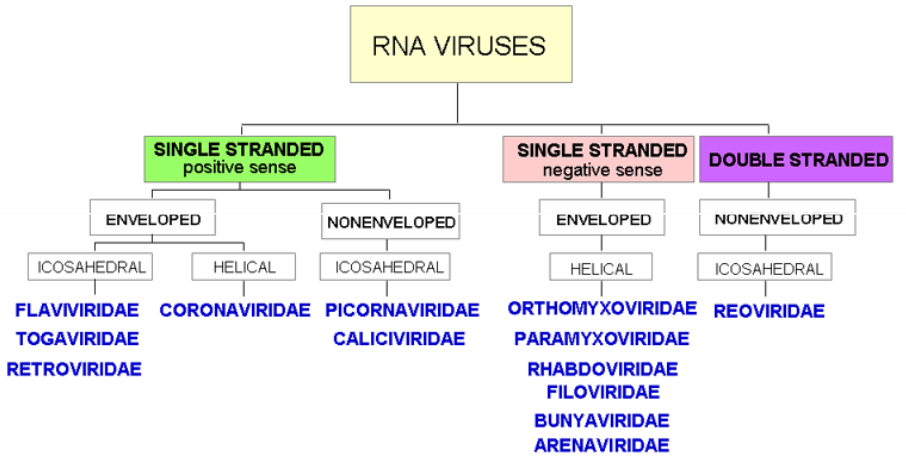


- Viral particles contain the viral genome and enzymes required for initial steps in replication
- Its structural components allow survival in the environment and binding to host cells
- By nature viruses can mutate very quickly

Classifications of viruses

- Classification systems:
  - Type and structure of nucleic acid
  - Symmetry of virus capsid
  - Presence of lipid envelope
    - With: respiratory, parenteral and sexual routes
    - Without: fecal-oral route

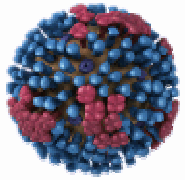


- From clinical point of view:
  - Transient viral infections
  - Persistent viral infections

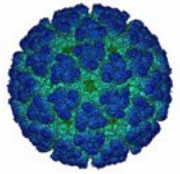
Modified from Essentials of Medical Microbiology, 4th Ed

Transient viral infections

- Exhibit ‘hit and run’ principle
  - Droplet contact: influenza, RSV, PIV, rhinovirus,…
  - Fecal-oral transmission: coxsackie A, hepatitis A,…
  - Indirect via vector: dengue, zika, chikungunya,…
- Only early therapeutic intervention (may) influence outcome
- Require fast diagnostic techniques



influenza

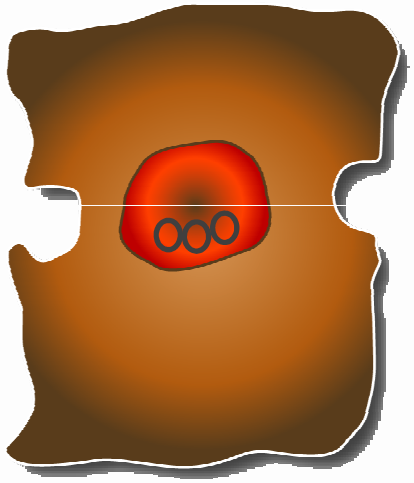


chikungunya

RSV: respiratory syncytial virus, PIV: parainfluenza virus

Persistent viral infections

- Integrate in host genome (e.g. HIV, HBV,…) or escape from host defense (e.g. HCV)
- Can cause acute or chronic disease, or enter a latency state
- During latency flares can occur
- Therapy aims suppression of the virus in case of chronic infection, or is initiated during acute infection or a flare
- Diagnostic techniques (ideally) should differentiate flare from latency



HBV infected hepatocyte

HBV: hepatitis B virus, HCV: hepatitis C virus

Diagnostic tools for viral infections: old stuff

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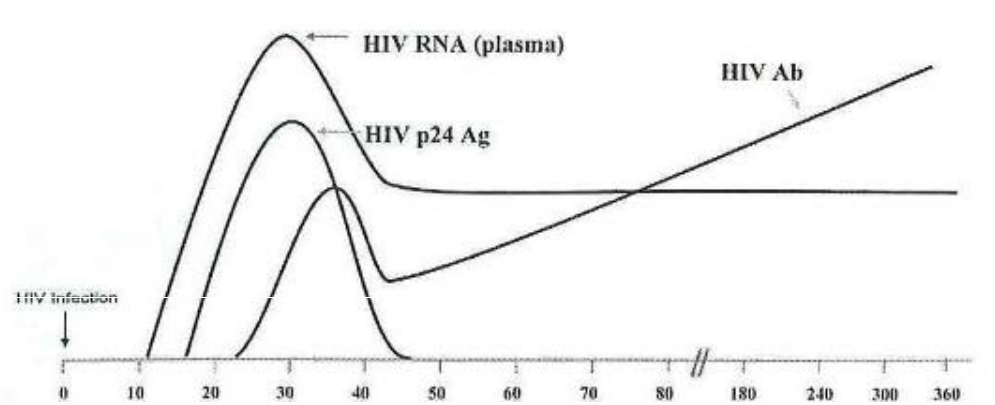
- (Culture)

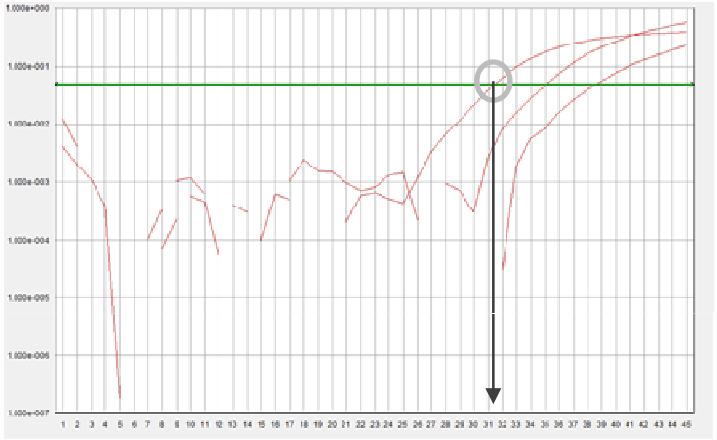


- Serology
  - 'Windows phase'
  - IgM: false positivity and can persist for long period
  - IgG avidity may provide additional information
  - Immunoblot has increased specificity
- Antigen detection and combotest
  - Enhanced sensitivity as test becomes positive during viremia
  - Commercially available for influenza (sens. ~61%), RSV (sens. ~75%), dengue, CMV, HIV and HCV

Bruning *et al*, 2017

Diagnostic tools for viral infections: new stuff

- Molecular tests
  - 'in-house'
  - PCR has optimal sensitivity
  - Semi-quantification by means of rtPCR (C_t value)
  - 'Multi-parameter' **syndromic** approach by testing a battery of viruses
  - Resistance testing by sequencing
- T-lymphocyte activation test
  - Allows the detection of CMV primed T-cells
  - Can identify patients post allo-HSCT at risk for CMV disease



rtPCR

Courtesy of M. Reynders
Nesher *et al*, 2016

rtPCR: real-time PCR, C_t: threshold value,
HSCT: hematopoetic stemcell transplantation

Diagnostic testing: rtPCR

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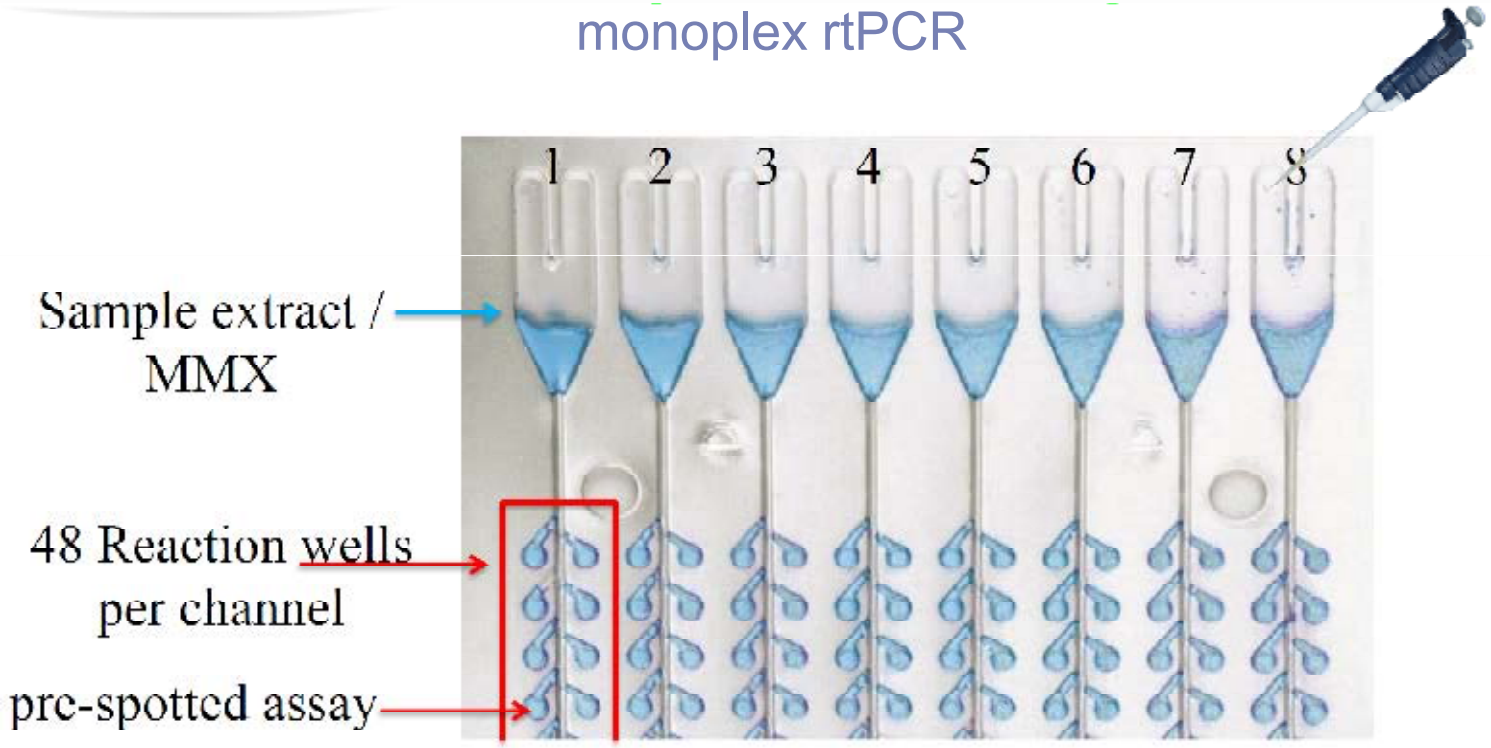
The micro-array Taqman® amplification card allows performing multiple monoplex rtPCR



1well = 1µl reaction volume = 1 Real Time PCR reaction

Courtesy of M. Reynders

rtPCR testing: respiratory samples

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- Respi TAC AZ Sint-Jan version 11 detects 35 pathogens
  - Rhinovirus (n=2), enterovirus (n=2), influenza A (n=6), influenza B, RSV-A, RSV-B, PIV (n=4), adenovirus (n=2), hMPV, coronavirus (n=4), parechovirus, boca, CMV, HSV-1/2
  - *Streptococcus pneumoniae*, *Haemophilus influenzae*.
  - *Bordetella holmesii*, *Bordetella parapertussis*, *Bordetella pertussis*, *Bordetella bronchiseptica*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Legionella pneumophili*, *Coxiella Burnetii*, *Chlamydophila psittaci*
  - *Aspergillus fumigatus, Pneumocystis jirovercii*
  - Controls: 18S, PDV control, Human Rnase Pgen
- Nasopharyngeal swabs detect upper airway infection or asymptomatic shedding
- BAL specimens or endotracheal aspirates are needed to exclude lower respiratory tract infection
- RSV, PIV, hMPV, adenovirus have clinical impact in adult population, especially in patients with risk factors

Courtesy of M. Reynders

hMPV: human metapneumovirus

hMPV: clinical impact

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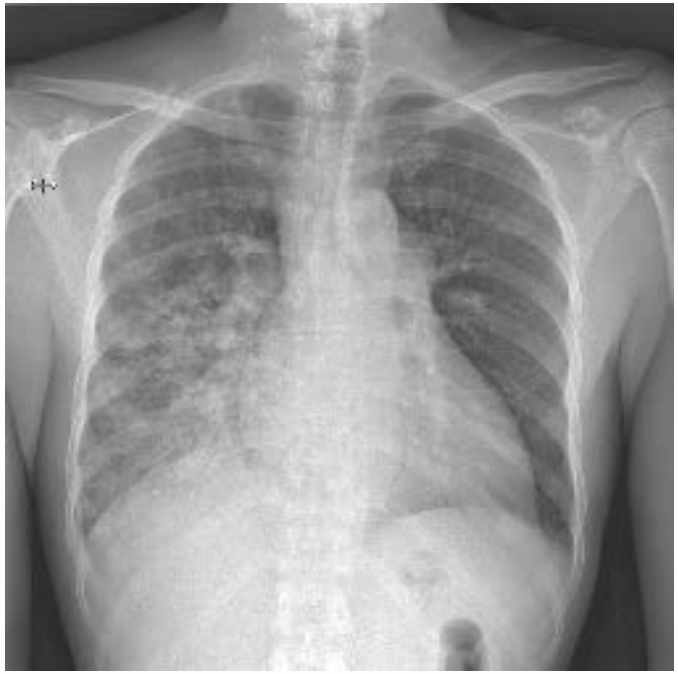

Orthomyxovirussen		
Influenza A	[BAL]	Niet detecteerbaar.
Influenza B	[BAL]	Niet detecteerbaar.
Adenovirussen		
Adenovirussen	[BAL]	Niet detecteerbaar.
Paramyxovirussen		
RSV - A	[BAL]	Niet detecteerbaar.
RSV - B	[BAL]	Niet detecteerbaar.
Humaan Metapneumovirus	[BAL]	Viraal RNA werd gedetecteerd in het staal
Extreem hoge virale lading: acute hMPV infectie!		
Parainfluenza Type 1	[BAL]	Niet detecteerbaar.
Parainfluenza Type 2	[BAL]	Niet detecteerbaar.
Parainfluenza Type 3	[BAL]	Niet detecteerbaar.
Parainfluenza Type 4	[BAL]	Niet detecteerbaar.
Bofvirus	[BAL]	Niet detecteerbaar.
Mazelenvirus	[BAL]	Niet detecteerbaar.
Picornavirussen		
Rhinovirus	[BAL]	Niet detecteerbaar.
Parechovirus	[BAL]	Niet detecteerbaar.
Enterovirus	[BAL]	Niet detecteerbaar.
Coronavirussen		
Coronavirus NL63	[BAL]	Niet detecteerbaar.
Coronavirus OC43	[BAL]	Niet detecteerbaar.
Coronavirus 229E	[BAL]	Niet detecteerbaar.
Coronavirus HKU1	[BAL]	Niet detecteerbaar.
Parvovirussen		
Bocavirus	[BAL]	Niet detecteerbaar.
Herpesvirussen		
CMV	[BAL]	Niet detecteerbaar.
Bacteriële DNA detectie		
Mycoplasma pneumoniae	[BAL]	Niet detecteerbaar.
Legionella pneumophila	[BAL]	Niet detecteerbaar.
Bordetella pertussis	[BAL]	Niet detecteerbaar.
Bordetella parapertussis	[BAL]	Niet detecteerbaar.
Chlamydophila pneumoniae	[BAL]	Niet detecteerbaar.
Chlamydophila psittaci	[BAL]	Niet detecteerbaar.
Coxiella burnetii	[BAL]	Niet detecteerbaar.

H.J., 35-year old dialysis patient, unknown cause of ESRD, presenting with fever and respiratory failure

rtPCR testing: encephalitis and GI

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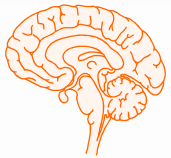
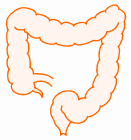


- Encephalitis:
  - *H. influenzae*, *N. meningitidis*, *S. pneumoniae*, *S. agalactiae*, *L. monocytogenes*, *E coli*
  - HSV-1, HSV-2, VZV, enterovirus, parechovirus, CMV, HHV-6
  - *Crytococcus gatti/neoformans*



- Gastro-intestinal:
  - Norovirus (n=3), adenovirus (n=2), astrovirus, sapovirus (n=4), rotavirus, enterovirus, hepatitis E virus
  - *C. difficile*, *Campylobacter sp.*, *C. jejuni*, *C. coli*, *Salmonella sp.*, enteropathogenic *E. coli*, enteroaggregative *E. coli*, entero-invasive *E. coli*, enteropathogenic *E. coli*, enterotoxinogenic *E. coli*, STEC and *Y. enterocolitica*.
  - *Giardia lamblia*; *Cryptosporidium sp.*, *Entamoeba sp.*, *Strongyloides stercoralis*, *Dientamoeba fragilis*, *Blastocystis sp.*, *Ascaris lumbricoides*, *Microsporidium sp.* and *Schistosoma sp.*

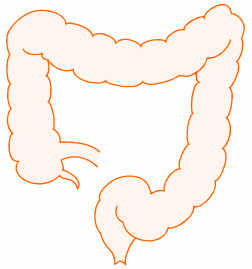
2 caveats:

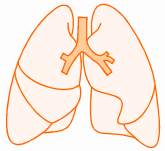
- Limit of detection HSV is 1500 copies/ml in CSF (versus 150 in monoplex)
- CMV is not on the GI card

Courtesy of M. Reynders

Diagnosis of CMV disease

- C_t values are converted to IU/ml by using a WHO standard
- rtPCR for CMV on stool is a good exclusion test for colitis
- Confirmation is needed by rtPCR on tissue is needed:
  - > 0,084 IU CMV/cell: indicative for CMV disease
  - > 0,006 IU CMV/cell: suspect for CMV disease
- BAL is required for diagnosis of CMV pneumonitis
  - Cutt-of not established (200-500 IU/ml versus 5500 IU/ml)
- Detection of viremia allows quantitative monitoring:
  - Cut-offs to differentiate disease from latency are less well established
  - Trends in viral loads over time may be more important in predicting disease





Ganzenmueller T *et al*, 2009, Ljungman *et al*, 2016

Viral resistance testing

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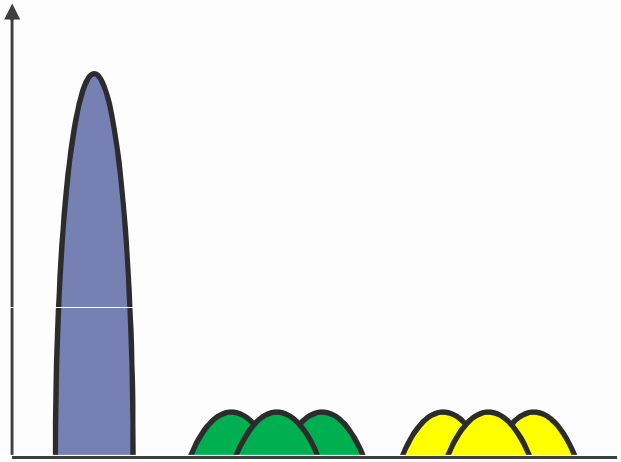


Production of ~10^{11} HIV viruses per day

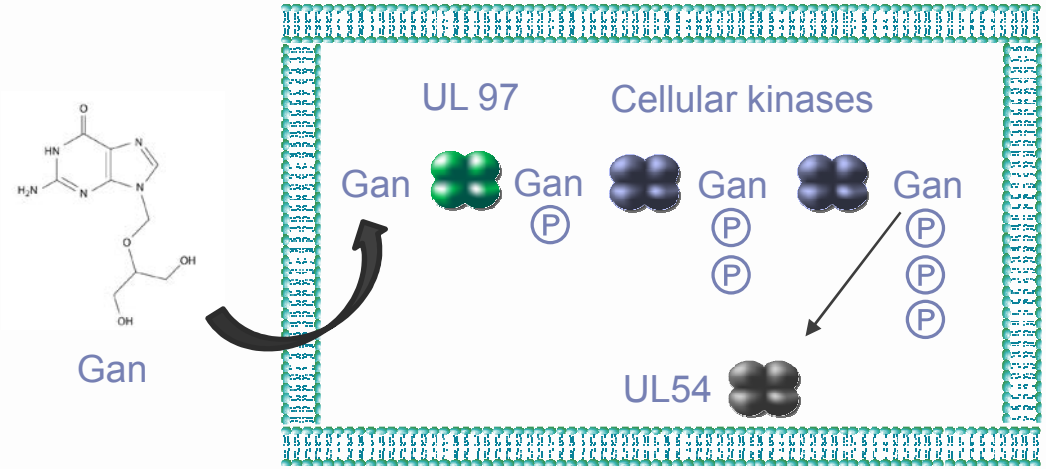
- Available for adenovirus, HSV, VZV, CMV, HHV-6, HBV and HIV
- Phenotyping: determination of drug susceptibility profile by measuring EC_{50} on viral cultures
- Genotyping: DNA sequencing of genes and correlation with genetic database
- Often different mutations or even quasi species are present (% of mutants can not be quantitated)

EC_{50}: 50% effective concentration, HHV-6: herpes virus 6

https://rega.kuleuven.be/regavir/tests
Aids Reference Laboratories

Viral resistance testing: CMV

- Phenotypic: ganciclovir, cidofovir, foscarnet and adefovir
- Genotypic:
  - UL 97, protein kinase: ganciclovir
  - UL 54, DNA polymerase: ganciclovir, cidofovir and foscarnet

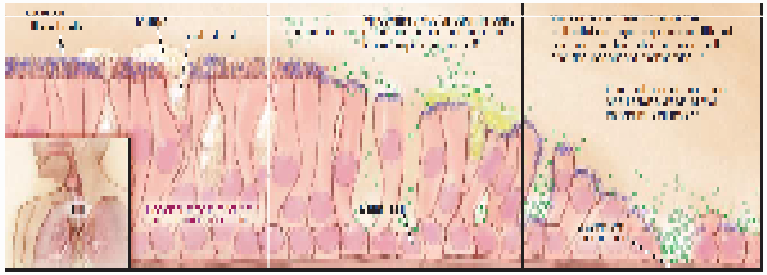


Parallel situation for HSV:
- UL 97 ≈ HSV thymidine kinase
- UL 54 ≈ HSV DNA polymerase

Drew, 2010
https://rega.kuleuven.be/regavir/tests

Molecular tests: wrap up of caveats

- Detection of a pathogen does not mean it causes the patients illness
  - Rhinovirus predisposes to *S. pneumoniae* infection
  - Influenza is associated with bacterial co-infection (*S. aureus*, *S. pneumoniae* and *S. pyogenes*) as well as invasive aspergillosis



Chertow, 2013

- Prolonged shedding after infection, especially in immunocompromised hosts
- Clinical validation of C_t values is needed to differentiate latency from disease
- Clinical meaning of many polymorphisms is unclear

Principles of antiviral treatment

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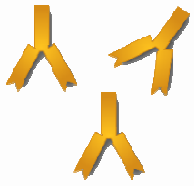
Antiviral drugs

- Prophylactic or therapeutic
- Most target a specific viral enzyme
- Ribavirin has pleiotropic antiviral effects
- Plasma PK reflects less the cellular concentration because some drugs are activated and retained intracellularly

Neutralizing antibodies

- Prophylactic or therapeutic
- No hard evidence, trials ongoing (influenza, CMV…)
- CMV immunglobulines as adjunct therapy for CMV disease “remains at best controversial”
- Palivizumab effective in preventing RSV hospitalisation in infants and children at high risk for serious disease



PK: pharmacokinetics

Principles of antiviral treatment: transient infections

- Treatment especially mandatory in an immunocompromised host:
  - Adenovirus: ribavirin (spec. C), cidofovir or brincidofovir* post allo-HSCT
  - Hepatitis E: weight-based ribavirin PO
  - RSV: (ribavirin aerosols) > ribavirin PO or (IV) post allo-HSCT
  - PIV and hMPV: uncertain effect of ribavirin
- For boca virus, rhinovirus, coronavirus,… only ‘supportive care’ is available

*can be requested as compasionate use

Waghmare *et al*, 2016

Principles of antiviral treatment: influenza

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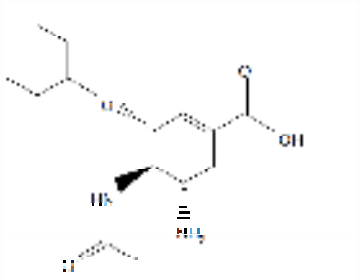
- Oseltamivir is a neuraminidase inhibitor which interferes with the release of influenza from infected cells
- Treatment important for patients with **underlying risk factors** (e.g. CKD) and those with severe or progressive clinical illness
- Start treatment before laboratory confirmation



Uncomplicated

- Standard duration of treatment is 5 days
- Oseltamivir 75 mg 2 dd 1
- Most effective when administered within 48 hours

Complicated (pneumonia and clinical progression)

- Consider prolongation of treatment to 10 days and monitor for clearance weekly
- Consider oseltamivir 150 mg 2 dd 1
- Indicated in hospitalized patients even if duration of illness is more than 48 hrs:
  - Benefit for patient
  - Reduction of nosocomial transmission

CDC, 2018

Principes of antiviral treatment: influenza in CKD

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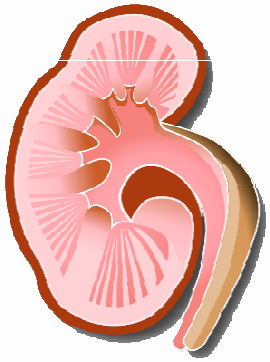

- Oseltamivir is mainly renally cleared ($T_{1/2}$ 6-10 hrs)
- Common adverse events are nausea, vomiting and headache
- Dose adjustments according to the package insert:
  - CKD stage 3: 30 mg 2 dd 1 of 75 mg 1 dd 1
  - CKD stage 4: 30 mg 1 dd 1
- Dose adjustments according to guidelines based in 2 studies in CKD stage 5 (n=34):
  - (30 mg immediately, and then) 30 mg after HD session (low flux)
  - 75 mg after each HD session (high flux)
  - single dose of 75 mg (APD)/ single dose of 30 mg (CAPD)
  - CRRT high-flux dialysis: 30 mg dd or 75 mg every other day
- Given the variability of residual renal function and safety of osteltamivir: 'treat CKD stage 5 as stage 4' (JVP)
- Consider prophylaxis in dialysis unit (30 mg after dialysis)

Robson *et al*, 2006, Patel *et al*, 2015, Choo *et al*, 2011

Principes of antiviral treatment: persistent infections

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- For HIV, HBV and HCV treatment dose adjustments or drugs with hepatic clearance should be considered by ID specialist or hepatologist
- Available treatments for herpesviridae in Belgium:
  - HSV and VZV: (val)acyclovir, foscarnet, cidofovir and brivudine (not active against HSV-2)
  - CMV: (val)gancyclovir, foscarnet and cidofovir
  - HHV-6: foscarnet
- Cidofovir also has activity against BK virus and papilloma viruses

Treatment of CMV and VZV: PK/PD

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- Drug activity is dependent on AUC and can be considered as 'time-dependent'
- All drugs have mainly renal clearance (>60%) and are eliminated by dialysis (>50%)
- The AUC of the valgancyclovir and valacyclovir is comparable to IV dosing

	C_{max}/C_{min} (IV, µg/ml)	C_{max}/C_{min} SS (PO, µg/ml)
Acyclovir	9,8 / 0,7 (5 mg/kg) 20,7 / 2,3 (10 mg/kg)	0,5 / 0,3 (200 mg) 1,3 (±1,5 hrs) / 0,8 (800 mg)
Valacyclovir	NA	5,2 (±2 hrs) / - (1 g)
Gancyclovir	10,4 / 0,6-1,2 (5 mg/kg)	
Valgancyclovir*	NA	*5,3-6,7 (± 3,5 hrs) / - (900 mg)
Foscarnet	450- 575 / 80-150 (µM)	
Cidofovir	19,6 / -	

*AUC is higher when administered with food
SS: steady state

Treatment of CMV and VZV: PK/PD

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- All inhibit the DNA polymerase of HSV, VZV and/or CMV
- Major toxicity is dependent on AUC

	In vitro EC_{50} (µg/ml, range/mean)	*In vivo* toxicity (µg/ml, C_{max}/C_{min})	Major toxicity
Acyclovir	0,02-1,9 / 0,2 (HSV-1)	>30-55 / >6	Neurologic*, renal
Acyclovir	0,3-2,9 / 0,7 (HSV-2)	>30-55 / >6	Neurologic*, renal
Acyclovir	0,8-5,2 / - (VZV)	>30-55 / >6	Neurologic*, renal
Ganciclovir	0,02-3,57 / - (CMV)	>14 / >2,8	Bone marrow
Cidofovir	0,2-0,9 / - (CMV)	NA	Renal
Foscanet	100-300 /- (CMV, µmol/L)	>1000/- (µmol/L)	Renal and electrolytes (act as chelator)

*A delay of 24 to 48 hours has been reported
Gill and Burgess, 1990, Shepp *et al*, 1985

Treatment of VZV with acyclovir in renal failure

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CrCl (ml/min/1,73 m²)	IV		Oral (high dose)	
	Standard dose (%)	Dosing interval (h)	Dose (mg)	Dosing interval (h)
>50	100	8	800	4
25-50	100	12	800	4
10-25	100	24	800	8
<10	50[1,4]	24	800[2,3]	12

[1]For HD patients: 60-100% after dialysis
[2]For HD patients: 200 mg 2 dd 1, and 400 mg after dialysis (predicted mean SS conc. 1,35 µg/ml)
[3]CAPD: 600-800 mg dd (predicted mean SS conc 0,9-1,8 µg/ml)
[4]CRRT: '5-7,5 mg/kg q24 h' (predicted mean SS conc 1,35 µg/ml)

HD ref
Laskin *et al*, 1982 (n=6)
Almond *et al*, 1995 (n=7)

PD ref
Burgess and Gill, 1990 (n=4)
Stathoulopoulou *et al*, 1996 (n=10)

CRRT ref
Boulieu R *et al*, 1997 (n=3)
Bleyzac N *et al*, 1999 (n=1)
Khajehdehi P *et al*, 2000 (n=1)

Treatment of VZV with valacyclovir in renal failure

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CrCl (ml/min/1,73 m2)	Dose
>50	1g every 8 hrs
25-50	1 g every 12 hrs
10-25	1 g every 24 hrs
<10	*500 mg every 24 hrs

*One study in PD patients (n=12) found 500 mg 2 dd lead to steady-state concentrations overpassing the therapeutic range in all patients, without apparent toxicity

Stathoulopoulou *et al*, 2002

Treatment with (val)gancyclovir in renal failure

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CrCl (ml/min)	IV	
	Standard dose (mg/kg)	Dosing interval (h)
>70	5	12
50-69	2,5	12
25-49	2,5	24
10-24	1,25	24
<10	1,25[1,2]	After dialysis

CrCl (ml/min)	PO	
	Standard dose (mg/kg)	Dosing interval (h)
>60	900	12
40-59	450	12
25-39	450	48
10-24	450	twice a week
<10	NR	NR
HD	NR	NR

CAPD: no data

[1]HD: peak plasma level of 3,7 mg/ml, with a SS level of 2,6 mg/ml

[2]CRRT (CVVHDF): 2,5 mg/kg/d (AUC > 50 mg·h/l and trough concentration of > 2 mg/l)

HD ref
Combarnous *et al*, 1994 (n=1)

CRRT ref
Horvatits *et al*, 2014 (n=9)

Antiviral treatment in CKD: a case for TDM?

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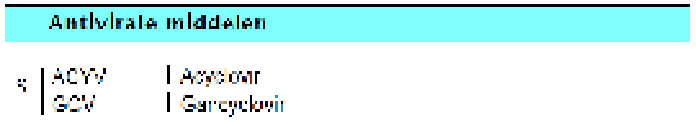
- Residual renal function and effect of dialysis technique are often unpredictable
- TDM of IV administration
  - Peak at the end of 1-hr infusion, trough before next administration
  - Steady-state concentration for continuous infusion*
- TDM of PO administration
- Use PK indices from patients with normal renal function?



	C_{max}/C_{min} (IV, µg/ml)	C_{max}/C_{min} SS (PO, µg/ml)
Acyclovir	9,8 / 0,7 (5 mg/kg) 20,7 / 2,3 (10 mg/kg)	0,5 / 0,3 (200 mg) 1,3 (**±1,5 hrs**) / 0,8 (800 mg)
Valacyclovir	NA	5,2 (**±2 hrs**) / - (1 g)
Gancyclovir	10,4-13,3 / 0,6-1,2	NA
Valgancyclovir	NA	5,3-6,7 (**±3,5 hrs**) / - (900 mg)

*acyclovir is 24 hours stable at 5 mg/ml
Winston *et al*, 2005, Höglund *et al*, 2001

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Take home messages

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- Syndromic approach with multi-parameter detection allows a rapid diagnosis of transient viral infections
- Standardized rtPCR will probably be able to discern latent state from active disease in the near future
- Fast treatment with drugs or neutralizing antibodies is needed for transient infections
- Treat influenza in CKD 5 as CKD 4
- Given the toxicity of antiherpetic drugs TMD is probably needed for dose adjustment in renal failure