Diagnosis and treatment of viral infections in patients with CKD

Jens Van Praet
17/03/2018
Introduction to viral infections

- 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
• 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

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: hepatitis B virus, HCV: hepatitis C virus
Diagnostic tools for viral infections: old stuff

- **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<sub>t</sub> 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: real-time PCR, C<sub>t</sub>: threshold value, HSCT: hematopoietic stemcell transplantation
Diagnostic testing: rtPCR

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

Sample extract / MMX

48 Reaction wells per channel

pre-spotted assay

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

Courtesy of M. Reynders
rtPCR testing: respiratory samples

- 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 jirovecii
  - Controls: 18S, PDV control, Human Rnase P gen

- 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

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

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

• 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*, enteroinvasive *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:
  - $> 0.084$ IU CMV/cell: indicative for CMV disease.
  - $> 0.006$ IU CMV/cell: suspect for CMV disease.
- BAL is required for diagnosis of CMV pneumonitis.
  - Cut-off 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.

Viral resistance testing

- 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)

Production of $\sim 10^{11}$ HIV viruses per day

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

• Prolonged shedding after infection, especially in immunocompromised hosts
• Clinical validation of C<sub>t</sub> values is needed to differentiate latency from disease
• Clinical meaning of many polymorphisms is unclear

Chertow, 2013
### Principles of antiviral treatment

#### 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 immunoglobulines 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

- 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
Principles of antiviral treatment: influenza in CKD

- 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 oseltamivir: ‘treat CKD stage 5 as stage 4’ (JVP)
- Consider prophylaxis in dialysis unit (30 mg after dialysis)

Principes of antiviral treatment: persistent infections

- 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**

- 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>( \frac{C_{\text{max}}}{C_{\text{min}}} ) (IV, µg/ml)</th>
<th>( \frac{C_{\text{max}}}{C_{\text{min}}} ) SS (PO, µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>9.8 / 0.7 (5 mg/kg) 20.7 / 2.3 (10 mg/kg)</td>
<td>0.5 / 0.3 (200 mg) 1.3 (±1.5 hrs) / 0.8 (800 mg)</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>NA</td>
<td>5.2 (±2 hrs) / - (1 g)</td>
</tr>
<tr>
<td>Gancyclovir</td>
<td>10.4 / 0.6-1.2 (5 mg/kg)</td>
<td></td>
</tr>
<tr>
<td>Valganclovir*</td>
<td>NA</td>
<td>*5.3-6.7 (± 3.5 hrs) / - (900 mg)</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>450-575 / 80-150 (µM)</td>
<td></td>
</tr>
<tr>
<td>Cidofovir</td>
<td>19.6 / -</td>
<td></td>
</tr>
</tbody>
</table>

*AUC is higher when administered with food
SS: steady state
Treatment of CMV and VZV: PK/PD

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

<table>
<thead>
<tr>
<th></th>
<th>( \text{In vitro} \text{ EC}_{50} (\mu g/mL, \text{range/mean}) )</th>
<th>( \text{In vivo toxicity (}\mu g/mL, \frac{C_{\text{max}}}{C_{\text{min}}}))</th>
<th>\text{Major toxicity}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>0.02-1.9 / 0.2 (HSV-1)</td>
<td>&gt;30-55 / &gt;6</td>
<td>Neurologic*, renal</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>0.3-2.9 / 0.7 (HSV-2)</td>
<td>&gt;30-55 / &gt;6</td>
<td>Neurologic*, renal</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>0.8-5.2 / - (VZV)</td>
<td>&gt;30-55 / &gt;6</td>
<td>Neurologic*, renal</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>0.02-3.57 / - (CMV)</td>
<td>&gt;14 / &gt;2.8</td>
<td>Bone marrow</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>0.2-0.9 / - (CMV)</td>
<td>NA</td>
<td>Renal</td>
</tr>
<tr>
<td>Foscanet</td>
<td>100-300 /- (CMV, \mu mol/L)</td>
<td>&gt;1000/- (\mu mol/L)</td>
<td>Renal and electrolytes (act as chelator)</td>
</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
<th>CrCl (ml/min/1.73 m²)</th>
<th>IV</th>
<th></th>
<th>Oral (high dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard dose (%)</td>
<td>Dosing interval (h)</td>
<td>Dose (mg)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>100</td>
<td>8</td>
<td>800</td>
</tr>
<tr>
<td>25-50</td>
<td>100</td>
<td>12</td>
<td>800</td>
</tr>
<tr>
<td>10-25</td>
<td>100</td>
<td>24</td>
<td>800</td>
</tr>
<tr>
<td>&lt;10</td>
<td>50¹,4</td>
<td>24</td>
<td>800²,³</td>
</tr>
</tbody>
</table>

¹For HD patients: 60-100% after dialysis
²For HD patients: 200 mg 2 dd 1, and 400 mg after dialysis (predicted mean SS conc. 1.35 µg/ml)
³CAPD: 600-800 mg dd (predicted mean SS conc 0.9-1.8 µg/ml)
⁴CRRT: ‘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

<table>
<thead>
<tr>
<th>CrCl (ml/min/1.73 m²)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>1 g every 8 hrs</td>
</tr>
<tr>
<td>25-50</td>
<td>1 g every 12 hrs</td>
</tr>
<tr>
<td>10-25</td>
<td>1 g every 24 hrs</td>
</tr>
<tr>
<td>&lt;10</td>
<td>*500 mg every 24 hrs</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>IV</th>
<th>Standard dose (mg/kg)</th>
<th>Dosing interval (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;70</td>
<td>5</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>50-69</td>
<td>2.5</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>25-49</td>
<td>2.5</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>10-24</td>
<td>1.25</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>&lt;10</td>
<td>1.25</td>
<td></td>
<td>After dialysis</td>
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<table>
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<tr>
<th>CrCl (ml/min)</th>
<th>PO</th>
<th>Standard dose (mg/kg)</th>
<th>Dosing interval (h)</th>
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<tbody>
<tr>
<td>&gt;60</td>
<td>900</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>40-59</td>
<td>450</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>25-39</td>
<td>450</td>
<td></td>
<td>48</td>
</tr>
<tr>
<td>10-24</td>
<td>450</td>
<td></td>
<td>twice a week</td>
</tr>
<tr>
<td>&lt;10</td>
<td>NR</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>HD</td>
<td>NR</td>
<td></td>
<td>NR</td>
</tr>
</tbody>
</table>

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?

- 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?

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* acyclovir is 24 hours stable at 5 mg/ml

M. Reynders/V. Grootaert/D. Borrey
Take home messages

• 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