## Experimental COVID-19 Therapies - Dose recommendations for patients with renal impairment

Please refer to the additional notes on the following pages for further details and complete dose recommendations.

### Experimental COVID-19 Antiviral Therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>≥50 ml/min</th>
<th>30-49 ml/min</th>
<th>10-29 ml/min</th>
<th>&lt;10 ml/min</th>
<th>Renal Replacement Therapy (RRT)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atazanavir</strong></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Azithromycin</strong></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%, with caution b1</td>
<td>100%, with caution b2</td>
</tr>
<tr>
<td><strong>Chloroquine</strong></td>
<td>100%</td>
<td>50% c1</td>
<td>100% c1</td>
<td>50% (following a loading dose) c2</td>
<td>50% c3</td>
<td>50% c3</td>
</tr>
<tr>
<td><strong>Favipiravir</strong></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Hydroxychloroquine</strong></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Interferon beta</strong></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>Use with caution f1</td>
<td>Use with caution f1</td>
</tr>
<tr>
<td><strong>Ivermectin</strong></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Lopinavir/ritonavir</strong></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Nitazoxanide</strong></td>
<td>100%</td>
<td>100%, with caution h1</td>
<td>100%, with caution h1</td>
<td>100%, with caution h1</td>
<td>100%, with caution h1</td>
<td>100%, with caution h2</td>
</tr>
<tr>
<td><strong>Remdesivir</strong></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td><strong>Ribavirin</strong></td>
<td>100%</td>
<td>Alternating 200/400 mg every other day</td>
<td>200 mg daily</td>
<td>200 mg daily</td>
<td>200 mg daily</td>
<td>200 mg daily</td>
</tr>
</tbody>
</table>

### Experimental COVID-19 Immune Therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>≥50 ml/min</th>
<th>30-49 ml/min</th>
<th>10-29 ml/min</th>
<th>&lt;10 ml/min</th>
<th>Renal Replacement Therapy (RRT)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anakinra</strong></td>
<td>100%</td>
<td>100%</td>
<td>100% every other day k1</td>
<td>100% every other day k1</td>
<td>100% every other day k1</td>
<td>100% every other day k1</td>
</tr>
<tr>
<td><strong>Baricitinib</strong></td>
<td>100%</td>
<td>2 mg once daily l1</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td><strong>Canakinumab</strong></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Dexamethasone</strong></td>
<td>100%</td>
<td>100% n1</td>
<td>100% n1</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Hydrocortisone</strong></td>
<td>100%</td>
<td>100%, with caution e1</td>
<td>100%, with caution e1</td>
<td>100%, with caution e1</td>
<td>100% e2</td>
<td>100% e2</td>
</tr>
<tr>
<td><strong>Ruxolitinib</strong></td>
<td>100%</td>
<td>100% p1</td>
<td>5 mg twice daily p1</td>
<td>Not recommended</td>
<td>10 mg single dose or 5 mg twice daily p2</td>
<td>Use with caution. Consider dosing as for eGFR 10-30 ml/min p2</td>
</tr>
<tr>
<td><strong>Sarilumab</strong></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100% q1</td>
<td>100% q1</td>
</tr>
<tr>
<td><strong>Tocilizumab</strong></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100% r1</td>
<td>100% r1</td>
</tr>
</tbody>
</table>

### Abbreviations

- **eGFR**: Estimated glomerular filtration rate
- **CRRT**: Continuous renal replacement therapies
- **PD**: Peritoneal dialysis
- **PD**: Peritoneal dialysis

Use CKD-EPI formula: the Abbreviated Modification of Diet in Renal Disease (aMDRD) or the Cockcroft-Gault (CG) equation may be used as an alternative; see www.chip.dk/Tools-Standards/Clinical-risk-scores

No recommendation to use experimental therapy for COVID-19 is made. Data for many agents are limited or absent; therefore, risk-benefit assessment for any individual patient rests with prescribers.
Atazanavir
Atazanavir undergoes minimal renal elimination (13%, of which 7% is unchanged drug).
- a1) Comparable clearance expected in patients with and without dialysis. Atazanavir/ritonavir is recommended to achieve adequate exposure in patients undergoing RRT.

Azithromycin
Approximately 6-12% of an IV dose of azithromycin is excreted unchanged in urine.
- b1) In patients with severe renal impairment (GFR <10 ml/min) systemic exposure to azithromycin increased by 33-35%.
- b2) The extent to which azithromycin is removed with haemodialysis or CVVH is unknown; use with caution.
- b3) Azithromycin is not substantially removed by CAPD.

Chloroquine
Approximately 50-60% of chloroquine is renally eliminated, of which 50-70% is unchanged. For short treatment durations in COVID-19, exposure is largely dependent on distribution and not on clearance. A prolonged half-life is expected in renal impairment.
- c1) No evidence to support reduced dose in eGFR 10-50 ml/min.
- c2) A 50% dose reduction for maintenance dosing, after a standard loading dose, is recommended in patients with eGFR <10 ml/min due to renal elimination.
- c3) Approximately 5.3%-14.5% of a dose is cleared by haemodialysis. Data is lacking for other RRT but the same dosing recommendations for those with eGFR < 10 ml/min are applied. Consider dose reduction >day 2 (after loading dose) due to large volume of distribution.

Favipiravir
Favipiravir is 90.5% renally excreted, the majority of which (82-92%) as M1 metabolite which is responsible for toxicity.
- d1) M1 may accumulate in renal impairment with a 2.5-fold increase in moderate impairment based on a single patient studied in global phase 3 with eGFR 30-50 ml/min. Uric acid increases may also be a concern in renal impairment. No data is available to make any statement of safety in patients with renal impairment or dependent on RRT.

Hydroxychloroquine
Compared with chloroquine, hydroxychloroquine is less dependent on renal elimination for its clearance (40-50% renally eliminated of which 16-30% unchanged). The USA product label states that no dose adaptations should be made in patients with impaired renal function as there is no correlation between creatinine clearance and renal clearance of hydroxychloroquine.
- e1) Hydroxychloroquine does not appear to be dialysed. Plasma concentrations before and after dialysis did not significantly alter and hydroxychloroquine was not detected in the dialysate in three patients on dialysis (all on hydroxychloroquine therapy for at least six months). The increased exposure is expected based on the renal elimination of hydroxychloroquine.

Interferon beta
Approximately 40% of interferon beta is renally eliminated. Increased exposure is expected, particularly in severe renal impairment.
- f1) Use interferon beta with caution in patients with severe renal dysfunction or those on RRT. The interferon molecule is too large to be dialysed and will not undergo renal degradation.

Ivermectin
Less than 1% of ivermectin and its metabolites are excreted in urine.
- g1) Ivermectin has not been studied in patients with renal impairment. Renal elimination is negligible and dose adjustment in renal impairment is not required.

Lopinavir/ritonavir
Lopinavir/ritonavir is minimally renally eliminated (~10%, of which ~2% is unchanged drug).

Nitazoxanide
Approximately one third of an oral dose of nitazoxanide is excreted in the urine.
- h1) Nitazoxanide has not been studied in patients with compromised renal function.
- h2) No data are available in RRT.

Remdesivir
Approximately 74% of remdesivir is renally eliminated, the majority (49%) as the metabolite GS-441524 and 10% as remdesivir.
- i1) The pharmacokinetics of remdesivir have not been evaluated in patients with renal impairment. Use in these patients is based on potential risk and benefit considerations.
- i2) The excipient (sulfobutylether-β-cyclodextrin sodium salt) is renally cleared and accumulates in patients with decreased renal function. Remdesivir is not recommended in patients with eGFR <30 ml/min unless the potential benefit outweighs the potential risk.

Ribavirin
Approximately 62% of ribavirin is renally cleared. The main toxicities (anaemia) increase with declining renal function.
- j1) Ribavirin is not cleared by haemodialysis.
Notes (Immune Therapies)

**Anakinra**
Anakinra is eliminated by glomerular filtration and subsequent tubular metabolism. Plasma clearance of anakinra decreases with decreasing renal function.

- Plasma clearance of anakinra decreased by 70% in severe renal insufficiency and by 75% in end stage renal disease (CrCl < 30 ml/min). Every other day dosing is recommended.
- Less than 2.5% of an administered dose was removed by dialysis (HD or CAPD). Every other day dosing is recommended.

**Baricitinib**
Approximately 75% of an administered dose was eliminated in the urine through filtration and active secretion, predominately as unchanged drug (69%). Renal function significantly affects baricitinib exposure.

- For patients with eGFR 30-60 ml/min, a dose of 2 mg once daily is recommended in the European product label and dose of 1 mg once daily is recommended in the US product label. Given short duration of therapy in COVID-19, 2 mg once daily advised for this indication.
- Not recommended for use in patients with eGFR <30 ml/min.
- Baricitinib is likely to be removed during CRRT. Dose as in eGFR 30-60ml/min.

**Canakinumab**
Canakinumab is eliminated via intracellular catabolism. Due to its molecular size, little canakinumab is expected to be filtered by the kidney.

- No formal studies have been conducted to examine the pharmacokinetics of canakinumab administered subcutaneously in patients with renal impairment. Canakinumab is a human IgG immunoglobulin with large molecular size (~150 kDa), and little intact immunoglobulin is expected to be filtered by the kidney. Therefore, impaired renal function or renal replacement therapies are unlikely to affect the pharmacokinetics of canakinumab.

**Dexamethasone**
Dexamethasone is metabolised mainly in the liver, with up to 65% of the dose excreted unchanged in the urine.

- Particular care is required when considering the use of systemic corticosteroids in patients with renal insufficiency and frequent patient monitoring is necessary.

**Hydrocortisone**
Hydrocortisone is metabolised mainly in the liver and is minimally excreted in the urine.

- Particular care is required when using systemic hydrocortisone in patients with renal insufficiency, patient monitoring is advised.
- Hydrocortisone is unlikely to be dialysed.

**Ruxolitinib**
Approximately 74% of an administered dose was eliminated in the urine, mainly as metabolites (<1% unchanged drug). Clearance of ruxolitinib metabolites decreases with increasing severity of renal impairment. The safety of increased exposure to these metabolites is unknown; close patient monitoring is advised in addition to dose adjustment recommendations.

- The US product label for ruxolitinib recommends to avoid in moderate/severe renal impairment if platelets <100. Avoid if eGFR < 15ml/min.
- Use with caution. Administer post dialysis on dialysis days only. Ruxolitinib metabolites appeared to be dialysable to varying degrees by a 4-hour haemodialysis procedure. No data is available for dosing for patients on PD or CVVH.

**Sarilumab**
Sarilumab is not metabolised or excreted by the kidneys. No effect of renal impairment is expected.

- Sarilumab’s large molecular weight prevents clearance via glomerular filtration or RRT.

**Tocilizumab**
Tocilizumab is not metabolised or excreted by the kidneys. No effect of renal impairment is expected.

- Tocilizumab’s large molecular weight prevents clearance via glomerular filtration or RRT.
Please check www.covid19-druginteractions.org for updates. Please note that if a drug is not listed it cannot automatically be assumed it is safe to coadminister.
No recommendation to use experimental therapy for COVID-19 is made. Data for many agents are limited or absent; therefore, risk-benefit assessment for any individual patient rests with prescribers.

References

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