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

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.

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

Drug	Renal Impairment eGFR*				Renal Replacement Therapy (RRT)			References
	≥50 ml/min	30-49 ml/min	10-29 ml/min	<10 ml/min	Haemodialysis	CRRT	PD	
Experimental COVID-19 Antiviral Therapies								
Atazanavir	100%	100%	100%	100%	100% [a1]	100% [a1]	100% [a1]	1-3
Azithromycin	100%	100%	100%	100%, with caution [b1]	100%, with caution [b2]	100%, with caution [b2]	100%, with caution [b3]	4-7
Chloroquine	100%	100% [c1]	100% [c1]	50% (following a loading dose) [c2]	50% [c3]	50% [c3]	50% [c3]	7-10
Favipiravir [d1]	100%	No recommendation possible	No recommendation possible	No recommendation possible	No recommendation possible	No recommendation possible	No recommendation possible	11
Hydroxychloroquine	100%	100%	100%	100%	100% [e1]	100% [e1]	100% [e1]	12-14
Interferon beta	100%	100%	100%	Use with caution [f1]	Use with caution [f1]	Use with caution [f1]	Use with caution [f1]	15-18
Ivermectin [g1]	100%	100%	100%	100%	100%	100%	100%	19, 20
Lopinavir/ritonavir	100%	100%	100%	100%	100%	100%	100%	3, 21, 22
Nitazoxanide	100%	100%, with caution [h1]	100%, with caution [h1]	100%, with caution [h1]	100%, with caution [h1]	100%, with caution [h2]	100%, with caution [h2]	23
Remdesivir [i1]	100%	100%	Not recommended [i2]	Not recommended [i2]	Not recommended	Not recommended	Not recommended	24, 25
Ribavirin	100%	Alternating 200/400 mg every other day	200 mg daily	200 mg daily	200 mg daily [j1]	200 mg daily	200 mg daily	26, 27
Experimental COVID-19 Immune Therapies								
Anakinra	100%	100%	100% every other day [k1]	100% every other day [k1]	100% every other day [k2]	100% every other day [k2]	100% every other day [k2]	28, 29
Baricitinib	100%	2 mg once daily [l1]	Not recommended [l2]	Not recommended [l2]	Not recommended	2 mg once daily [l3]	Not recommended	7, 30, 31
Canakinumab [m1]	100%	100%	100%	100%	100%	100%	100%	32, 33
Dexamethasone	100%	100% [n1]	100% [n1]	100% [n1]	100% [n1]	100% [n1]	100% [n1]	7, 34
Hydrocortisone	100%	100%, with caution [o1]	100%, with caution [o1]	100%, with caution [o1]	100% [o2]	100% [o2]	100% [o2]	7, 35
Ruxolitinib	100%	100% [p1]	5 mg twice daily [p1]	Not recommended [p1]	10 mg single dose or 5 mg twice daily [p2]	Use with caution. Consider dosing as for eGFR 10-30 ml/min [p2]	Use with caution. Consider dosing as for eGFR 10-30 ml/min [p2]	7, 36-38
Sarilumab	100%	100%	100%	100%	100% [q1]	100% [q1]	100% [q1]	39
Tocilizumab	100%	100%	100%	100%	100% [r1]	100% [r1]	100% [r1]	7, 40, 41

Abbreviations

eGFR Estimated glomerular filtration rate

* 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

CRRT Continuous renal replacement therapies

PD Peritoneal dialysis

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Notes (Antiviral Therapies)

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.

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Notes (Immune Therapies)

Anakinra

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

k1) 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.

k2) 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.

l1) 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.

l2) Not recommended for use in patients with eGFR <30 ml/min.

l3) 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.

m1) 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.

n1) 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.

o1) Particular care is required when using systemic hydrocortisone in patients with renal insufficiency, patient monitoring is advised.

o2) 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.

p1) The US product label for ruxolitinib recommends to avoid in moderate/severe renal impairment if platelets <100. Avoid if eGFR < 15ml/min.

p2) 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.

q1) 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.

r1) Tocilizumab's large molecular weight prevents clearance via glomerular filtration or RRT.

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