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.

COVID-19 Antiviral Therapies (Licensed and Under Clinical Investigation)

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	
Azithromycin	100%	100%	100%	100%, with caution	100%, with caution	100%, with caution	100%, with caution	1-4
Bamlanivimab/ Etesevimab	100%	100%	100%	100%	100%	100%	100%	5
Casirivimab/ Imdevimab	100%	100%	100%	100%	100%	100%	100%	6, 7
Chloroquine	100%	100%	100%	50% (following a loading dose)	50%	50%	50%	4, 8-10
Favipiravir	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%	100%	100%	12-14
Interferon beta	100%	100%	100%	Use with caution	Use with caution	Use with caution	Use with caution	15-18
Ivermectin	100%	100%	100%	100%	100%	100%	100%	19, 20
Molnupiravir	100%	100%	100%	100%	100%	100%	100%	21
Niclosamide	100%	100%	100%	100%	100%	100%	100%	22, 23
Nirmatrelvir + ritonavir	100%	Nirmatrelvir: 50% Ritonavir: 100% (i.e. 1 tablet of each)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	24, 25
Nitazoxanide	100%	100%, with caution	100%, with caution	100%, with caution	100%, with caution	100%, with caution	100%, with caution	26
Remdesivir	100%	100%	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	27, 28
Ribavirin	100%	Alternating 200/400 mg every other day	200 mg daily	200 mg daily	200 mg daily	200 mg daily	200 mg daily	29, 30
Sotrovimab	100%	100%	100%	100%	100%	100%	100%	31, 32
Tixagevimab/ Cilgavimab	100%	100%	100%	100%	100%	100%	100%	33

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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Azithromycin

Approximately 6-12% of an IV dose of azithromycin is excreted unchanged in urine.

In patients with severe renal impairment (GFR <10 ml/min) systemic exposure to azithromycin increased by 33-35%.

The extent to which azithromycin is removed with haemodialysis or CVVH is unknown; use with caution. Azithromycin is not substantially removed by CAPD.

Bamlanivimab/ Etesevimab

Bamlanivimab and etesevimab are not eliminated intact in the urine. Renal impairment is not expected to affect the exposure of bamlanivimab or etesevimab.

No dosage adjustment is recommended in patients with renal impairment.

Casirivimab/ Imdevimab

Casirivimab and imdevimab are monoclonal antibodies and are therefore not likely to undergo renal excretion. Renal impairment is not expected to affect the exposure of casirivimab and imdevimab

No dosage adjustment is required in individuals with mild or moderate renal impairment, or in patients with creatinine clearance (CrCl) < 15 mL/min including those on dialysis.

Based on population PK analysis, trough concentrations of casirivimab and imdevimab in serum at steady state were comparable between patients with mild or moderate renal impairment, or patients with CrCl <15 ml/min including those on dialysis, and patients with normal renal function. Limited data are available in patients with severe renal impairment (n=3).

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.

No evidence to support reduced dose in eGFR 10-50 ml/min.

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.

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.

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.

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.

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.

Ivermectin has not been studied in patients with renal impairment. Renal elimination is negligible and dose adjustment in renal impairment is not required.

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Notes - Antiviral Therapies (Licensed and Under Clinical Investigation) [continued]

Molnupiravir

Molnupiravir is hydrolysed to n-hydroxycytidine (NHC) prior to reaching systemic circulation. Renal clearance is not a meaningful route of elimination for NHC.
No dose adjustment in patients with any degree of renal impairment is needed. In a population PK analysis, mild or moderate renal impairment did not have a meaningful impact on the pharmacokinetics of NHC. The pharmacokinetics of molnupiravir and NHC has not been evaluated in patients with eGFR <30 mL/min or on dialysis.

Niclosamide

Niclosamide has poor bioavailability when administered orally and low systemic absorption via the intranasal/inhaled route.
Niclosamide may be given safely to patients with kidney diseases.

Nirmatrelvir +ritonavir

The primary route of elimination of nirmatrelvir when administered with ritonavir was renal excretion of intact drug. Approximately 49.6% of the administered dose was recovered in urine.
Compared to healthy controls with no renal impairment, nirmatrelvir Cmax and AUC were 30% and 24% higher in patients with mild renal impairment, 38% and 87% higher in patients with moderate renal impairment, and 48% and 204% higher in patients with severe renal impairment.
Nirmatrelvir and ritonavir are highly protein bound, therefore, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis.

Nitazoxanide

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

Remdesivir

Remdesivir is not cleared unchanged in urine to any substantial extent, but its main metabolite GS-441524 is renally cleared and the metabolite levels in plasma may theoretically increase in patients with impaired renal function. The excipient betadex sulfobutyl ether sodium is renally cleared and accumulates in patients with decreased renal function.
The pharmacokinetics of remdesivir have not been evaluated in patients with renal impairment. Patients with eGFR ≥30 mL/min have received remdesivir for treatment of COVID-19 with no dose adjustment.
All patients should have eGFR determined prior to starting remdesivir and while receiving it as clinically appropriate. Remdesivir should not be used in patients with eGFR <30 ml/min as administration of drugs formulated with betadex sulfobutyl ether sodium (such as remdesivir) is not recommended in patients with eGFR <30 ml/min.
Note, a renal toxicity signal has been noticed for remdesivir and is currently under investigation by the European Medicines Agency (Gérard AO *et al*. Clin Pharmacol Ther, 2021, 109(4):1021-1024).

Ribavirin

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

Sotrovimab

Renal impairment is not expected to impact the pharmacokinetics of sotrovimab since mAbs with molecular weight >69 kDa do not undergo renal elimination.
No dosage adjustment is recommended in patients with renal impairment.
Due to its molecular weight, dialysis is not expected to impact the pharmacokinetics of sotrovimab.

Tixagevimab/ Cilgavimab

Tixagevimab and cilgavimab are monoclonal antibodies and are therefore not likely to undergo renal excretion. Renal impairment is not expected to affect the exposure of tixagevimab and cilgavimab
There is no difference in the clearance of tixagevimab and cilgavimab in individuals with mild or moderate renal impairment compared to individuals with normal renal function. There were insufficient subjects with severe renal impairment to draw conclusions.

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COVID-19 Host-directed Therapies (Licensed and Under Clinical Investigation)

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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	
Anakinra	100%	100%	100% every other day	100% every other day	100% every other day	100% every other day	100% every other day	34, 35
Baricitinib	100%	2 mg once daily	Not recommended	Not recommended	Not recommended	2 mg once daily	Not recommended	4, 36, 37
Budesonide (inhaled)	100%	100%	100%	100%	100%	100%	100%	7, 38, 39
Canakinumab	100%	100%	100%	100%	100%	100%	100%	40, 41
Colchicine	100%	100%, with caution. Contraindicated with P-gp or strong CYP3A4 inhibitors.	Reduce dose or increase dosing interval and monitor closely. Contraindicated with P-gp or strong CYP3A4 inhibitors.	Contraindicated	Not recommended in SmPC. See US product label for alternative dosing options.	Not recommended in SmPC. See US product label for alternative dosing options.	Not recommended in SmPC. See US product label for alternative dosing options.	42, 43
Dexamethasone (low dose)	100%	100%	100%	100%	100%	100%	100%	4, 44
Hydrocortisone	100%	100%, with caution	100%, with caution	100%, with caution	100%	100%	100%	4, 45
Infliximab	100%	100%, with caution	100%, with caution	100%, with caution	100%, with caution	100%, with caution	100%, with caution	4, 46, 47
Methylprednisolone	100%	100%	100%	100%	100%	100%	100%	4, 48, 49
Ruxolitinib	100%	100%	5 mg twice daily	Not recommended	10 mg single dose or 5 mg twice daily	Use with caution. Consider dosing as for eGFR 10-30 ml/min	Use with caution. Consider dosing as for eGFR 10-30 ml/min	4, 50-52
Sarilumab	100%	100%	100%	100%	100%	100%	100%	53
Tocilizumab	100%	100%	100%	100%	100%	100%	100%	4, 54, 55

Abbreviations

eGFR Estimated glomerular filtration rate

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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 30-60 ml/min.

Budesonide (inhaled)

The metabolites of budesonide are excreted as such or in conjugated form mainly via the kidneys. No unchanged budesonide has been detected in the urine.
There are no data regarding the specific use of inhaled budesonide in patients with renal impairment. No dose adjustment is required in renal impairment.
Budesonide is unlikely to be dialysed.

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.

Colchicine

Colchicine is significantly excreted in urine in healthy subjects. Clearance of colchicine is decreased in patients with impaired renal function.
Total body clearance of colchicine was reduced by 75% in patients with end-stage renal disease undergoing dialysis.
Use with caution in patients with mild renal impairment. For patients with moderate renal impairment, reduce dose or increase interval between doses.
Such patients should be carefully monitored for adverse effects of colchicine.
Colchicine is contraindicated in patients with severe renal impairment.
Colchicine is contraindicated in patients with any degree of renal impairment who are taking a P-gp inhibitor or a strong CYP3A4 inhibitor.
Colchicine should not be used in patients undergoing haemodialysis since it cannot be removed by dialysis or exchange transfusion.

Dexamethasone (low dose)

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 (eGFR <50 ml/min); patient monitoring is advised.
Hydrocortisone is unlikely to be dialysed.

Infliximab

The elimination pathways for infliximab have not been characterised but it is likely to be eliminated via its target antigen.
Unchanged infliximab was not detected in urine.
Infliximab has not been studied in patients with renal impairment. No dose recommendations can be made. Infliximab is not dialysed.

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Notes – Host-directed Therapies (Licensed and Under Clinical Investigation) [continued]

Methylprednisolone

Methylprednisolone is metabolized by CYP3A4 to inactive metabolites which are excreted 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.
Methylprednisolone is dialysed - dose as in normal renal function.

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 <15 ml/min.
Use with caution in patients on RRT. 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.

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