COVID-19 - clinical management of children admitted to hospital with suspected COVID-19

Health Policy team

This guidance outlines key principles for the clinical management of children admitted to hospital with suspected COVID-19. It is aimed at general paediatricians treating children during the COVID-19 pandemic. It covers medical management of paediatric patients, including advice on use of antiviral treatments.

This guidance has been produced with the British Paediatric Respiratory Society and the British Paediatric Allergy, Immunity and Infection Group.

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This guidance is subject to change with emerging evidence and will be updated as we learn more about COVID-19 in children.

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If you have any questions relating to this guidance, please contact us on health.policy@rcpch.ac.uk.

Summary

Reassure parents and involve them in caring for their child, keep up-to-date using the evidence, and communicate well with colleagues.

Be extra-vigilant in children with pre-existing conditions but reassure parents that the risks of co-morbidities are much greater in adults than children.

Chest x-rays (CXR), bloods, and blood gases are not routinely indicated in all children. However, these should be monitored in children with persistent fever, altered fluid balance, signs of liver dysfunction, or respiratory failure.

Although recommended in some adult papers, the following medical treatments are likely to have more side-effects than beneficial effects in children and are not routinely indicated for empiric treatment of COVID-19, but should be used if otherwise clinically indicated: bronchodilators, systemic steroids, antibiotics, antivirals, and diuretics.

Despite emerging concern about Angiotensin Converting Enzyme (ACE) Inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs), there is insufficient evidence for stopping these medications if children have been taking them for pre-existing conditions and such an action may be harmful. In otherwise well children, paracetamol should be taken as the first-line antipyretic, and ibuprofen only taken with caution.

Escalate respiratory support as per local respiratory failure pathways. Do not use high flow nasal cannula oxygen if the child is saturating adequately with low flow oxygen. Consider carefully the use of HFNCO and nebulisation.

The use of specific treatment (anti-viral and immune modulation treatments) should be used within a treatment trial. Their use should always be discussed with a paediatric infectious diseases consultant.

It is crucial that we learn as much as we can about this emerging disease and our guidance on surveillance and data collection should be utilised. Information should be reported to Public Health England. In all cases the Clinical Characteristics and Outcomes should be reported in the NIHR-funded Clinical Characterisation Protocol (CCP-UK) led by Professor Calum Semple. NHS England have developed a clinical dashboard which can feed information about admission rates in children on a twice-weekly basis to hospital trusts. The British Paediatric Surveillance Unit is running a data collection programme for infants <29 days who test positive for COVD-19, led by Dr Christopher Gale.

NHS clinical management guidance

NHS England has produced general guidance on the clinical management of COVID-19. Please note that this is not specific to paediatric patients.

The guidance covers:

- Early recognition of patients with suspected COVID-19 infection;
- Early supportive therapy and monitroing;
- Management of hypoxaemic respiratory failure and ARDS;
- Management of septic shock;
- Practical management in critical care;
- Specific anti-COVID-19 treatments and clinical research;
- Special considerations for pregnant patients.

NICE has produced rapid guidelines for COVID-19, including for children and young people who are immunocompromised.

Key principles of good care during COVID-19 pandemic

Reassure: Most children will have much milder illness than is seen in adults. Reassure children and parents, as they are likely to be concerned from information (and misinformation) in mainstream and social media. Some children in the UK have died from complications of suspected COVID-19, and further information is needed to characterise these cases.

Involve parents: When parents feel disempowered they may become anxious and feel that their child is not being managed properly. The way healthcare professionals communicate with families is important.1 Reinforce that active monitoring and supportive therapy is the best strategy. Furthermore, identify ways to actively involve parents – in infection control procedures, entertaining and calming their child, supporting good nutritional intake, asking questions on their child's behalf, and helping avoid unnecessary investigations and interventions. Personal Protective Equipment (PPE) can look alarming to children, and it is important that parents and healthcare professionals proactively discuss the need for such measures, and reassure children. These crucial aspects of care are best done by parents.

Be vigilant: Some children will develop complications and comorbidities. Although the medical literature suggests that the vast majority of children will have self-limiting illness without complications, be aware of local sepsis guidelines, acute kidney injury guidelines, and respiratory failure guidelines.

Teamwork: The whole multidisciplinary team must work together to ensure the best outcome for the child. During times of viral epidemic, parents and children want to see healthcare professionals adhere to the same guiding principles of practice. Deviation is undermining to other professionals, and parents and children will pick up on differences in practice (however subtle). Written and verbal communication between professionals is crucial to prevent this.

Minimising spread of the virus in hospital is crucial. Be aware of local and national recommendations for doing this.

Pathology of COVID-19

COVID-19 is caused by a novel coronavirus (SARS-CoV-2). The first reported cases were in

the Wuhan District of China, and appeared to be potentially from a zoonotic spillover at Huanan Seafood Wholesale Market. Subsequent cases were because of person to person transmission.[2]

The virus is extremely contagious, particularly where there is close contact between people. The Reproduction number (R0) estimates the number of people that an average person may infect if they carried the virus. This is currently estimated at around 3 (ie one person infects 3 people).[3] The virus is stable in aerosol form for hours and on solid surfaces for days.[4]

The virus appears to directly infect cells via the ACE2 Receptor. This is expressed in various organs, including the lung. Cells in children's lungs express this receptor less than those in adult lungs. This may be one reason why the infection affects children less severely.

One proposed disease mechanism in severe cases is a 'cytokine storm'.[5] This describes a cascade process whereby the virus leads to increased levels of cytokines that cause direct tissue damage, recruitment of neutrophils to tissues, and other pro-inflammatory effects. This damage can lead to Acute Respiratory Distress Syndrome. Various cytokines have been implicated in this process in severe and fatal cases.[6] [7] [8] These include IP-10, MCP-1, TNF-1, IL1, and IL-6.

Extrapulmonary involvement and multi-organ failure have also been identified in people with severe or fatal illness. Some patients develop cardiac dysfunction.[7] This may be due to viral-induced direct damage (cardiac tissue carries ACE receptors), or hypoxic damage in people with respiratory failure. One study found an increased risk of admission amongst children with a history of arrythmia.[9] Viral infections can cause pericarditis, but this has not been consistently described in COVID-19. Liver damage and renal failure have been reported, and associated with severe infection. [7]

Clinical and laboratory features in children

No symptoms on admission consistently predict outcome in children, though in adults high fever on admission was associated with subsequent development of ARDS and death.[10] The commonest features in the history of children with COVID-19 are fever and/or cough (each in around 50%). Fever in children with COVID-19 tends to subside within three days.[11] [12] The cough is typically dry, productive cough was reported in 3% of cases in one study.[13] Myalgia, lethargy, and gastrointestinal symptoms are also reported.

Although not reported in literature to date, parental smoking and use of electronic cigarettes (parents and older children), housing quality, and nutritional status may be associated with illness frequency and severity.

The commonest white cell abnormality reported in 30% of children is leukopaenia. Only 10-20% of children are reported to have a raised CRP, and when actual levels were provided, the maximum reported value was 33.[12] In one study, leukopenia and CRP>10 were associated with pneumonia.[11]

Additional diagnostic tests for severely unwell children

The majority of children are expected to have asymptomatic or mild disease only. No additional blood tests are required for children with mild-moderate disease requiring only

supportive care, beyond those required to exclude alternative diagnoses. Given the relatively mild symptomatology of the majority of children with COVID19, it is vital that alternative diagnoses are considered in children presenting as unwell, following the same investigation and management practice and pathways in place prior to the outbreak.

Children presenting or deteriorating with severe features consistent with acute respiratory distress syndrome (ARDS) should have the following investigations (listed in below table).

Samples (respiratory and blood) should be sent for virology testing prior to initiating any antiviral or immunomodulatory treatment and all patients should be discussed with the infectious diseases team.

Initial diagnostic tests	
Haematology / biochemistry	FBC, U+E, LFT, CRP, Troponin, Ferritin, LDH, coagulation panel including D-Dimer *If considering immunomodulatory treatment send IL6 and soluble CD25
Microbiology	Blood cultures, urine MC&S, viral respiratory panel *HIV testing should be done in all children in whom treatment with lopinavir / ritonavir is being considered, but pending results should not delay treatment
Radiology	Chest x-ray
Other	Serum save, research bloods if appropriate in your setting In children <2 years of age consider lymphocyte subsets to exclude SCID (severe or critical illness only)
Suggested ongoing monitoring tests (if deteriorating patient)	
Haematology / biochemistry	FBC, U+E, LFT, CRP, Ferritin

Treatment criteria

Treatment criteria

Mild to moderate disease No O2 requirement Mild upper airway infection	All groups	Supportive care
Severe disease Mild - moderate ARDS**: 1. Unventilated requiring FiO2 >40% to maintain saturation 88-97% 2. Ventilation: • Oxygenation index: 4 ? 16 • Oxygenation saturation index: 5 ? 12.3	All groups Risk group*	Supportive care Treatment with antivirals may be considered Treatment with immunodulatory therapy may be considered (especially in a risk group*) if evidence of hyperinflammation (raised CRP, Ferritin, IL6, sCD25) Consider entry to RECOVERY trial – see details of the trial and training resources
Critical disease Severe ARDS**: • Oxygenation index ? 16 • Oxygenation saturation index: ? 12.3 Septic shock Altered consciousness Multi-organ failure	All groups	Supportive care Treatment with antivirals may be considered Treatment with immunodulatory therapy may be considered if evidence of hyperinflammation (raised CRP, Ferritin, IL6, sCD25) Consider entry to RECOVERY trial – see details of the trial and training resources

*Risk group: Children in risk groups should be seen as at particular risk of clinical deterioration and risk benefit based decisions relating to antiviral or immunomodulatory therapy should take this into account. See our guidance on children at increased risk for more information.

**ARDS as defined by the PARD criteria: Pediatric Acute Lung Injury Consensus Conference

Supportive medical care

This section covers: admission, radiology, fluids, antipyretics, respiratory support, antibiotics, bronchodilators / treatment of children with asthma attacks, and liver dysfunction.

Admission

Not all children with COVID-19 require admission. Many people with confirmed COVID-19 may be managed at home, in line with Public Health England guidance.

Radiology

Chest x-rays and CT scans may reveal non-specific findings even in asymptomatic children. They should not be conducted routinely, even if children require a small amount of oxygen on admission, and only used to answer a specific question. Where possible, portable chest x-rays should be performed to support isolation of children and to limit ongoing transmission. Consider chest x-rays in children whose clinical course is not following an expected disease progression, or who deteriorate, for example those still requiring oxygen on day three of admission, those with worsening hypoxaemia or those requiring CPAP.

Lobar collapse due to bacterial pneumonia is more likely if the child has respiratory failure, and persistent temperature. No studies have described lobar collapse, pneumothorax, or effusion in children with COVID-19. A number of studies advocate for the use of CT scans, but these are unlikely to help with diagnosis or management and are not indicated. Transferring infected children to the CT scanner puts other patients at risk.

Fluids

Acute Kidney injury (AKI) is a complication of viral infections. Most children with mild illness do not require fluid restriction below normal maintenance values. Fluid restriction may be indicated in children with moderate to severe respiratory compromise as this may reduce the risk of acute respiratory distress syndrome (ARDS). Be aware that febrile children, and those who are tachypnoeic, may have increased insensible losses. Pharyngitis or anorexia may limit oral intake. Monitor fluid balance, and measure daily weight in those children in whom fluid intake is a concern. Renal profile blood tests and urine dipstick are not required in all children but should be measured if there is a concern about fluid balance. Diuretics are not indicated routinely but should be considered (under consultant guidance) in children with worsening respiratory failure requiring CPAP or NIV, particularly if there is evidence of pulmonary oedema on chest x-ray. Involve critical care teams early in these cases.

Antipyretics

Paracetamol is the first line antipyretic. Avoid ibuprofen in children with poor fluid intake or suspected AKI. There are unsubstantiated reports of ibuprofen being implicated in severe cases of COVID-19. Parents should be aware of potential theoretical risks of ibuprofen (one theory is that NSAIDs can upregulate expression of ACE receptors in the lung). If a child is requiring ibuprofen for relief of fever, be aware that this may in fact reflect significant inflammation, or be a sign of sepsis, and have a lower threshold for checking blood

inflammatory markers.

RCPCH has recommended that parents treat symptoms of fever or pain related to COVID-19 with either paracetamol or ibuprofen.

Respiratory support

Most children, even those with lung involvement, are unlikely to develop respiratory failure. Children should receive low flow nasal cannula (LFNC) oxygen if they are hypoxic, rather than high flow nasal cannulae (HFNC). If children are hypoxic despite LFNC, then HFNC can be tried (with appropriate PPE). It should not be used routinely as a method of reducing work of breathing in children who are otherwise saturating adequately. There is no evidence in the literature about the benefit of blood gases – these should not be done routinely. They can be used in children who despite administration of HFNC appear to require further respiratory support. In such children capillary blood gas (not arterial or venous) may be used to evaluate for pH and pCO2.

Antibiotics

For children without pre-existing condition, consider antibiotics if:

- They are unusually sick at admission / day one (particularly fever and / or still on oxygen) or if there is a clinical deterioration.
- Antibiotics should be prescribed based on usual grounds and clinical judgement, rather than a prescribed time. Teams should ensure they have sought a focus of infection (urine, throat swab, blood culture +/- CSF as appropriate prior to starting antibiotics, as is best practice).
- Blood tests are suggestive of bacterial infection, e.g. raised CRP and neutrophil count.
- CXR changes reveal a pneumonic picture, e.g. lobar pneumonia and this is consistent with the clinical picture.*
- An alternative or co-incidental diagnosis is considered, don't forget sepsis, which may have overlapping clinical features.

*CXR changes should be mild in most children. Antibiotic choice may vary depending on findings, e.g. bilateral changes may indicate atypical infection and a macrolide may be indicated. However, bilateral CXR changes have been described in seemingly asymptomatic children, so interpret in the context of the clinical picture.

There is limited evidence regarding frequency or cause of bacterial coinfection in children with COVID-19. Mycoplasma infection was reported in 20% of a small (n=20) paediatric case series, but details of diagnostic methods or universal testing were unavailable.9 A systematic review of bacterial coinfection rates in the 2008/9 H1N1 pandemic estimated that 15% of patients had existing bacterial co-infection; this was lower in paediatric patients. However, methodology varied, and the evidence was not robust.14 It is likely that bacterial co-infection is associated with increased morbidity in all ages and increased mortality in adults.15

Antibiotic choice should be based on local guidelines. A respiratory sample for microbiological culture should ideally be sent prior to starting antibiotics. For children with co-morbidities, such as cystic fibrosis, antibiotic choice should be based on known bacterial colonisation where available.

Bronchodilators / treatment of children with asthma attacks

More information on aerosol generation from nebulisation is available in the download below.

Wheeze is not a common problem in children with COVID-19. Bronchodilators should not be used routinely unless there is strong suspicion of bronchoconstriction (wheeze, and prolonged expiratory phase). The side effects of bronchodilators include pro-inflammatory effects on the alveoli, worsening of V/Q mismatch, and tachycardia.

In children with acute wheeze or asthma attacks, prompt treatment with salbutamol and systemic steroids (within an hour of arrival) can reduce the risk of hospitalisation, and further need for nebulisation.

Salbutamol given via Metered dose inhaler (MDI) is as effective as nebulisation, and less likely to lead to admission. There is insufficient evidence to recommend using concomitant ipratropium bromide if salbutamol is given via MDI, and no evidence for using intravenous magnesium sulphate earlier than it is usually given. If nebulisation is required because a child is hypoxic and tachypnoeic, salbutamol and ipratropium bromide may be given concomitantly, but there is no evidence to suggest that more than one such combined nebuliser should be given.

Concerns have been raised about whether nebulisation is an aerosol-generating procedure. It is unclear whether visible aerosols come from the patient's airway and whether nebulisation procedures increase the risk of HCW developing acute respiratory infections (ARI) but there is no evidence to refute this suggestion. It is unknown whether fit-tested FFP3 masks reduce the risk of HCW developing ARI compared with surgical masks when performing nebulisation to adults or children. Current PHE guidance developed from NERVTAG is that nebulisation does not carry patient-derived viral particles.

Where nebulisation is currently routinely given, we ask for the use of pMDI via spacer rather than nebuliser could be encouraged. If a nebuliser is still needed, a risk assessment could be performed to determine the need for FFP3 mask, gown and visor use. This risk assessment would take into account the vulnerability of individual staff members, the clinical status of the patient, and the environment of the room that the child is in. Current experience suggests there is a low likelihood of a child with wheeze having a positive COVID-19 test (the majority of children tested with wheeze are negative and there are very few children who are symptomatic with COVID-19). Strategies to reduce the risk of nebulisation might include giving the parents the drug to add to the nebuliser, using appropriate PPE if the situation is high risk (although this is not routinely indicated), and using gloves before removing any interfaces or equipment that has been on the child's face.

There is concern that oral steroid use may prolong the duration of viral shedding, but in the absence of evidence to suggest otherwise, these should be used as normal in children with asthma attacks.

Liver dysfunction

Raised liver enzymes have been reported in children and adults with COVID-19. The prognostic value is unknown. Transient self-limiting transaminitis is described in children with a variety of viral infections. In COVID-19, this may be associated with severe illness,

pneumonia, and drug treatments. If bloods are clinically indicated for other reasons, repeat liver function tests (LFT) for monitoring purposes. If the transaminitis persists, synthetic function should be reviewed by performing a coagulation profile and albumin level. Do not check LFT routinely.

Use of antiviral and immunomodulatory treatment in children

This section covers possible antiviral management of paediatric patients with suspected or confirmed novel coronavirus infection (SARS-CoV-2) in the UK. It also covers potential off-label and/or experimental treatment use of medications and aims to provide a framework for case-by-case discussion with specialists who can provide additional advice. It also suggests appropriate laboratory investigations.

Whilst there are no antivirals licensed for use in this indication, data from SARS, MERS and in vitro, in vivo and limited clinical studies suggest some benefit may be obtained from antiviral therapy.[16] [17]

The decision to use antiviral medication should be based on signs of progressive respiratory deterioration regardless of comorbidity.

Our recommendation is that, as far as possible, all patients in the UK should only receive anti-viral or immunomodulatory treatments for COVID-19 within a treatment trial.

Patients could be considered for compassionate use of antiviral treatments on a case by case basis in discussion with the recommended specialists outlined below.

There are extremely limited supplies of all COVID-19 medications in the UK, this should be taken into account for all treatment decisions.

It appears that pharmacological antiviral treatment is most effective if initiated quickly upon clinical presentation, prior to clinical deterioration, however treatment of mild cases is not recommended and confirmatory evidence is pending.

All suspected or confirmed paediatric cases of COVID-19 for whom antiviral or immunodulatory treatment is being considered should be referred to a paediatric infectious diseases consultant and any decision to treat should be approved by local MDT and also be approved by a paediatric infectious diseases or immunology consultant from at least 1 additional centre in the UK or Ireland.

Criteria for antiviral and immunomodulatory treatment

There is currently limited evidence of efficacy of antiviral and immunomodulatory therapy for COVID19 in adults, and no evidence in children. The decision to start treatment should be made carefully on a case by case basis.

We recommend discussion within already established internal review pathways, but also suggest discussion with an external Paediatric Infectious Disease Specialist prior to starting antiviral therapy and/or a clinician with experience in the use of immunomodulatory therapy if

these are being considered (immunology, haematology, bone marrow transplant, rheumatology).

Antiviral treatment is likely to have the most benefit in the first phase of illness. Immunomodulatory therapy may only be indicated if clear evidence of hyperinflammation, or in the second phase of the illness, and evidence is currently extremely limited. Antiviral treatment and immunomodulatory treatment should be restricted for hospital use only and preferably in a clinical trial setting.

Antiviral treatment options

Samples (respiratory and blood) should be sent for virology testing prior to initialising treatment and all patients should be discussed with microbiology/infectious diseases.

For the agents mentioned in the below table, please contact pharmacy with regard to dosing in neonates or patients with renal impairment. University of Liverpool have developed guidance to check the potential for drug interactions.

For patients in whom treatment with lopinavir/ritonavir (Kaletra) is being considered, an HIV test should be performed to avoid selecting for resistance in an undiagnosed child.

There are four treatment options:

- Lopinavir-ritonavir (Kaletra) + Ribavirin; OR
- Chloroquine; OR
- Hydroxy-chloroquine; OR
- Remdesivir (GS-5734).

The treatment options below are not listed in any particular order.

Option one: Lopinavir-ritonavir (Kaletra) + Ribavirin

Lopinavir-ritonavir (Kaletra)*

- **Route**: Oral / NG
- **Formulation**: either oral liquid 100/100mg in 5mL or tablet
  - Liquid: 5mL = LPV/RTV 400/100mg (clear)
    - Note: Fridge (contains 42% ethanol and propylene glycol) - caution in neonates**
  - Tablets: 100/25mg and 200/50mg available
- **Duration**: both options for 7 days

Dose for oral liquid 400/100mg in 5mL:18

Weight	**Dose**
3-5kg	1mL 12 hourly
6-9kg	1.5mL 12 hourly
10-13kg	2mL 12 hourly

Weight	Dose
14-19kg	2.5mL 12 hourly
20-24kg	3mL 12 hourly

Dose for tablet:[18]

Weight	Dose
10-13kg	200/50mg morning 100/25mg at night
14-24kg	200/50mg 12 hourly
25-34kg	300/75mg 12 hourly
> 35kg	400/100mg 12 hourly

*For patients in whom treatment with lopinavir/ritonavir (Kaletra) is being considered, an HIV test should be performed to avoid selecting for resistance in an undiagnosed child.

**Do not use in neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days.

Ribavirin

- **Route**: Oral / NG
- **Formulation**: oral solution / tablet / capsule[19]
    - Round tablet / capsule doses to nearest 200mg, can split total daily dose of 20mg/kg into 3 to aid administration
    - Tablets can be crushed for NG if no oral solution available
- **Duration**: 7 days
- **Dose**: 10mg/kg (max 900mg) 12 hourly

Option two: Chloroquine

Chloroquine

- **Route**: Oral / NG
- **Formulation**: oral solution / tablet[20]
    - Chloroquine 250mg (containing 155mg chloroquine base) tablets; round to nearest half tablet where able
    - Crush tablets for NG administration
- **Duration**: 3 days only
- **Dose**: 10mg/kg chloroquine base (max 620mg) initial dose, followed by dose of 5mg/kg after 6 hours, then 5mg/kg once daily thereafter

Option three: Hydroxy-chloroquine

Hydroxy-chloroquine

- **Route**: Oral / NG

- **Formulation**: oral solution / tablet21
    - Oral solution (unlicensed special)
- **Duration**: 5 days
- **Dose**: 6.5 mg/kg 12hourly on day 1 (maximum initial dose = 400 mg), followed by 3.25 mg/kg 12hourly on days 2 - 5 (maximum dose = 200 mg)23

Option four: Remdesivir (GS-5734)

Remdesivir (GS-5734)

- **Route**: IV
- **Formulation**: 100mg or 150mg vials or powder/solution for infusion22
    - Compassionate use from Gilead, see below
- **Duration**: 10 days total including loading dose

Dose:

Weight	Dose
<40 kg	5mg/kg loading dose, then 2.5mg/kg once daily
?40 kg	200mg loading dose, then 100mg once daily

Obtaining remdesivir and clinical samples: There are currently extremely limited antiviral data for remdesivir that show activity against the SARS-CoV-2. However, we understand the virus is closely related to SARS-CoV and remdesivir is active against SARS-CoV and MERS-CoV both in vitro and in animal models. Remdesivir is not yet licensed or approved anywhere globally. While remdesivir is in development, Gilead is committed to providing the drug where appropriate for compassionate use, whilst managing the balance of potential global demand vs supply.

Immune modulation therapy

Some patients with SARS-CoV-2 infection and ARDS have clinical features / blood parameters which overlap with well recognised hyperinflammatory syndromes, including secondary Haemophagocytic Lymphohistiocytosis (sHLH), sepsis associate Macrophage Activation-Like Syndrome (MALS) and CAR-T cell therapy associated Cytokine Release Syndrome (CRS). Inflammatory pathology appears to more localised within the lung tissue in SARS-CoV-2 infection, and systemic inflammatory markers are generally lower than in these other syndromes.

Raised inflammatory markers (CRP, Ferritin, IL6)24 25 appear to be associated with more severe disease and a worse prognosis. Tocilizumab (a humanised anti-IL6 monoclonal antibody) is an established therapy for CRS following CAR-T cell therapy and has been used to treat hyperinflammation in SARS-CoV-2 infection with anecdotal success and no significant toxicity.26 There are ongoing randomised controlled trials of Tocilizumab in SARS-CoV-2 infection in Italy and China. Anakinra is a recombinant antagonist of the human IL1 receptor and is an established therapy in macrophage activation syndrome, sHLH (off-licence) and has demonstrated a survival benefit in patients with MALS.

Although both Tocilizumab and Anakinra are generally well tolerated, they both confer an

increased risk of infection, so careful assessment of co-infection should be made prior to use, especially as co-infection in the context of SARS-CoV-2 is a risk factor for poor outcome.

As with decisions to use antiviral medication the use of immunomodulatory therapy should be considered on a case by case basis involving broad MDT (including specialists in the use of these agents) and ethics team if necessary. It is also recommended to discuss with at least one specialist external to the treating Trust.

There are two treatment options:

- Tocilizumab; OR
- Anakinra

Option one: Tocilizumab

Route	Weight	Formulation	Dose	Duration
IV	<30 kg	20 mg/ml single dose vials. Dilute to 50ml with 0.9% Sodium Chloride	12 mg/kg	If no improvement at 12 hours, repeat with same dose
IV	?30 kg	20 mg/ml single dose vials. Dilute to 100ml with 0.9% Sodium Chloride	8 mg/kg (max dose 800mg)	If no improvement at 12 hours, repeat with same dose

Option two: Anakinra

Route	Weight	Formulation	Dose	Duration	Comments
SC		100mg in 0.67mL pre-filled syringe	2mg/kg once daily Increase dose by 2mg/kg per day if unresponsive Maximum dose 8mg/kg	Stop if no clinical benefit at maximum dose	

Route	Weight	Formulation	Dose	Duration	Comments
IV	<20 kg	100mg diluted in 0.9% sodium chloride, 24 ml total volume	2mg/kg stat loading dose, followed by a continuous infusion of 0.02ml/kg/hr (2mg/kg/day) Increase by dose by 2mg/kg/day every 12 hours if unresponsive Maximum dose 12mg/kg/day	Stop if no clinical benefit at maximum dose	Maximum dose in 24 hours 400mg (excluding loading dose) Syringe must be changed every 8 hours
IV	>20 kg	100mg diluted in 0.9% sodium chloride, 12 ml total volume	2mg/kg stat loading dose, followed by a continuous infusion of 0.01ml/kg/hr (2mg/kg/day) Increase by dose by 2mg/kg/day every 12 hours if unresponsive Maximum dose 12mg/kg/day	Stop if no clinical benefit at maximum dose	Maximum dose in 24 hours 400mg (excluding loading dose) Syringe must be changed every 8 hours

Clinical trials for COVID-19 and paediatric patients

The RECOVERY trial is enrolling paediatric patients as of 11 May 2020. This study is open at many sites, including district general hospitals, and now including children down to those just born.

If you are considering entering a child to RECOVERY, we suggest you check with your Regional Infectious Disease team as well as watch the relevant video(s) and view the FAQs on the study website. Note there are separate training videos in respect to children and infants of less than 29 days of age.

If you are still uncertain about eligibility, you can contact an "on-call" member of the study team to discuss further, but please only do this if you are particularly uncertain. If you think entry into RECOVERY is indicated, it can take place in the hospital where the child is admitted - you don't have to wait for them to be transferred to a regional centre.

The following interventional clinical trials and national observational studies are active in the

UK for recruitment for hospitalised patients:

- **RECOVERY TRIAL:** UK study, standard of care versus lopinavir / ritonavir vs. interferon-beta-1a vs. dexamethasone vs. hydroxychloroquine. Please note that the trial now allows for secondary randomisation (PDF) and transfer to a tertiary centre - see full guidance for paediatric patients (PDF).
- **REMAP-CAP:** International critical care study, UK sites, expanded to include COVID-19 specific arms for standard of care vs. lopinavir / ritonavir (Kaletra) and standard of care vs. interferon-beta-1a, and interleukin-1 receptor atagonist (Anakinra).
- **ISARIC-CCP:** UK Case Record Forums (CRF) are available for the collection of standardised clinical data on suspected or confirmed cases of COVID-19.

The following interventional clinical trials and national observational studies are emerging or proposed in the UK:

- **DISCOVERY trial:** WHO pan-European, standard of care vs. standard of care + remdesivir vs. standard of care + lopinavir / ritonavir vs. standard of care + lopinavir / ritonavir + interferon-beta-1a.
- Proposal to ameng the **REALIST trial** (acute respiratory distress syndrome) to include patients with COVID-19 / HLH and use of anakinra or tocilizumab.
- **ACTT trial:** remdesivir vs. standard of care.

Discharge

NHS England has guidance on discharge that covers:

- Discharge criteria;
- Stay at home guidance;
- Discharge advice to patients.

An example inpatient discharge leaflet (kindly shared by Airedale Hospitals) can be found in our acute services guidance.

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From Birmingham Children's Hospital: Prasad Nagakumar.

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Appendix A - Aerosol generation from nebulisation - rapid review. 1 April 2020.PDF 490.2 KB