

Management of Opioid Induced Respiratory Depression

Key Points

- This guideline summarises the acute management of patients with opioid toxicity with accompanying respiratory depression.
- It is designed to be used for patients attending the Emergency Department as well as on the wards.
- Flowcharts to guide management are provided for adult patients who are opioid-naïve or known opioid users, and for children 1-11 years old.
- Rapid reversal of opioids is undesirable for patients on long term opioid medication. Naloxone administration should be carefully titrated against respiratory rate, and not conscious level.
- For patients in the last 48 hours of life, naloxone may not be appropriate, and reduction or discontinuation of the regular opioids may be sufficient.
- Naloxone will only reverse the symptoms of opioid overdose and not sedation due to other medications or disease progression.

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Abbreviations

GCS	The Glasgow Coma Scale
IV, IM, SC	Intravenous, intramuscular, subcutaneous
mg, kg	milligram, kilogram
NEWS/PEWS	National Early Warning System / Paediatric Early Warning System

Summary

This guideline describes the use of **naloxone** for the management of opioid toxicity and accompanying opioid induced respiratory depression.

Frimley Park Hospital Palliative Care Team can be contacted on **Bleep 5799 and Extn 136755**, and out of hours advice is available from the duty palliative medicine consultant for FPH, contactable via hospital switchboard.

Wexham Park Hospital Palliative Care Team can be contacted during working hours on **Extn 154879** via WPH switchboard. Out of hours advice is available from the duty palliative medicine consultant for WPH, contactable via hospital switchboard.

Flowcharts for the Management of Opioid Induced Respiratory Depression in the following patients are given at the end of this document:

1. Naloxone use in opioid-naïve **adults and children aged 12 or above**
2. Naloxone use in **adults and children aged 12 or above** who are regular opioid users (both therapeutic and recreational users)
3. Naloxone use in **children 1-11 years old**.

Symptoms and signs of Opioid toxicity

Overdose of opioid agonists causes a number of effects.

- Respiratory depression is the only reliable sign of opioid toxicity.¹
- Accompanying signs can include drowsiness, reduced conscious level, myoclonic jerks and visual hallucinations.²

Opioid Induced Respiratory depression

Respiratory depression occurs at higher doses of opioids than that to achieve the analgesic effect. Therefore, analgesia is not compromised when naloxone administration is titrated to respiratory rate.^{3,4}

In Emergency medicine, a respiration rate (RR) of <10/minute is used as the cut off for naloxone treatment.⁵

In Palliative and End of Life care, RR <8/minute cut off is often used.²

- Oxygen saturations should be measured, and cyanosis excluded.
- Conscious level should be ascertained but should not be used alone when determining if naloxone is appropriate.

Pharmacology of Naloxone

Naloxone is a competitive antagonist at all opioid receptors (mu, delta and kappa).^{3,6-8}

It is short acting and will reverse all actions of opioids, including analgesic effect.^{7,9}

Naloxone can precipitate acute opioid withdrawal.^{10,11}

Routes of administration:^{1,4,8}

- IV, IM, SC
- Intranasal – variable effect and reserved for out of hospital use
- Cannot be given orally due to extensive first-pass metabolism

Onset of Action:^{1,4,8}

- 1-3 minutes when given IV
- Slower by the IM and SC routes – depending on blood pressure

Duration of Action:^{1,4,8}

- 20-90 mins
- Depends on dose of opioid agonist – the higher the opioid dose, the shorter the duration of naloxone
- The duration of action is less than that of all except the shortest acting opioid agonist

Efficacy:^{3,4,8}

- Opioids with high receptor affinity (e.g. fentanyl, buprenorphine) and higher initial doses, will require higher doses of naloxone to reverse effects – a naloxone infusion may be required.

Management of Respiratory Depression

Prior patient use of opioids should, if possible, be determined quickly before deciding on a suitable management pathway.

It should not be assumed that respiratory depression or depressed conscious level is caused by opioid toxicity. Other causes should be also considered (e.g. head injury).¹⁰

Opioid-Naïve patients

- For adult and paediatric patients who are opioid-naïve, priority should be given to reversal of respiratory depression. Precipitation of opioid withdrawal is less of a concern.
- Naloxone will not reverse depressed conscious level caused by other medications such as benzodiazepines.
- For dosing schedule, see 'Antidote – Naloxone' section and Flowchart for Opioid-Naïve patients (below).

Regular opioid users and patients receiving Palliative Care**1. Regular recreational opioid users:**

- a. 0.4mg naloxone is likely to precipitate acute withdrawal symptoms.^{5,8,12,13}
- b. Acute opioid withdrawal is not usually life-threatening, but it can cause agitation with a risk of aggression.
- c. Patients are at risk of self-discharging or causing harm to themselves or to others.
- d. If patients self-discharge soon after naloxone administration, they are at risk of becoming re-narcotised away from medical care due to naloxone's relatively short half-life compared to opioids.
- e. Administration of naloxone should be started at low doses (0.1mg boluses) and titrated as necessary.^{4,13}
- f. Naloxone will not reverse depressed conscious level caused by other medications such as benzodiazepines.
- g. For dosing schedule, see 'Antidote – Naloxone' section and Flowchart for Regular Opioid Users (below).

2. Patients taking long term prescribed opioids:

- a. Higher doses of naloxone will reverse the analgesic effect of the opioid as well as respiratory depression.^{3,4}
- b. This can lead to acute pain crises and agitation in regular therapeutic users.^{11,12}
- c. Re-titration of opioid analgesia can be more difficult following high dose naloxone administration.
- d. Administration of naloxone should be started at low doses (0.1mg boluses) and carefully titrated to respiratory rate, and not to conscious level.^{2,4,13}

- e. Initial bolus doses as low as 0.02mg (20 micrograms) naloxone IV can be considered.^{2,11,14}
- f. Naloxone can be given IM or SC if IV access is not practical or appropriate.²
- g. Naloxone will not reverse depressed conscious level caused by other medications such as benzodiazepines, or by clinical deterioration.
- h. For dosing schedule, see 'Antidote – Naloxone' section and Flowchart for Regular Opioid Users (below).
- i. If immediate life-threatening respiratory depression (minimal or no respiratory effort) treat as per Opioid-Naïve schedule² and provide emergency airway support.

Paediatric patients

- Opioid overdose may be characterised by delayed onset, unexpectedly severe toxicity and prolonged toxic effects.¹
- Children under 3 years who have been exposed to long-acting formulation of opioids or buprenorphine may benefit from 24 hours of monitoring.¹
- Standard Paediatric naloxone bolus dose is 0.1mg/kg IV.^{1,15,16,25}
- Discussion with the Paediatric Team is advised.
- For dosing schedule, see 'Antidote – Naloxone' section and Flowchart for Children 1 – 11 years old (below).

Post-operative patients

- Management mimics that for regular opioid users.¹⁷

Management Pathway

Standard toxicological management involves symptomatic/supportive care, decontamination, enhanced elimination techniques, and antidote use.

- *Symptomatic and Supportive (A-B-C-D-E) Treatment*
 - Place the patient in the recovery position, or onto their back.
 - Administer supplemental oxygen to maintain SaO₂ >95%²
 - Perform bag-valve-mask ventilation if necessary
 - Obtain IV access
- *Decontamination*
 - Look for and remove opioid patches
 - Stop opioid infusion if present
 - Consider gut decontamination with activated charcoal. Refer to Toxbase www.toxbase.org for latest guidance on doses. The Trust log in for Toxbase can be obtained from the Site manager or ED staff.
- *Antidote – Naloxone*²⁵. Naloxone can be prescribed via individual EPIC order or via Overdoses panel.
 - **Opioid-naïve**¹⁷
 - Give initial 0.4mg naloxone IV bolus
 - If no response after 1 min, give 0.8mg naloxone IV boluses for next two doses, at intervals of 1 min
 - If no response after 3 bolus doses, increase to 2mg naloxone IV bolus for 1 dose

- **Regular opioid user**^{1,2,4}
 - If immediate life-threatening respiratory depression (minimal or no respiratory effort) treat as per Opioid-Naïve schedule and provide emergency airway support.
 - Give initial 0.1mg naloxone IV bolus
 - If no response, repeat 0.1mg naloxone bolus IV every 2-3 minutes
 - Titrate naloxone administration to respiratory rate
 - If IV access is not possible/appropriate, naloxone can be given IM/SC
- **Child 1-11 years old**¹⁷
 - Give initial bolus of 0.1mg/kg naloxone IV bolus up to maximum of 2mg.
 - If no response, repeat at intervals of 1 min up to a maximum of 2mg

Following the acute reversal of respiratory depression, consideration should be given to determination and management of the cause of opioid toxicity.

Causes can include:

- Deliberate overdose
- Accidental overdose
- Iatrogenic overdose (which can also occur due to incomplete cross-tolerance following opioid switch)
- Drug accumulation due to long half-life
- Sepsis
- Deterioration in renal or hepatic function
- Drug interactions
- Reduction in analgesic requirement (i.e. post radiotherapy or steroids)

All incidents involving over infusion or iatrogenic accidental overdose should be reported via the Trust incident reporting system.

Monitoring

- After any dose of naloxone, the patient should receive:
 - continuous oxygen saturation monitoring for at least 2 hours
 - ½ hourly monitoring of other NEWS2/PEWS2 parameters for at least 2 hours
 - immediate escalation for clinical review, which includes whether the patient needs a transfer to a higher level of care.
- Patients are likely to need longer monitoring if high initial doses or long-acting preparations of opioids were used.^{1,2,4,18,19}
- Clear documentation in the medical notes of the immediate clinical response to naloxone (changes in RR, conscious level etc.) is essential.
- Recurrent opioid toxicity and repeat doses of naloxone should prompt strong consideration of a naloxone infusion, use of the Trust NEWS2/PEWS2 scoring and escalation to a high dependency care area.
- If re-narcotisation and respiratory depression will recur, it is likely to do so within 2 hours of a response to naloxone, either initial or subsequent boluses.¹⁹

Further assessments

- Consider the need for review by the psychiatric liaison team in the context of a deliberate overdose.

- In addition, make a Safeguarding referral for adults with caring responsibilities (i.e., access to children or vulnerable adults), and for any children presenting with deliberate overdose.

Special considerations

Side effects of naloxone

- Patients should be monitored for signs of opioid withdrawal, which can be precipitated by naloxone.^{8,10}
- Naloxone, especially at higher doses, may precipitate significant catecholamine release, leading to tachycardia, arrhythmia, hypertension, pulmonary oedema, and potentially cardiac arrest, in both adults and children.^{2-4,8,20-22} However, side effects can occur even at low doses.^{2,4} It is currently unclear whether these effects are directly caused by naloxone, or by respiratory depression and its reversal.^{1,2,4,8}
- Pulmonary oedema should be considered if there is persistent hypoxaemia and unexpected breathlessness despite oxygen administration. This should be treated as per acute pulmonary oedema due to cardiac causes.

Long-acting opioids

- Recurrence of respiratory depression is more common with long-acting opioid preparations.¹⁹
- Patients on long-acting preparations are likely to require at least 12-24 hours of observation following presentation of toxicity.²
- Long-acting preparations include:
 - Modified Release Morphine Sulfate and Oxycodone (12-hourly formulations)
 - Modified Release Tramadol and Tapentadol
 - Fentanyl and Buprenorphine patches
 - Methadone

Naloxone infusion

- If a patient has recurrent respiratory depression following the administration of bolus naloxone then an IV naloxone infusion should be considered.^{1,8}
- Long-acting preparations of opioids increase the need for naloxone infusion.
- Recurrence of respiratory depression can occur up to 2 hours following naloxone administration and is more common with long-acting opioid preparations.^{8,19}
- Using an IV infusion pump, adjust rate according to response
- Initial rate may be set at 60% of the initial resuscitative IV injection dose per hour. The initial resuscitative IV injection dose is that which maintained satisfactory ventilation for at least 15 minutes.^{17,23}

End of life care and syringe drivers

- For patients in the terminal phase of their illness (death expected within 48 hours) the use of naloxone and escalation to a high dependency care area is likely to be inappropriate.
- If opioid toxicity occurs any regular opioids or syringe driver should be stopped and the patient observed.
- If naloxone is required, give as per schedule for regular opioid users.
- It is likely that PRN breakthrough doses of analgesia or other medications will be needed as drug levels fall.
- Consider need to restart syringe driver (at lower dose) once respiration rate is satisfactory.

Tramadol

- Naloxone may only partially reverse the effects of tramadol, but evidence is inconclusive.²

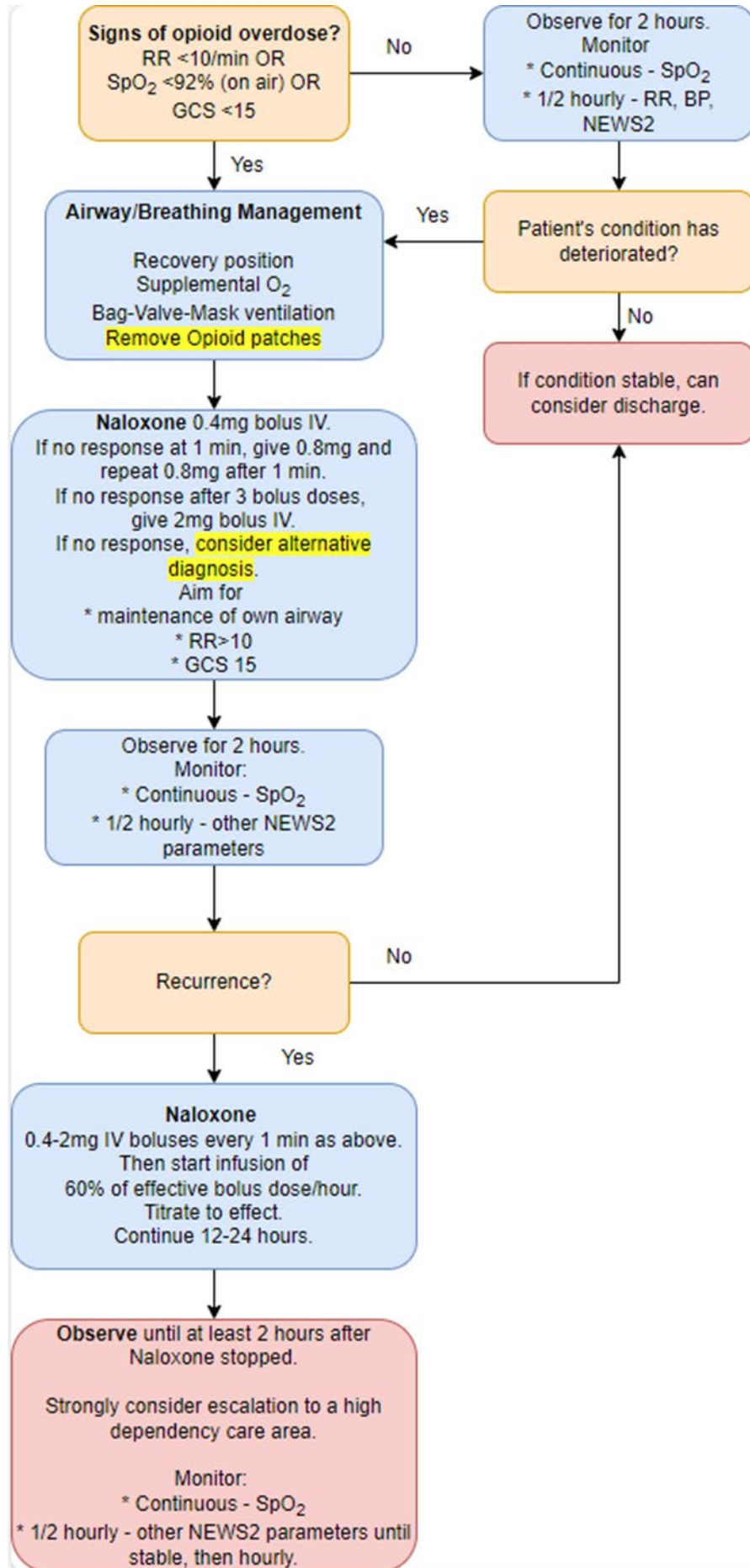
Buprenorphine

- Naloxone will only partially reverse the effects of buprenorphine.⁷
- Reversal of respiratory depression may take significantly longer than with other opioids.^{4,24}
- Buprenorphine induced respiratory depression often requires high doses of naloxone to reverse. The response is bell shaped, with very high doses no longer being effective.^{2-4,24}
- Protocol for Buprenorphine-induced respiratory depression:²
 - Given 2mg IV naloxone stat
 - Commence naloxone infusion 4mg/h IV
 - Continue infusion until respiratory rate is satisfactory
 - Monitor patient for 24 hours and restart naloxone infusion if necessary
- Buprenorphine can be restarted at half the previous dose.

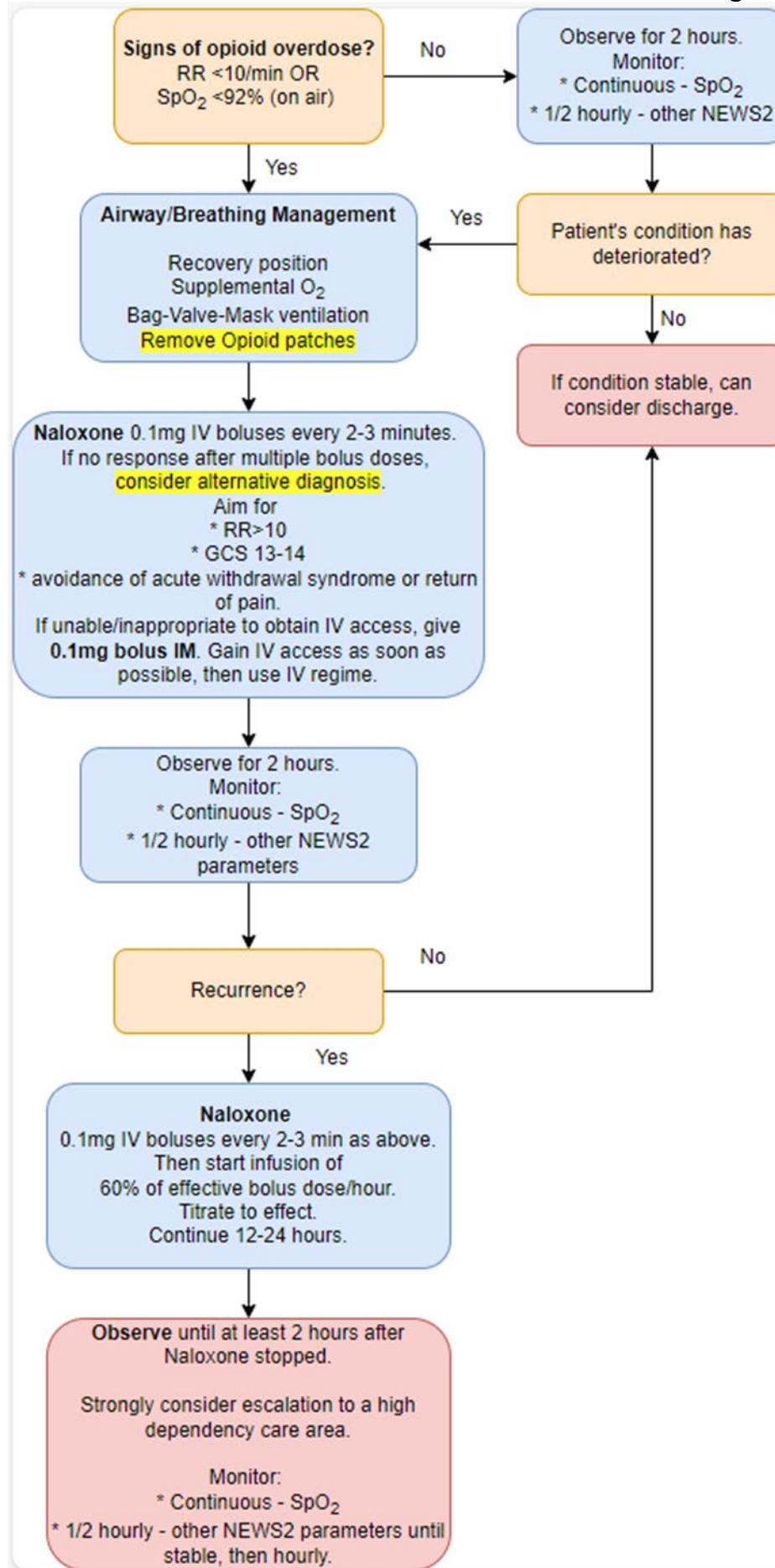
Restarting opioid analgesia

- Opioid analgesia should only be restarted when there is sustained respiratory improvement and should be restarted at a lower dose. Opioid switching can be considered.²

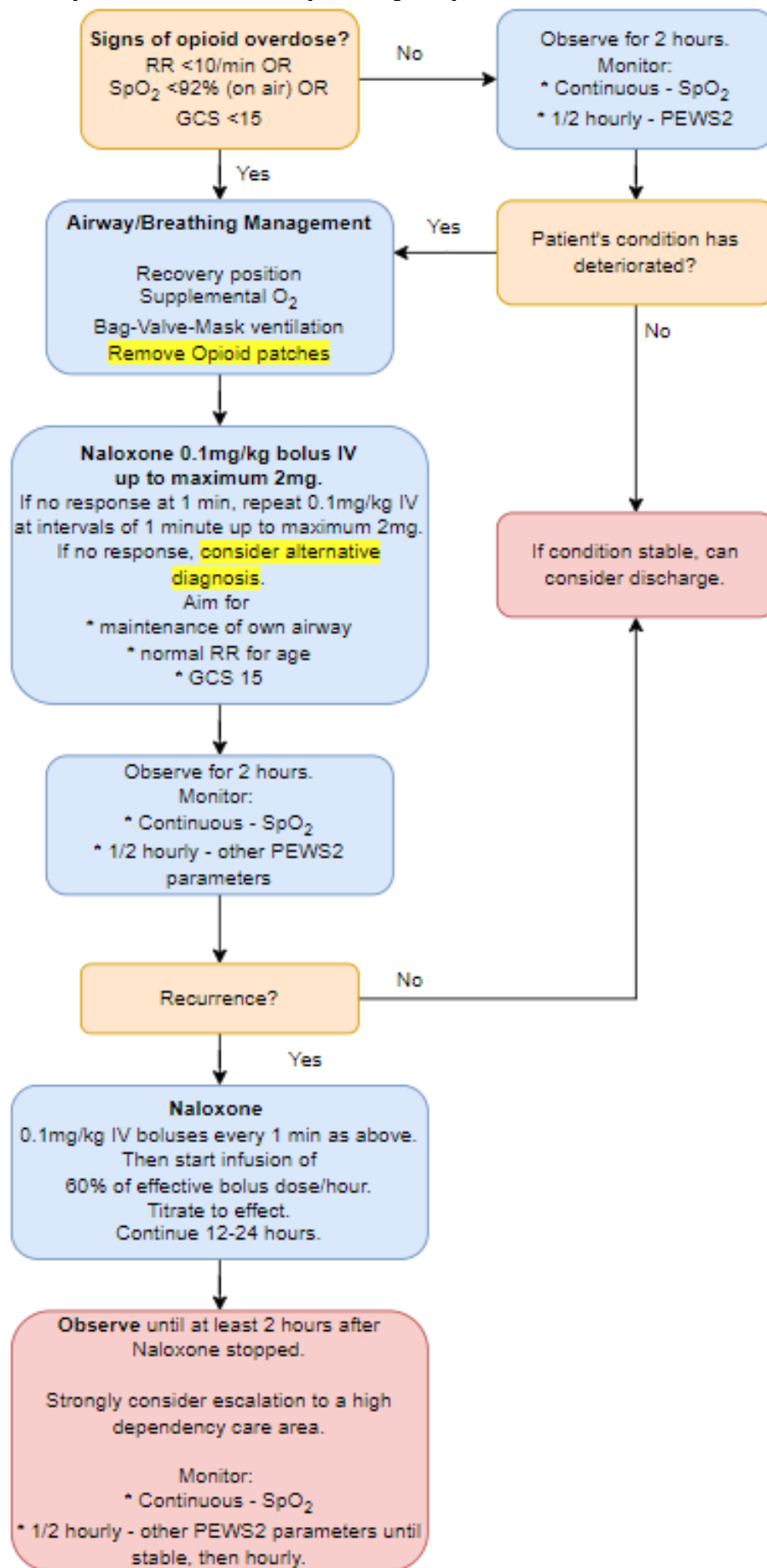
Treatment of Opioid Induced Respiratory Depression in Opioid-Naïve ADULTS AND CHILDREN AGED 12 OR ABOVE



Treatment of Opioid Induced Respiratory Depression in ADULTS AND CHILDREN AGED 12 YEARS OR ABOVE who are Regular Opioid Users



Treatment of Opioid Induced Respiratory Depression in **CHILDREN 1-11 YEARS**



References

1. Boyer EW. Management of Opioid Analgesic Overdose. *N Engl J Med*. 2012;367(2):146-155. doi:10.1056/NEJMr1202561
2. Wilcock A, Howard P, eds. *PCF 8. Palliative Care Formulary, Eight Edition*. The Pharmaceutical Press 2022
3. Dahan A, Aarts L, Smith TW. Incidence, Reversal, and Prevention of Opioid-induced Respiratory Depression. *Anesthesiology*. 2010;112(1):226-238. doi:10.1097/ALN.0b013e3181c38c25
4. Rzasa Lynn R, Galinkin J. Naloxone dosage for opioid reversal: current evidence and clinical implications. *Ther Adv Drug Saf*. 2018;9(1):63-88. doi:10.1177/2042098617744161
5. Clarke SFJ, Dargan PI, Jones AL. Naloxone in opioid poisoning: walking the tightrope. *Emergency Medicine Journal*. 2005;22(9):612-616. doi:10.1136/emj.2003.009613
6. Branford R, Wighton E, Ross J. Principles of drug therapy: focus on opioids. In: Cherny N, Fallon M, Kaasa S, Portenoy R, Currow DC, eds. *Oxford Textbook of Palliative Medicine*. Fifth. Oxford University Press; 2015.
7. Fallon M, Cherny N. Opioid therapy: optimizing analgesic outcomes. In: Cherny N, Fallon M, Kaasa S, Portenoy R, Currow DC, eds. *Oxford Textbook of Palliative Medicine*. Fifth. Oxford University Press; 2015.
8. Clarke S, Török R, Dargan P, Jones A. Emergency Room Use of Opioid Antagonists in Drug Intoxication and Overdose. In: Dean R, Bilsky E, Negus S, eds. *Opiate Receptors and Antagonists: From Bench to Clinic*. Humana Press; 2009.
9. Evans LE, Swainson CP, Roscoe P, Prescott LF. Treatment of drug overdosage with naloxone, a specific narcotic antagonist. *Lancet*. 1973;1(7801):452-455. doi:10.1016/s0140-6736(73)91879-5
10. Buajordet I., Naess A.C., Jacobsen D., Brors O. Adverse events after naloxone treatment of episodes of suspected acute opioid overdose. *Eur J Emerg Med*. 2004;11(1):19-23. doi:10.1097/00063110-200402000-00004
11. Manfredi P.L., Ribeiro S., Chandler S.W., Payne R. Inappropriate use of naloxone in cancer patients with pain. *J PAIN SYMPTOM MANAGE*. 1996;11(2):131-134. doi:10.1016/0885-3924(96)00150-6
12. Pursell R., Godwin J., Moe J., et al. Comparison of rates of opioid withdrawal symptoms and reversal of opioid toxicity in patients treated with two naloxone dosing regimens: a retrospective cohort study. *Clin Toxicol*. 2020;((Pursell, Godwin, Moe, Kestler, DeWitt, Scheuermeyer, Erdelyi, Rowe, Cochrane, Ng, Jiang, Ho, Brubacher) Department of Emergency Medicine, University of British Columbia, Vancouver, Canada). doi:10.1080/15563650.2020.1758325
13. Williams R.H., Erickson T. Emergency diagnosis of opioid intoxication. *Lab Med*. 2000;31(6):334-342. doi:10.1309/QY8T-KGBN-BVA6-H706

14. Connors NJ, Nelson LS. The Evolution of Recommended Naloxone Dosing for Opioid Overdose by Medical Specialty. *J Med Toxicol*. 2016;12(3):276-281. doi:10.1007/s13181-016-0559-3
15. Sesso A.M., Rodzvilla J.P. Naloxone therapy in a seven month old with methadone poisoning. *CLIN PEDIATR*. 1975;14(4):388-389.
16. McCulloch R, Collins J. Paediatric pain control. In: Cherny N, Fallon M, Kaasa S, Portenoy R, Currow DC, eds. *Oxford Textbook of Palliative Medicine*. Fifth. Oxford University Press; 2015.
17. NICE-The National Institute for Health and Care Excellence. BNF/BNFc: British National Formulary - NALOXONE HYDROCHLORIDE. Last accessed 3/12/24. <https://bnf.nice.org.uk/drug/naloxone-hydrochloride.html>
18. Willman M.W., Liss D.B., Schwarz E.S., Mullins M.E. Do heroin overdose patients require observation after receiving naloxone? *Clin Toxicol*. 2017;55(2):81-87. doi:10.1080/15563650.2016.1253846
19. Watson W.A., Steele M.T., Muelleman R.L., Rush M.D. Opioid toxicity recurrence after an initial response to naloxone. *J Toxicol Clin Toxicol*. 1998;36(1-2):11-17. doi:10.3109/15563659809162577
20. Litell J., Arens A., Love S., Spindler C., Cole J. Extracorporeal membrane oxygenation for cardiopulmonary failure following fentanyl analogue overdose treated with high-dose naloxone. *Clin Toxicol*. 2018;56(10):1009-1010. doi:10.1080/15563650.2018.1506610
21. Deshpande G., Gill A. Cardiac arrest following naloxone in an extremely preterm neonate. *Eur J Pediatr*. 2009;168(1):115-117. doi:10.1007/s00431-008-0720-3
22. Farkas A., Lynch M., Westover R., et al. Pulmonary complications of opioid overdose treated with naloxone. *J Med Toxicol*. 2018;14(1):11. doi:10.1007/s13181-018-0655-7
23. Goldfrank L, Weisman RS, Errick JK, Lo MW. A dosing nomogram for continuous infusion intravenous naloxone. *Ann Emerg Med*. 1986;15(5):566-570. doi:10.1016/s0196-0644(86)80994-5
24. Gal TJ. Naloxone reversal of buprenorphine-induced respiratory depression. *Clin Pharmacol Ther*. 1989;45(1):66-71. doi:10.1038/clpt.1989.10
25. Toxbase. <https://www.toxbase.org/>

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This guideline has been registered with the Trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt, contact a senior colleague or expert. Caution is advised when using guidelines after the review date.

This guideline is for use in Frimley Health NHS Foundation Trust hospitals only. Any use outside this location will not be supported by the Trust and will be at the risk of the individual using it.

Version History

Version	Date	Guideline Lead	Status	Comments
1	Oct 2021	Consultant in Palliative Medicine	Final	Amalgamation and expansion on two previous Guidelines. FPH Management of Opioid Overdose. WPH Management of Parenteral Opioid Induced Respiratory Depression in Adult Palliative Care Patients.
2	Dec 2024	Dr Beata LeBon - Consultant in Palliative Medicine	Final	

Related Documents

None