1. Introduction

This guideline is to be used in the management of adult patients admitted to UHL who, in line with the recommended assessment and management, require an intravenous aminophylline infusion to manage a LIFE-THREATENING or NEAR-FATAL asthma exacerbation or for an ACUTE exacerbation of Chronic Obstructive Lung Disease (COPD) as an adjunct where there is an inadequate response to nebulised bronchodilators.

For most people with acute severe asthma intravenous aminophylline is not likely to result in any additional bronchodilation compared with standard care with inhaled bronchodilators and steroids. Some patients with life-threatening asthma or those with a poor response to initial therapy may gain additional benefit from intravenous aminophylline, although the evidence base is weak.

Before using intravenous aminophylline for an exacerbation of COPD please consider whether the patient is suitable for Non Invasive Ventilation (For example patients with hypercapnic respiratory failure and a pH <7.35). Please discuss use of intravenous aminophylline with a Respiratory Consultant or SpR as potential side effects may outweigh benefits and evidence of benefit in COPD is weak.

Aminophylline is a xanthine derivative and is used in the treatment of asthma and COPD as it relaxes the bronchial smooth muscle causing bronchodilation.

Aminophylline is a complex of theophylline with ethylenediamine and therefore aminophylline generally behaves like theophylline.

Theophylline is metabolised by cytochrome P450 isoenzymes in the liver, principally by CYP1A2. Many drugs interact with theophylline by inhibition or potentiation of its metabolism. In addition, the metabolism of theophylline is affected by gender, smoking, liver and cardiac disease, viral infections, pregnancy and genetic differences in CYP1A2 function. These factors must be taken into account when prescribing xanthines.

2. Scope

This guideline applies to all adult patients with acute severe life-threatening or near-fatal asthma not responding to treatment with bronchodilators, steroids and magnesium as appropriate, according to BTS/SIGN Asthma guidelines OR for acute exacerbation of COPD as an adjunct to the management of exacerbations where there is an inadequate response to nebulised bronchodilators and who have been assessed by a senior specialist clinician (Specialist Registrar (SpR) or Consultant) as requiring intravenous aminophylline.

It is intended for use by any member of the Multidisciplinary Team (MDT) treating these patients. Discuss with a pharmacist for any advice needed.

See Appendix 1 for Aminophylline Intravenous Short Prescribing Guideline and Intravenous Infusion Prescribing and Administration Record.

3. Recommendations, Standards and Procedural Statements

Clinical management:

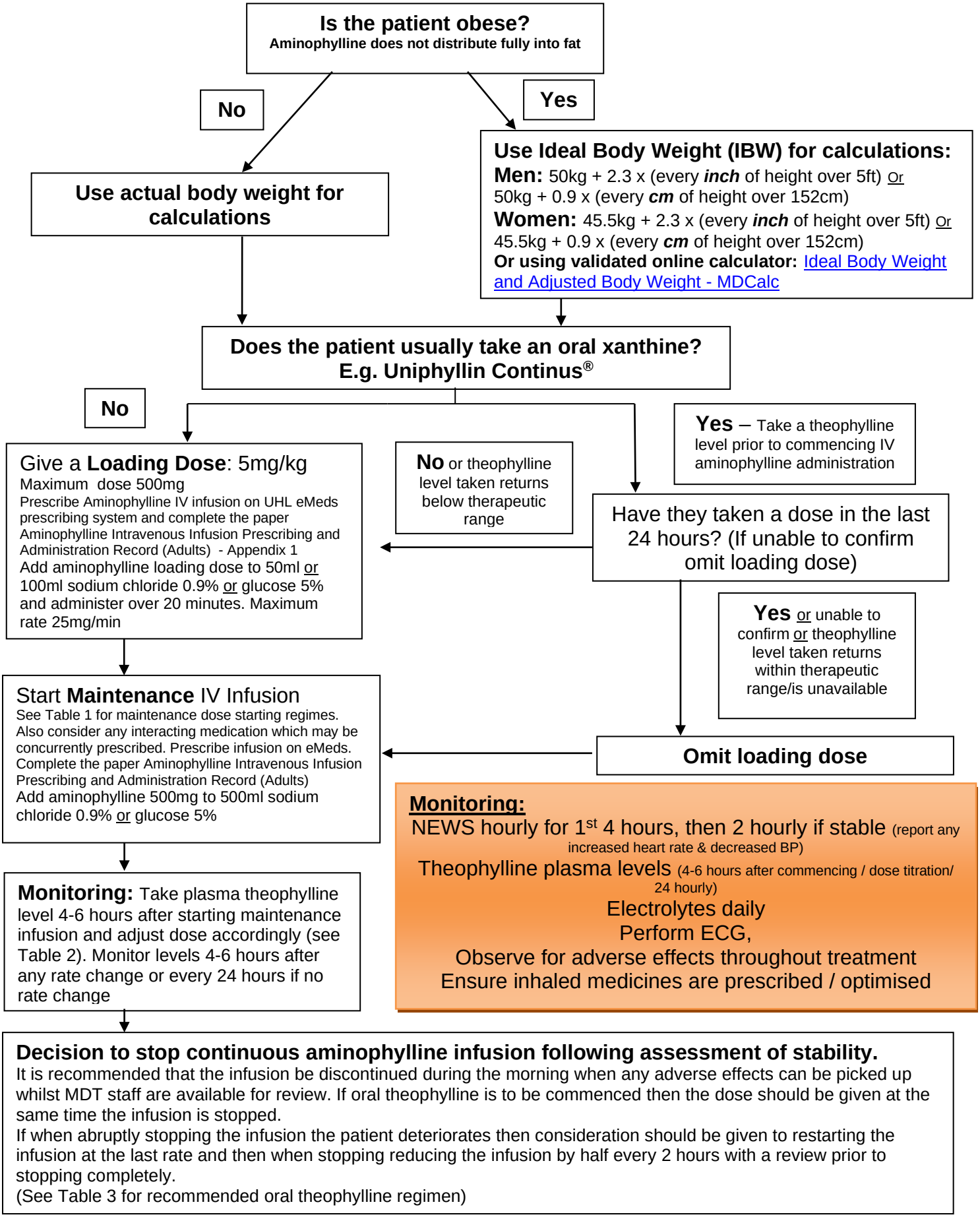

Table 1: Aminophylline Maintenance Infusion Starting Regimen

Patient	Dosing regimen
Non-smoking adult	0.5mg/kg/hr
Older patient (age >55) or those with cor pulmonale	0.3mg/kg/hr
Congestive cardiac failure (CCF) or hepatic disease	0.2mg/kg/hr
Smoking younger adult	0.8mg/kg/hr

A full list of drug interactions can be found in the BNF (https://www.medicinescomplete.com/#/content/bnf/_986714576_interactions) or eMC (https://www.medicines.org.uk/emc/product/6560/smpc)

Patient weight (kg) **Use ideal body weight (IBW) for obese patients**	**Initial maintenance infusion rate (mL/hr)** **Aminophylline 500mg in 500ml**			
	Non-smoking adult **Dose: 0.5mg/kg/hr**	**Age >55 years or those with cor pulmonale** **Dose: 0.3mg/kg/hr**	**CCF or hepatic disease** **Dose: 0.2mg/kg/hr**	**Smoking younger adult** **Dose: 0.8mg/kg/hr**
40 kg	20	12	8	32
45kg	22.5	13.5	9	36
50kg	25	15	10	40
55kg	27.5	16.5	11	44
60kg	30	18	12	48
65kg	32.5	19.5	13	52
70kg	35	21	14	56
75kg	37.5	22.5	15	60
80kg	40	24	16	64
85kg	42.5	25.5	17	68
90kg	45	27	18	72
95kg	47.5	28.5	19	76
100kg	50	30	20	80

PRESCRIBING

Loading dose (if required) to be prescribed on UHL eMeds prescribing system and paper chart. Maintenance infusion to be prescribed on UHL eMeds prescribing system for record of administration AND dose/rate prescribed and adjusted on the paper Intravenous Infusion Prescribing and Administration Record (Adult) as contained in Appendix 1.

MONITORING

As aminophylline is a salt of theophylline, levels measured are theophylline levels. Theophylline has a narrow therapeutic range and small increases in serum concentrations can result in toxicity. In most individuals, a plasma-theophylline concentration of 10–20 mg/L is required for satisfactory bronchodilation, although a lower plasma-theophylline concentration of 5–15 mg/L may be effective.

In the therapeutic range, theophylline metabolism exhibits first order kinetics so that the dose is proportional to the serum levels achieved. At higher serum theophylline levels, metabolism can become saturated and small increases in dose can cause disproportionately large increases in serum concentrations. Because of this and the multitude of factors that determine serum theophylline levels, the table below is a guide only. For specific advice please discuss with your Ward Pharmacist, the Medicines Information Service or the On-call Pharmacist.

Monitoring of levels is **essential** during intravenous aminophylline therapy.

- Check plasma theophylline level within 4-6 hours of starting maintenance infusion
- Re-check plasma theophylline level after any dose adjustment, within 4-6 hours
- Check plasma theophylline level every 24 hours, even if no adjustments are made.

Table 2: Intravenous Aminophylline Infusion Dose Titration Guidance

Theophylline level (mg/L)	Symptoms and dose tolerance	Action
<9.9	**Not controlled** Current dosage tolerated (Note: some patients may get benefit from sub-therapeutic levels.)	INCREASE rate by 25% if still symptomatic
10-14.9	**Controlled** Current dosage tolerated	Maintain rate of infusion
15-19.9	**Controlled** Current dose is tolerated	DECREASE rate by 10% to provide a greater margin of safety even if current dosage is tolerated. Note: For patients on ICU at the discretion of the treating clinician the rate may be continued with close monitoring.
20-24.9	High level Signs of toxicity may be absent	Stop infusion Recheck level after a minimum of 6 hours. If restarting ensure level <15mg/L and DECREASE rate by at least 25%
>25	High level	Stop infusion for 24 hours. Consider if overdose treatment required. If restarting check level <15mg/L and DECREASE rate by at least 50%

TOXICITY

Theophylline toxicity results from adenosine antagonism and catecholamine release causing sympathomimetic effects. Theophylline is metabolised by the cytochrome P450 enzymes CYP1A2, CYP2E1 and CYP 3A3.

As aminophylline is a salt of theophylline, levels measured are theophylline levels. Theophylline has a narrow therapeutic range and small increases in serum concentrations can result in toxicity.

Symptoms of serious toxicity such as seizures and arrhythmias can occur even without preceding symptoms of toxicity. Coma may develop in very severe cases.

Signs of toxicity: (theophylline concentration > 20 mg/L but note some patients may experience signs of toxicity at lower concentrations than this) (This list is not exhaustive- refer to BNF or discuss with ward pharmacist) include:

- Nausea, vomiting (which may be severe and resistant to standard antiemetics), dizziness, headache, insomnia, tachycardia, tremor, agitation, restlessness, confusion, hallucinations, hypotension, diarrhoea, gastric irritation, palpitation.
- Metabolic features include: Hypokalaemia, hyperglycaemia, hypophosphataemia, hypomagnesaemia, hypercalcaemia
- Metabolic acidosis and respiratory alkalosis may be seen
- Complications include: Supraventricular and ventricular tachycardia (electrolyte disturbance may increase the likelihood of arrhythmias developing), hyperthermia, rhabdomylosis and renal failure.

Treatment of toxicity is supportive. Clinical features rather than theophylline concentration are the best guide for treatment.

It is important to:

- Perform 12-lead ECG and check cardiac rhythm, QT interval and QRS duration.
- Check U&Es, FBC, calcium, magnesium, phosphate, blood glucose, arterial or venous blood gases.
- Restoration of fluid and electrolytes balance as necessary. Correct any hypokalaemia. Hypomagnesaemia may occur with severe hypokalaemia and should also be corrected.
- Repeated oral administration of activated charcoal enhances the elimination of theophylline from the body even after intravenous administration. Aggressive antiemetic therapy may be required to allow administration and retention of activated charcoal. (seek specialist advice)
- Seek specialist advice for the management of serious side effects such as cardiac arrhythmias and seizures.
- In general, theophylline is metabolised rapidly and haemodialysis is not warranted. In patients with congestive cardiac failure or liver disease, haemodialysis may increase theophylline clearance by as much as 2-fold. (Seek specialist advice)

For specific advice on the management of toxicity please contact your Ward Pharmacist, the Medicines Information Service or the On-Call Pharmacist for advice.

Table 3: Recommended Oral Theophylline Regime

Note: Not all patients requiring intravenous aminophylline need to be commenced on long term oral xanthine. The decision to initiate **NEW** long term oral xanthine should be made by a senior clinician (Registrar or Consultant).

When converting from aminophylline to oral theophylline, a conversion factor is necessary. Aminophylline contains 80% theophylline, therefore the conversion factor = 0.8

If oral theophylline is to be commenced then the dose should be given at the same time the infusion is stopped.

Example:

Aminophylline infusion rate 30mL/hr=30mg/hr

Total daily aminophylline dose = 720mg

Therefore daily dose of theophylline = 720 x 0.8 = 576mg

Prescribe the nearest practical dose = Uniphyllin Continus® 300mg BD

Hourly IV Aminophylline Dose (mg/hr)	Recommended Oral Theophylline Regimen (ensure 12 hourly dosing interval)
18 - 23	Uniphyllin Continus® 200mg BD
24 - 29	Uniphyllin Continus® 300mg OM & 200mg ON
30 - 35	Uniphyllin Continus® 300mg BD
36 – 40	Uniphyllin Continus® 400mg OM & 300mg ON
>41	Uniphyllin Continus® 400mg BD

If oral theophylline commenced: Re-check plasma theophylline level after 3 days (4-6 hours post morning dose)

Note: Consider patients smoking history and any quit attempts.

For patients who have difficulty swallowing or with enteral feeding tubes there are anecdotal reports of using aminophylline injection enterally. For specific advice please discuss with your Ward Pharmacist, the Medicines Information Service or the On-call pharmacist.

4. Education and Training

None

5. Monitoring and Audit Criteria

Key Performance Indicator	Method of Assessment	Frequency	Lead
100% correct Aminophylline prescribing and monitoring	Audit	Annually	Respiratory Prescribing Group (RPG)

6. Supporting Documents and Key References

1. SIGN 158 British Guideline on the Management of Asthma. Revised edition published 2019. Accessed from www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma/

2. National Institute for Health and Clinical Excellence (NICE). Chronic obstructive pulmonary disease in over 16s: diagnosis and management. Accessed from www.nice.org.uk/guidance/ng115

3. Aminophylline Injection BP - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

4. Aminophylline (toxbase.org)

7. Key Words

Aminophylline

Asthma

COPD

This line signifies the end of the document

This table is used to track the development and approval and dissemination of the document and any changes made on revised / reviewed versions

DEVELOPMENT AND APPROVAL RECORD FOR THIS DOCUMENT		
Author / Lead Officer:	Joanne Priestley	**Job Title:** Advanced Specialist Pharmacist
Reviewed by:	Respiratory Prescribing Group	
Approved by:	**Policy and Guideline Committee**	**Date Approved: 17.5.24**

REVIEW RECORD			
Date	**Issue Number**	**Reviewed By**	**Description Of Changes (If Any)**

DISTRIBUTION RECORD:			
Date	**Name**	**Dept**	**Received**

Appendix 1: Adult Intravenous Aminophylline Short Prescribing Guideline

Adult Intravenous Aminophylline SHORT Prescribing Guideline

Please refer to FULL guideline for further details

Aminophylline is a xanthine and a pro-drug of Theophylline. Theophylline is a bronchial smooth muscle relaxant causing bronchodilation.

Indication	Intravenous Aminophylline may be used for: 1) LIFE-THREATENING or NEAR FATAL asthma exacerbation 2) ACUTE exacerbation of COPD Who have been assessed by a senior specialist clinician (Specialist Registrar or Consultant) as requiring IV aminophylline for the treatment of severe airway obstruction and/or respiratory failure due to Asthma/COPD
Check the Medication History	For patients who usually take an oral xanthine daily (e.g. Uniphyllin Continus®) Check the serum theophylline level on admission. Omit the loading dose if level within range (or if level unavailable at point of prescribing omit loading dose if patient has taken a dose in the last 24 hours or if unable to confirm)
For Obese Patients use IBW for Dosing	**Use Ideal Body Weight (IBW) for calculations (Devine Formula):** **IBW (kg)Men = 50 + 2.3 x (every inch of height over 5ft) Or = 50 + (0.9 x every cm of height over 152cm)** **IBW (kg) Women = 45.5 +(2.3 x every inch of height over 5ft) Or = 45.5 + (0.9 x every cm of height over 152cm)**
Major Factors Influencing Serum Levels	Hepatic impairment, congestive cardiac failure, Cor Pulmonale, smoker, older patients. Interacting medicines e.g. antibacterials (azithromycin, ciprofloxacin, clarithromycin, erythromycin, isoniazid, rifampicin), antifungals (fluconazole, ketoconazole), fluvoxamine, carbamazepine, cimetidine, phenytoin, oral contraceptives This list is not exhaustive – Refer to BNF or Ward Pharmacist for further information
Loading Dose (if required)	**Loading Dose**: 5mg/kg Maximum dose 500mg. If acute adverse effects occur, slow the rate or stop the infusion for 5-10 minutes
Maintenance Dose	**Non-smoking adult:** 0.5mg/kg/hr **Older patient (Age >55) or those with cor pulmonale:** 0.3mg/kg/hr **Congestive cardiac failure or hepatic disease**: 0.2mg/kg/hr **Smoking younger adult:** 0.8mg/kg/hr
Administration	**LOADING DOSE:** Add aminophylline loading dose to 50ml or 100ml sodium chloride 0.9% or glucose 5% and administer over 20 minutes. Maximum dose 500mg; Maximum rate 25mg/min **MAINTENANCE INFUSION:** Add aminophylline 500mg to 500ml sodium chloride 0.9% or glucose 5% and administer at prescribed rate as per Intravenous Infusion Prescribing and Administration Record. Expiry once diluted: 24 hours
Monitoring	NEWS hourly for 1st 4 hours, then 2 hourly if stable (report any increased heart rate & decreased BP) **Theophylline plasma levels**: 4-6 hours after commencing infusion / dose titration; Electrolytes daily Perform ECG and Observe for adverse effects throughout treatment
Adverse Effects	Hypotension, arrhythmias, and convulsions especially if given rapidly. Hypersensitivity reactions (including skin reactions), nausea, vomiting, dizziness, headache, CNS stimulation, insomnia, diarrhoea, gastric irritation, tachycardia, palpitation This list is not exhaustive – Refer to BNF or Ward Pharmacist for a full list of adverse effects
Therapeutic Drug Monitoring (TDM)	In most individuals, a plasma-theophylline concentration of 10–20 mg/L is required for satisfactory bronchodilation, although a lower plasma-theophylline concentration of 5–15 mg/L may be effective. **Please refer to the full guideline Table 2 for Aminophylline Infusion dose titration guidance**

<table>
<tr><td>Patient details (use addressograph if available)</td><td rowspan="3"><h1>AMINOPHYLLINE</h1>Intravenous Infusion Prescribing and Administration Record (Adult)
Also prescribe on eMeds or paper prescription chart where eMeds not available</td><td colspan="2">University Hospitals of Leicester NHS
NHS Trust</td></tr>
<tr><td>Hospital number:</td><td>Ward:</td><td>Hospital:</td></tr>
<tr><td>First Name:</td><td colspan="2"></td></tr>
<tr><td>Surname:</td><td rowspan="2">Record NEWS hourly for 4 hours then if stable reduce to 2 hourly
Check allergy status on main prescription chart</td><td colspan="2">Consultant:</td></tr>
<tr><td>DOB:</td><td>Weight (kg):</td><td>IBW (kg):</td></tr>
</table>

Aminophylline infusion should only be prescribed following discussion with a senior specialist clinician (Specialist Registrar or Consultant)

<table>
<tr><td colspan="4">LOADING DOSE: 5mg/kg over 20 minutes (Use IBW if obese; Maximum dose 500mg; Maximum rate 25mg/min)</td><td colspan="3">No loading dose if taking oral theophylline (or unable to confirm) on admission</td><td colspan="4">ADMINISTRATION RECORD</td></tr>
<tr><td>Date</td><td>Aminophylline</td><td>mg</td><td colspan="2">In 50ml or 100ml Sodium Chloride 0.9% / Glucose 5% (circle as appropriate)</td><td>Sign
Print</td><td>Pharm</td><td>Batch No</td><td>Sign
Witness</td><td>Start time</td><td>Stop time</td></tr>
<tr><td colspan="7">MAINTENANCE DOSE: To start immediately after loading dose (if loading dose has been prescribed)</td><td colspan="4">ADMINISTRATION RECORD</td></tr>
<tr><td>Date</td><td>Aminophylline 500mg in 500ml</td><td>Sodium chloride 0.9% / Glucose 5% (circle as appropriate)</td><td>Dose
(mg/kg/hr)</td><td>Rate
(mL/hr)</td><td>Sign
Print</td><td>Pharm</td><td>Batch No.</td><td>Sign
Witness</td><td>Start time</td><td>Stop time</td></tr>
<tr><td colspan="4">Theophylline level</td><td colspan="4">Date and time taken:</td><td colspan="2">Level:</td><td>mg/L</td></tr>
<tr><td>Date</td><td>Aminophylline 500mg in 500ml</td><td>Sodium chloride 0.9% / Glucose 5% (circle as appropriate)</td><td>Dose
(mg/kg/hr)</td><td>Rate
(mL/hr)</td><td>Sign
Print</td><td>Pharm</td><td>Batch No.</td><td>Sign
Witness</td><td>Start time</td><td>Stop time</td></tr>
<tr><td colspan="4">Theophylline level</td><td colspan="4">Date and time taken:</td><td colspan="2">Level:</td><td>mg/L</td></tr>
<tr><td>Date</td><td>Aminophylline 500mg in 500ml</td><td>Sodium chloride 0.9% / Glucose 5% (circle as appropriate)</td><td>Dose
(mg/kg/hr)</td><td>Rate
(mL/hr)</td><td>Sign
Print</td><td>Pharm</td><td>Batch No.</td><td>Sign
Witness</td><td>Start time</td><td>Stop time</td></tr>
<tr><td colspan="4">Theophylline level</td><td colspan="4">Date and time taken:</td><td colspan="2">Level:</td><td>mg/L</td></tr>
</table>

AMINOPHYLLINE

(prescription continuation)

Intravenous Infusion Prescribing and Administration Record (Adult)

Also prescribe on eMeds or paper prescription chart where eMeds not available

University Hospitals of Leicester NHS Trust

Patient details (use addressograph if available)	
Hospital number:	
First Name:	
Surname:	
DOB:	
Ward:	**Hospital:**
Consultant:	
Weight (kg):	**IBW (kg):**

Record NEWS hourly for 4 hours then if stable reduce to 2 hourly

Check allergy status on main prescription chart

Theophylline level				**Date and time taken:**				**Level:**		**mg/L**
Date	Aminophylline 500mg in 500ml	Sodium chloride 0.9% / Glucose 5% (circle as appropriate)	Dose (mg/kg/hr)	Rate (mL/hr)	Sign / Print	Pharm	Batch No.	Sign / Witness	Start time	Stop time
Theophylline level				**Date and time taken:**				**Level:**		**mg/L**
Date	Aminophylline 500mg in 500ml	Sodium chloride 0.9% / Glucose 5% (circle as appropriate)	Dose (mg/kg/hr)	Rate (mL/hr)	Sign / Print	Pharm	Batch No.	Sign / Witness	Start time	Stop time
Theophylline level				**Date and time taken:**				**Level:**		**mg/L**
Date	Aminophylline 500mg in 500ml	Sodium chloride 0.9% / Glucose 5% (circle as appropriate)	Dose (mg/kg/hr)	Rate (mL/hr)	Sign / Print	Pharm	Batch No.	Sign / Witness	Start time	Stop time
Theophylline level				**Date and time taken:**				**Level:**		**mg/L**
Date	Aminophylline 500mg in 500ml	Sodium chloride 0.9% / Glucose 5% (circle as appropriate)	Dose (mg/kg/hr)	Rate (mL/hr)	Sign / Print	Pharm	Batch No.	Sign / Witness	Start time	Stop time
Theophylline level				**Date and time taken:**				**Level:**		**mg/L**