THE NORTHERN HOSPITAL

N-ACETYLCYSTEINE (NAC)

"Saint Catherine of Alexandria", oil on canvas, 1598, Michelangelo Merisi da Caravaggio. (Thyssen-Bornemiza Collection, Madrid).

Caravaggio had arrived here in 1593, and had been promptly told what he was supposed to do if he was ever to become a great artist.

First, draw old sculpture. Plenty of that lying around.

Second, take yourself after the old masters, Raphael perhaps.

Be humbled. Copy. And learn.

What you get at the end of it all was the point of art, an idea of perfect form and ideal beauty.

If you could make those celestial mysteries visible using your own brushes, then you'd be ready to convey that vision of perfection where it counted, in the War for Souls.

Oh yeah? Caravaggio didn't think so.

Visions of paradise? Who the hell knew about that?

What he knew was right in front of his nose, down here on Earth, in the studio, the here and now - that would be the point of his art.

Drawing - who needed it?

Caravaggio never drew a thing in his life.

He just looked. Eyeballed. Then he'd paint.

When someone asked him what he was going to do for models he pointed at the street,

"Them", he said, and he brought THEM into his studio…

The theater of cruelty was everywhere in Rome; not just decapitations, but public burnings of heretics, such as Giordano Bruno, and the grim weekly display of felons hanging from gibbets. Caravaggio was close to this violence. Now he was officially part of the cardinal's household he could carry a sword, or rather have a boy servant carry it for him. This didn't prevent the police from trying to arrest him for wearing a weapon without a license, provoking from Caravaggio a rather grand statement of his rights as a member of del Monte's retinue.

He was leading two lives, and they were not always kept strictly apart. On the one hand he was the privileged, famously gifted painter of the Cardinal, doing ceiling paintings for his suburban villa and much sought after by other Roman grandees. But he was also the unpredictable, sword carrying, dagger-wielding eccentric with the hair trigger temper. When his brother Giovanni Battista came to the Palazzo Madama to seek him out hoping, (the innocent), to encourage him to marry and have children, the painter flatly denied having a brother at all! Bewildered and, presumably, hurt by this repudiation, Giovanni Battista left without ever setting eyes on him. Then there was the company he kept;

whores and courtesans such as Fillide Melandroni and her Sienese friend Anna Bianchini, both often cited by the law for violent assaults. Despite the fact that there had been specific church bans on the painting of women of ill repute, especially in sacred history paintings, Caravaggio repeatedly and lovingly used them as models. The whole power of his art, after all, turned on his utter determination to give physical presence to what had previously been wan stereotypes.

So while shocked critics complained that a Magdalene was nothing more than a working girl drying her long hair, for Caravaggio that was precisely the point - especially since the learned would have remembered that in her reborn life, Mary Magdalene had used her hair to dry the feet of the exhausted Christ in the house of the Pharisee. To have Fillide, the most scandalous teenage courtesan in the city, pose for a painting of Mary Magdalene, the orange blossom of her conversion held against her provocatively low and sumptuous décolletage, would not have been just an act of defiant nose-thumbing at the scruples of the Church. Caravaggio was using the palpable presence of the worldly woman to make the force of her conversion even more dramatic. A make-up pot and comb lie discarded on the table, and the convex mirror remains dark, save for a square patch of brilliant reflective light - the light that makes Caravaggio's art possible and gives hope of a redeemed life to the sinner.

Caravaggio might have won an argument with the frowning fathers about posing a courtesan as the Magdalene, but it was even more outrageous to use Fillide as the sainted Catherine of Alexandria, 1598, beside the spiked wheel of her martyrdom her index finger toying with the edge of what must have been Caravaggio's own dueling rapier. It was the complete opposite of the customary image of the saint as pallid, angelic virgin. She exudes power, even danger. This Catherine's eyes glitter as sharply as the weapon. But, if pressed, Caravaggio could turn any suspicion of indecency back on the obtuseness of the questioners. Why were the saint's throat and neck so conspicuously bare? To remind worshippers of her beheading, naturally! Why was she clad in the sumptuous velvet and embroidered damask that seemed more likely to be the kind of dress in which Fillide received her high-born Florentine lover and protector, Giulio Strozzi? Remember that Catherine was a princess, the picture of resolute calm, not of eye-rolling terror - someone, in other words, to reckon with!

Whatever mutterings there may have been about the liberties that Caravaggio took, del Monte at any rate ignored them, knowing that his star painter was in the process of creating an entirely new kind of Christian art: more palpably dramatic and emotionally direct than anything that had been produced since Michelangelo.

Simon Schama, "The Power of Art", BBC Books, 2006.

In matters of great works of religious art, the Church most severely frowned upon "low born" models depicting the saints. But that was before Caravaggio. To create a realistic and powerful vision, realistic and powerful personalities were needed. Scandalously he used the teenaged "courtesans" Fillide Melandroni and her Sienese friend Anna Bianchini, both often cited by the law for violent assaults, as models for some of Italy's, most revered saints. His Saint Catherine was like no other that had gone before. She has the look of defiance, and a very strong will. She fingers the rapier (probably

Caravaggio's own) as if to say, "come any closer and I'll use it, go on just try!" The people were stunned and mesmerized by the work. They knew who the girl was and the reputation that she had - but this only made the work even more notorious - more titillating - more sensational - more irresistibly compelling. All of Rome wanted to see it. Cardinal del Monte ignored the muted mutterings of scandal; he most definitely knew a winner when he saw one!

Using scandalous courtesans as models for saints was an absolute contraindication before Caravaggio. But the grandee Cardinals grudgingly relented when his "Saint Catherine" was widely acclaimed and much admired. It seemed new rules were in play - notorious courtesans were now a... "relative"... contraindication in great Art.

The agent N-acetylcysteine is the specific life-saving antidote for paracetamol toxicity. Drugs are contraindicated when they are not required. But in some situations such as the delayed presentation of a significant paracetamol overdose over 8 hours before, then we play a most dangerous game by awaiting confirmatory blood test results. Instead we must take the Caravaggio approach - to hell with the "rules"! - NAC is immediately commenced!

"Saint Catherine of Alexandria" (Detail), oil on canvas, 1598, Michelangelo Merisi da Caravaggio.

N-ACETYLCYSTEINE (NAC)

Introduction

N-acetylcysteine (**NAC**) (also known more simply as **acetylcysteine**) is the specific antidote for **paracetamol toxicity**.

It ensures survival if administered appropriately within **8 hours** of paracetamol ingestion.

Traditionally NAC was administered as a 3 bag infusion regime. Current expert opinion now favours a **2 bag** infusion regime.

The 2 bag infusion regime has 2 advantages:

- Less anaphylactoid reactions (slower initial infusion rate)
- Less complex to administer, (hence less chance of dosing errors).

There is no loss of efficacy with the 2 bag protocol

N-acetylcysteine is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system

See also separate document on:

- **Paracetamol Toxicity (in Toxicology folder).**

History

Acetylcysteine has been in clinical use since 1968.

Oral acetylcysteine and **methionine** were also used in the past to prevent hepatotoxicity due to paracetamol poisoning. These oral regimens often provoked vomiting and were problematic in non-cooperative or very unwell patients, so had very limited utility. Neither of these are registered now for use in Australia or New Zealand.

In the 1970's a 3 bag intravenous (IV) weight-based n-acetylcysteine dosage regimen (150 mg/kg body weight over 15 minutes, then 50 mg/kg over 4 hours and 100 mg/kg over 16 hours 300 mg/kg total was used.

The regime was empirically derived and not subject to any dose ranging studies.

Although the regimen has proven to be highly efficacious (when compared to no treatment at all) it frequently led adverse **anaphylactoid** reactions due to the high rates of infusion, especially with the first "loading dose". The dosing regimen was also complex and prone to not infrequent errors in administration.

The safer and slower 2 bag regimen came into widespread use in Australia in 2019.

Weight- based dosing charts were introduced to reduce the risk of errors due to complex dosing calculations.

Chemistry

Acetylcysteine is the N-acetyl derivative of the naturally occurring amino acid, **L-cysteine.**

Preparation

N-acetylcysteine as:

Ampoules:

- N-acetylcysteine is packaged as **2 grams in 10 ml ampoules** for intravenous infusion.

  Each ampoule contains **200 mg/ml** (or **20%**) N-acetylcysteine.

Mechanism of Action

N-acetylcysteine provides a source of sulfhydryl (-SH) groups, which bind excess toxic NAPQI (i.e **N-a**cetyl-**p**-benzo **q**uinone **i**mine) metabolites.

Paracetamol is metabolised in the liver, mainly by conjugation with glucuronide and sulfate.

It is also metabolised by cytochrome P450 to form a reactive, potentially **toxic** metabolite.

This metabolite is normally detoxified by conjugation with hepatic glutathione, to form nontoxic derivatives.

In paracetamol overdosage, the glucuronide and sulfate conjugation pathways are **saturated,** so that **more of the toxic metabolite** is formed.

As hepatic glutathione stores are depleted, this toxic metabolite may then bind to hepatocyte proteins, leading to liver cell damage and necrosis.

NAC is a sulphydryl (SH) group donor, and so protects the liver from damage by restoring depleted hepatic reduced glutathione levels.

Pharmacodynamics

NAC ensures survival if administered appropriately **within 8 hours** of paracetamol ingestion.

N-Acetylcysteine also reduces mortality if commenced in late presenting patients with established paracetamol-induced fulminant hepatic failure, although mechanisms of action in this period may be different. In this setting, acetylcysteine reduces inotrope requirements, decreases cerebral oedema and increases the rate of survival by about 30%

Pharmacokinetics

Absorption:

- NAC is administered intravenously as a 2 bag infusion over a total of **20 hours.**

Distribution:

- Protein binding is around 66 - 87 %.
- NAC can cross the human placenta.
- It is unknown if NAC is distributed into human breast milk.

Metabolism and excretion:

- Acetylcysteine is the N-acetyl derivative of the naturally occurring amino acid, L-cysteine, and is de-acetylated in the liver to cysteine, or oxidised to other metabolites
- Renal clearance accounts for about 30% of total body clearance.

Indications

When a clinical risk assessment (see above) suggests the possibility of hepatic injury in the setting of paracetamol toxicity.

Clinical scenarios include:

1. Acute single ingestions taken within 8 hours, when the serum paracetamol level falls above the treatment nomogram line.
2. When toxicity is suspected and the patient presents after 8 hours of ingestion, infusion must be commenced immediately.

   Subsequent treatment will then depend on serum paracetamol levels, as well as clinical and other biochemical parameters, including in particular the liver transaminases, (see above).
3. Multiple or staggered overdose of paracetamol.
4. Repeated supratherapeutic toxicity.

5. Patients who have established fulminant hepatic failure due to paracetamol toxicity.

Contra-indications/precautions

There is rarely a true contraindication to the use of N-acetylcysteine.

The occurrence of an anaphylactoid reaction **does not** preclude the use of N-acetylcysteine on another occasion.

If there has been a genuine history of a severe **life threatening reaction**, the exact nature of this reaction should be ascertained and the case discussed with a **specialist toxicologist**.

Oral methionine and cysteamine, have been used as alternative agents to prevent hepatotoxicity, however they are associated with more adverse effects than N-acetylcysteine. Their requirement to be administered orally makes their use more problematic, especially in unwell, vomiting or uncooperative patients.

Methionine is also less effective, particularly after 8 hours, compared to N-acetylcysteine.

Pregnancy

NAC is classified as a category B2 drug with respect to pregnancy

Category B2 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

Maternal use of acetylcysteine as an antidote following acute paracetamol overdose has not been associated with an increased risk of congenital malformations.

The management of paracetamol overdose in pregnant women is the same as in non-pregnant women, where acetylcysteine therapy appears to prevent harm to both the mother and the fetus.

Case reports of acetylcysteine use for other indications have not identified adverse effects attributed to the medicine.

Note that in general the benefits of NAC in paracetamol poisoning far outweigh any potential adverse reactions. NAC is considered safe to use in pregnancy.

Breast feeding

Published reports describing the use of acetylcysteine during breastfeeding have not been located and it is unknown whether acetylcysteine is excreted into breast milk.

As acetylcysteine is completely cleared from maternal circulation approximately 30 minutes following oral administration, the amount of medicine reaching the breastfed infant is expected to be low.

Intravenous acetylcysteine has been administered to preterm neonates for therapeutic indications at doses far above those that would be obtained from breast milk, without causing toxicity.

Therefore, acetylcysteine is considered safe to use during breastfeeding.

Adverse Reactions

1. Minor **anaphylactoid** reactions are relatively common (10-50%) and manifest as:

    - Rash.
    - Hypotension.
    - Occasionally wheeze.

    These reactions are often related to the rate of infusion as well as host susceptibility factors. They are a result of direct histamine release rather than immunologically mediated allergic reactions.

    Management of these reactions consists of:

    - Momentarily ceasing the infusion.
    - Laying the patient flat.
    - Fluid loading.
    - Anti-histamine administration.

    Once the reaction has settled, the N-acetylcysteine infusion may be recommenced at a **slower rate,** (usually at **half the previous rate** and then **slowly increased to the full rate again over 30 minutes**).

2. True IgE immunologically mediated **anaphylaxis**, manifesting as a life-threatening reaction is **very rare**, but may occur in predisposed individuals such as those with a history of asthma.

    - If this type of reaction occurs, N-acetylcysteine infusion must be ceased immediately and treatment continued according to standard anaphylaxis protocols.

- Expert toxicologist opinion should then be sought regarding the ongoing management of the patient.

  Oral **methionine** - if available - may be an alternative option.

Dosing

Traditionally NAC was administered as a 3 bag infusion regime. Current expert opinion now favours a **2 bag** infusion regime.

The 2 bag infusion regime has 2 advantages:

- Less anaphylactoid reactions (slower initial infusion rate)
- Less complex to administer, (hence less chance of dosing errors).

There is no loss of efficacy with the 2 bag protocol

Each stage contains different doses, totalling **300 mg/kg** over a period of **20 hours**.

Prescription of N-acetylcysteine requires a two stage calculation to determine the appropriate weight-based dose and then the volume required.

- Calculation or transcription errors may lead to potentially fatal dosing errors.

  It is for this reason that specific **dosing tables** are recommended. These will preclude the need for calculations and decrease the potential for error, (**see dosing tables below**).

- Calculation of N-acetylcysteine dosing is based on estimated **body weight** to the nearest 10 kg, to a maximum weight of 110 kg.
- Volumes are weight adjusted for children

See Appendix 2 below for dosing tables.

Therapeutic End Point:

This is usually based on normalization of **liver transaminases (ALT)**.

Note that paracetamol overdose in patients without hepatic injury (i.e normal LFTs) causes a mild increase in **INR** by reducing functional Factor VII levels.

NAC can also cause a small rise INR however most of the rise in INR is due to a direct paracetamol effect.

Therefore an isolated increase in INR (in the setting of normal liver function tests) is an expected consequence of paracetamol toxicity, (with or without NAC treatment) and so a

mildly elevated INR (in the setting of normal liver function tests) is not of itself an indication to continue NAC therapy in cases of paracetamol overdose.

The increase in INR will resolve naturally.

The increase in INR should not present management problems for clinicians aware of this phenomenon because the changes in INR are lesser and occur earlier (median time 16 hours, as opposed to peaking at day 3 to 4) than those observed with established paracetamol hepatotoxicity (e.g. ALT or AST > 1,000 U/L).

Some patients will require **ongoing** treatment with **acetylcysteine** if they have:

- A persistently high paracetamol concentration of **> 10 mg/L (66 µmol/L)**

Or

- If the **ALT is > 50 U/L** *and* **increasing**.

If hepatic injury is suspected after the 2 infusion stages N-acetylcysteine is continued at the rate of the second infusion stage, (i.e. 100 mg/kg per 16 hours).

Higher infusion rates may be warranted for massive paracetamol ingestions, especially if the paracetamol concentration is **≥ 100 mg/L (660 µmol/L)** at the completion of the initial acetylcysteine infusion. A **clinical toxicologist** should be consulted in such cases. Regular clinical review and at least 12 hourly blood tests are recommended for those requiring prolonged treatment.

Hepatotoxicity and Liver Failure:

Only a small proportion of patients develop **hepatotoxicity** (i.e. **ALT > 1000 U/L**).

Early symptoms include:

- **Nausea, vomiting**
- **Abdominal pain**
- **Right upper quadrant tenderness**.

Of these only a minority will develop **fulminant hepatic failure**

Typically, in those with paracetamol induced acute liver injury the ALT and AST will rise for 3 - 4 days before recovering.

In those patients who require acetylcysteine **beyond 20 hours** n-acetylcysteine can be ceased if all the following criteria have been met:

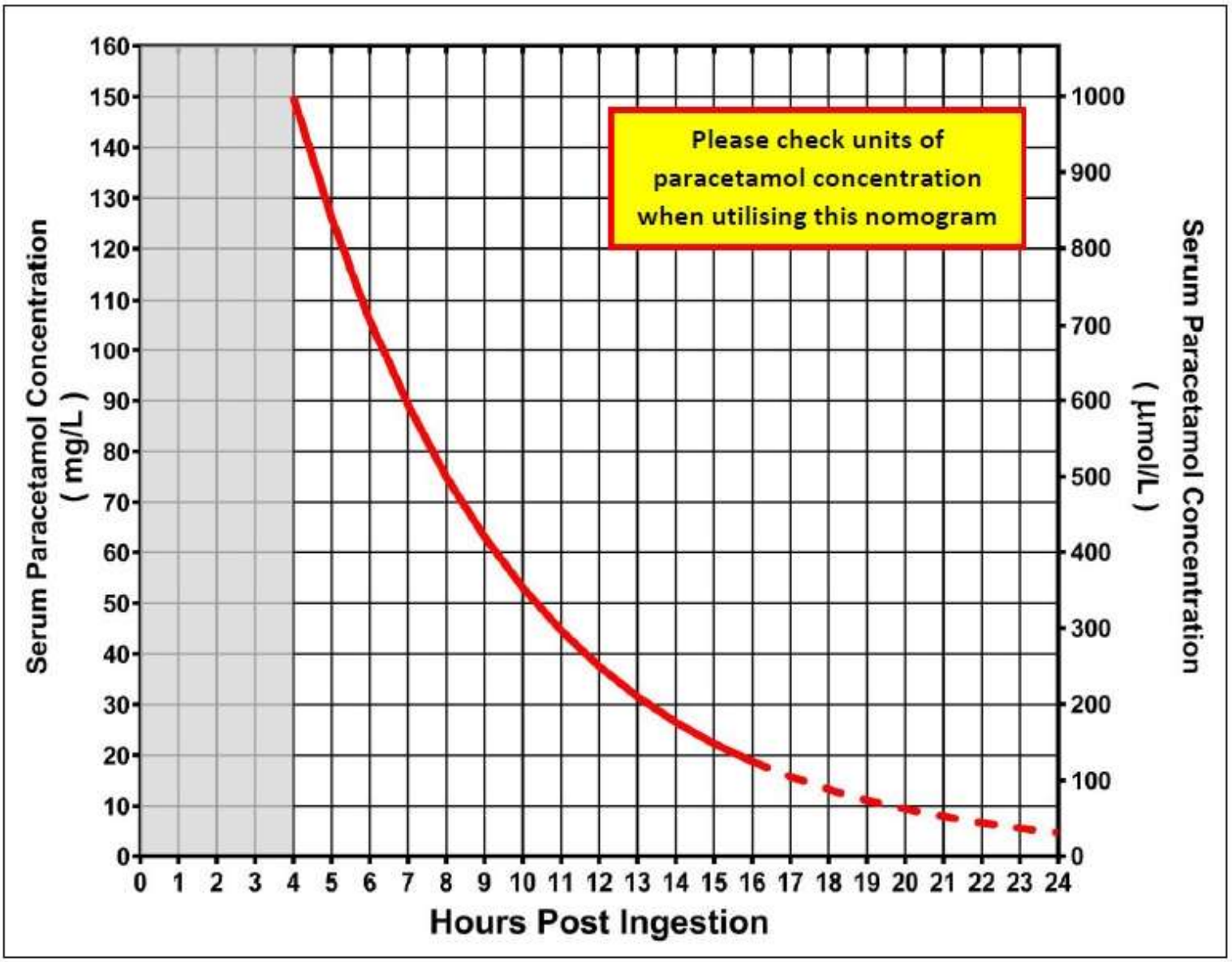
- ALT or AST are decreasing

- INR < 2.0
- Patient is clinically well

AND

- For modified-release ingestions and those with an initial paracetamol concentration greater than double the nomogram line: paracetamol concentration < 10 mg/L (66 μmol/L)

Appendix 1: *Australasian Consensus Nomogram for Paracetamol Toxicity:*



This Australian consensus nomogram is based on the older Rumack-Mathew nomogram, which it simplifies in two ways:

- *The Rumack-Mathew nomogram was a log scaled nomogram and this made plotting levels accurately more problematic. The new nomogram is **not** log scaled and thus facilitates more accurate plotting of paracetamol levels.*

- *A single treatment line is used instead of the original two, that required a risk assessment stratification for those thought to be at a theoretically increased risk of paracetamol toxicity. There was however no good consensus even among experts about whether or not treatment should be given at the lower line.*

  In practice this risk assessment was ill defined and imprecisely applied. The new treatment line is conservative and thus provides both a margin for safety for

patients possessing theoretical risk factors and a small margin of error for estimation of time of ingestion. The need for several potentially confusing lines is thus avoided.

Appendix 2

NAC Dosing:

ADULTS:

- Infusion 1:
  - ♥ 200 mg / kg Acetylcysteine in 500 mL in 5% dextrose over 4 hours
- Infusion 2:
  - ♥ 100 mg / kg Acetylcysteine in 1000 mL in 5% dextrose over 16 hours

CHILDREN > 20 kg body weight:

- Infusion 1:
  - ♥ 200 mg / kg Acetylcysteine in 250 mL of 0.9% Sodium Chloride + 5% Dextrose over 4 hours
- Infusion 2:
  - ♥ 100 mg / kg Acetylcysteine in 500 mL of 0.9% Sodium Chloride + 5% Dextrose over 16 hours

CHILDREN ≤ 20 kg body weight:

- Infusion 1:
  - ♥ 200 mg / kg Acetylcysteine in 7 mL/kg of 0.9% Sodium Chloride + 5% Dextrose over 4 hours
- Infusion 2:
  - ♥ 100 mg / kg Acetylcysteine in 14 mL/kg of 0.9% Sodium Chloride + 5% Dextrose over 16 hours

Adult (≥ 50 kgs) NAC Infusion Table:

Using 2 grams in 10 mL ampoules Acetylcysteine (200 mg/mL)

ADULT INFUSION 1: 200mg/kg Acetylcysteine in 500mL in 5% dextrose over 4 hours (125mL/hour)

Actual Body Weight (kg)	Dose of NAC	Volume of NAC (mL)
50	10,000mg	50mL
60	12,000mg	60mL
70	14,000mg	70mL
80	16,000mg	80mL
90	18,000mg	90mL
100	20,000mg	100mL
110 (ceiling)	22,000mg	110mL (maximum dose)

ADULT INFUSION 2: 100mg/kg Acetylcysteine in 1000mL in 5% dextrose over 16 hrs (63mL/hour)

Actual Body Weight (kg)	Dose of NAC	Volume of NAC (mL)
50	5,000mg	25mL
60	6,000mg	30mL
70	7,000mg	35mL
80	8,000mg	40mL
90	9,000mg	45mL
100	10,000mg	50mL
110 (ceiling)	11,000mg	55mL (maximum dose)

Children (20 - 50 kgs) NAC Infusion Table:

Using 2 grams in 10 mL ampoules Acetylcysteine (200 mg/mL)

INFUSION 1:

200 mg/kg Acetylcysteine in TOTAL volume **250 mL** over 4 hours (62.5 mL/hour)

INFUSION 2:

100 mg/kg Acetylcysteine in TOTAL volume **500 mL** over 16 hrs (31.25 mls/ hour)

	INFUSION ONE: (200mg/kg)		INFUSION TWO: (100mg/kg)	
Actual Body Weight (kg)	Dose of NAC	Volume of NAC (mL)	Dose of NAC	Volume of NAC (mL)
20	4,000mg	20mL	2,000mg	10mL
25	5,000mg	25mL	2,500mg	12.5mL
30	6,000mg	30mL	3,000mg	15mL
35	7,000mg	35mL	3,500mg	17.5mL
40	8,000mg	40mL	4,000mg	20mL
45	9,000mh	45mL	4,500mg	22.5mL
50	10,000mg	50mL	5,000mg	25mL

Children (≤ 20 kgs) NAC Infusion Table:

Using 2 grams in 10 mL ampoules Acetylcysteine (200 mg/mL)

INFUSION 1:

200 mg/kg Acetylcysteine in TOTAL volume 250mL** over 4 hours (62.5 mL/hour)

INFUSION 2:

100 mg/kg Acetylcysteine in TOTAL volume 250 mL over 16 hrs (15.6 mL/hour)

**INFANTS: smaller volumes may be required. Doses can be diluted in 100 ml bags

	INFUSION ONE: (200mg/kg)		INFUSION TWO: (100mg/kg)	
Actual Body Weight (kg)	Dose of NAC	Volume of NAC (mL)	Dose of NAC	Volume of NAC (mL)
1	200mg	1mL	100mg	0.5 mL
2	400mg	2mL	200mg	1mL
3	600mg	3mL	300mg	1.5 mL
4	800mg	4mL	400mg	2mL
5	1,000mg	5mL	500mg	2.5mL
6	1,200mg	6mL	600mg	3 mL
7	1,400mg	7mL	700mg	3.5mL
8	1,600mg	8mL	800mg	4mL
9	1,800mg	9mL	900mg	4.5mL
10	2,000mg	10mL	1,000mg	5mL
11	2,200mg	11mL	1,100mg	5.5mL
12	2,400mg	12mL	1,200mg	6mL
13	2,600mg	13mL	1,300mg	6.5mL
14	2,800mg	14mL	1,400mg	7mL
15	3,000mg	15mL	1,500mg	7.5mL
16	3,200mg	16mL	1,600mg	8mL
17	3,400mg	17mL	1,700mg	8.5mL
18	3,600mg	18mL	1,800mg	9mL
19	3,800mg	19mL	1,900mg	9.5mL
20	4,000mg	20mL	2,000mg	10mL

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