

# N-ACETYLCYSTEINE RESCUE PROTOCOL FOR NEPHROTOXICITY IN CHILDREN CAUSED BY IFOSFAMIDE

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## ABSTRACT

Nephrotoxicity is a serious side effect associated with ifosfamide use. It can affect up to 30% of children who are treated with this chemotherapeutic drug, and treatment may necessitate lifelong supplementations, renal dialysis, renal transplant, and in severe cases may result in death. The antioxidant n-acetylcysteine is a promising strategy for mitigating this renal toxicity. It is currently used in children for acetaminophen overdose in the 21-hour IV protocol, a dose which has also been suggested to provide renal protection against ifosfamide. Of significance, both *in vitro* and *in vivo* studies suggest n-acetylcysteine does not interfere with the antitumor actions of ifosfamide. Most importantly, n-acetylcysteine has successfully protected against ifosfamide-induced nephrotoxicity in both cell and rodent models, as well as in several paediatric cases, suggesting it should be evaluated as a treatment option for children on ifosfamide who present with renal dysfunction. The purpose of this paper is to outline strategies and recommendations for treating patients at risk or suffering from nephrotoxicity during ifosfamide therapy. These recommendations may be used when deciding who to treat, how and when to treat, as well as several considerations when exact recommendations cannot be met. They have been created to increase both the quality of care and quality of life of paediatric oncology patients.

**Key Words:** *Ifosfamide, nephrotoxicity, n-acetylcysteine, rescue protocol*

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In the United States alone, there are over 270 000 adult survivors of childhood cancer<sup>1</sup>, with a majority who are suffering from late effects secondary to their cancer treatment. These survivors suffer illnesses which may seriously affect their quality of life and/or may be life threatening.<sup>2</sup> Nephrotoxicity, primarily manifesting as proximal tubule dysfunction, in particular can be a devastating late effect which may necessitate lifelong supplementations, renal dialysis and renal transplant, and in severe cases

may result in death.<sup>3</sup> This renal damage can be caused by the chemotherapy drug ifosfamide (IFO)<sup>4</sup> and despite a large body of preclinical evidence supporting the effectiveness of n-acetylcysteine (NAC) in its ability to rescue individuals from permanent kidney damage, its use has yet to be adopted regularly in a clinical setting. We summarize below two published case reports wherein NAC was successfully used as renal protectant during IFO treatment, and report for the first time, a third successful case. The

objective of this document is to summarize the evidence supporting the use of NAC as both prevention and treatment for children suffering from IFO nephrotoxicity and to present a NAC rescue protocol. It is hoped that additional clinicians will join those who have followed this protocol in order to develop a prospective randomized trial.

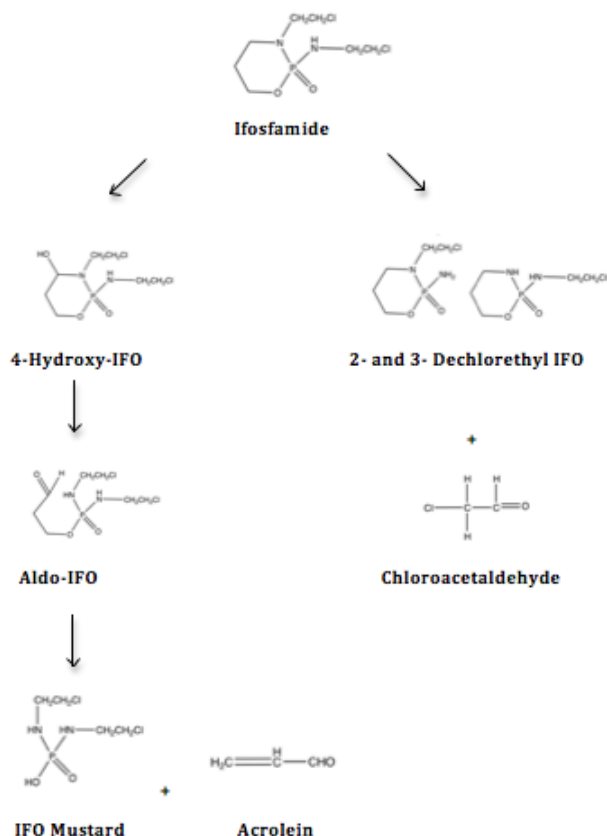
**Ifosfamide**

IFO is an antineoplastic agent used in the treatment of paediatric solid tumours, including Ewing's tumours, osteosarcoma, rhabdomyosarcoma, and non Hodgkin's lymphoma, as well as acute lymphoblastic leukemia.<sup>5,6</sup> While a promising treatment in the

battle against childhood cancer, showing a higher cure rate for most cancers than its analogue cyclophosphamide<sup>7</sup>, IFO use does not come without consequences. Nephrotoxicity affects up to 30% of children who are treated with this chemotherapeutic drug.<sup>3,8</sup> While these children may benefit from its antineoplastic potential and be cured of their cancer, their health and quality of life may be seriously impacted by this late effect.

IFO, a nitrogen mustard, is a pro-drug, which is metabolized to the active antineoplastic agent IFO mustard.<sup>9</sup> Metabolic activation to IFO mustard occurs via ring hydroxylation by CYP P450 3A4, 3A5, and 2B6 yielding both IFO mustard and acrolein<sup>9</sup> (Figure 1).

**FIG. 1** IFO metabolism. Ring hydroxylation and side chain oxidation of IFO resulting in the active agent IFO mustard, and reactive metabolites acrolein and CAA.



IFO may also be metabolized via the alternate metabolic pathway, side chain oxidation, producing 2- and 3-dechloroethyl IFO and chloroacetaldehyde (CAA).<sup>9,10</sup> Both acrolein and CAA are toxic reactive metabolites which are known to be responsible for some of the toxicities associated with IFO use.<sup>10,11</sup> Neurotoxicity, myelosuppression, GI toxicity, nephrotoxicity and urotoxicity have all been identified as adverse effects of IFO chemotherapy, with the latter two being the most severe.<sup>4</sup> In the past, IFO use was limited by the commonly occurring, severe urotoxicity. However, this late effect has been overcome with the co-administration of 2-mercaptoethanosulphonate (MESNA), a synthetic thiol which protects the bladder epithelium against the reactive metabolite acrolein, allowing for an almost complete reduction in the incidence of urotoxicity. This allowed for the ability to increase both dose and frequency with which IFO was given, following which nephrotoxicity emerged as the most severe, and dose limiting toxicity.<sup>4</sup>

### Nephrotoxicity

Cumulative dose, unilateral nephrectomy, prior platinum therapy and age, are all risk factors predisposing patients to kidney toxicity.<sup>3</sup> With respect to those affected, nephrotoxicity presents in each child to varying degrees. 30% of children who are treated with IFO will suffer mild to moderate renal dysfunction with 5% suffering from its most severe form, Fanconi syndrome.<sup>3,8</sup> Described as a proximal tubule dysfunction, Fanconi syndrome results in urinary loss of important solutes such as glucose, amino acids,  $\beta$ 2-microglobulin, phosphate and bicarbonate.<sup>8</sup> It may lead to renal tubular acidosis and/or hypophosphatemic rickets, and the need for lifelong supplementation with phosphate, bicarbonate and potassium.<sup>12,13</sup> Up to 30% of children may also suffer from declining glomerular function, resulting in the need for dialysis, renal transplant, and/or causing death.<sup>8</sup> Treatment options are limited to supportive care with most children seeing little to no improvement in their renal function over time and many seeing persistent declines in renal function<sup>8</sup> (Table 1).

**TABLE 1** Clinical relevant renal toxicities associated with ifosfamide use.

Affected Part of Kidney	Clinical features	Treatment options
<b><i>Proximal Tubular</i></b>	Fanconi syndrome including: <ul style="list-style-type: none"> <li>• Urinary loss of glucose, amino acids, and Low Molecular Weight proteins</li> <li>• Phosphaturia</li> <li>• Kaluria</li> <li>• Hypokalemia</li> <li>• Bicarbonaturia</li> </ul> Hypophosphatemic Rickets Proximal Renal Tubular Acidosis	Phosphate, bicarbonate and potassium supplements
<b><i>Glomerular Toxicity</i></b>	Reduced GFR Increased serum urea and creatinine concentrations Chronic Renal Failure	Renal dialysis Renal transplant

The metabolite CAA, formed by side chain oxidation of IFO, is responsible for this late effect associated with IFO.<sup>14</sup> However, studies show that systemic concentrations of CAA do not correlate with severity of nephrotoxicity, suggesting hepatic metabolism of IFO does not play a role in kidney toxicity.<sup>15</sup> Of importance, while the majority of xenobiotic metabolism is thought to be hepatic, there is evidence that the kidney is also capable of such biotransformation.<sup>11</sup> Moreover, there are studies available which demonstrate that in the case of IFO, the kidney possesses the enzymes responsible for its metabolism and is capable of producing levels of CAA which have been shown to be toxic to kidney tubules.<sup>11,14,16</sup> Therefore, the kidney creates its own poison and is unable to detoxify at the same rate with which it is being produced, resulting in toxicity.

The mechanism by which CAA exerts its toxicity within the kidney is oxidative stress. Increases in reactive oxygen species and products of lipid peroxidation<sup>17</sup>, as well as increased calcium and sodium concentrations have been observed effects of CAA.<sup>18,19</sup> While increased calcium can be detrimental to the cell, causing damage to the cytoskeleton, cell membrane, and potentially causing cell death, low levels of sodium are important for proper solute reabsorption, which is disturbed in patients presenting with Fanconi syndrome.<sup>20,21</sup> CAA may also result in loss of mitochondrial membrane potential, depletion of ATP and increases in pro-inflammatory cytokines TNF- $\alpha$ , IL $\beta$  and IL6.<sup>22,24</sup> Given the primary mechanism of CAA toxicity is oxidative damage, most crucial, is the depletion of glutathione (GSH) as a result of CAA.<sup>14,17,25</sup> As our intracellular protective mechanism against oxidative stress, GSH's ability to protect against CAA becomes critical to cell survival in environments with increased oxidative stress.

### **N-acetylcysteine**

Much like in the way that MESNA, routinely given with IFO, protects the bladder, there is hope for such an antidote for kidney toxicity. With an awareness of the mechanism through which CAA exerts its toxicity it becomes easier to define promising prophylactic and/or rescue strategies. With strong evidence supporting the main mechanism of kidney toxicity as oxidative stress, with a critical depletion in GSH<sup>17,25,26</sup>, antioxidants are a promising strategy. While several antioxidants such as resveratrol, thymoquinone, melatonin, taurine, glycine and L-histidinol have been assessed in the prevention of IFO-induced nephrotoxicity<sup>19,24,26-30</sup>, none of these options directly addresses the issue of depleted GSH. Even more importantly, none of these compounds are currently used clinically in children for any indication. Our group has chosen to assess the protective potential of NAC against IFO nephrotoxicity. Not only does NAC function as a nucleophile, detoxifying ROS, it also acts as a precursor to GSH synthesis by providing the cysteine essential for its formation.<sup>31,32</sup> Even further to the advantage of NAC, is that it is currently used clinically in children for acetaminophen overdose.<sup>31,32</sup> This provides safety data which is not only unavailable for alternative protective strategies, but can be very difficult to obtain in vulnerable populations such as children.

Currently used in the 21-hour IV schedule for acetaminophen overdose worldwide, this dose, along with several oral protocols (72 and 36 hours) have been demonstrated to exhibit similar efficacy when given within the 8 hour window following poisoning<sup>34</sup>, with the 36 and 72 hour oral and 48 hour IV protocols being more effective for late treated patients.<sup>35,36</sup> These protocols all demonstrate similar safety (Table 2).

**TABLE 2** Oral and IV protocols if N-acetylcysteine, used for acetaminophen overdose in order of highest to lowest systemic exposure.

Protocol	Dose	Total Systemic Dose (mg/kg) *Based on 4-10% oral bioavailability
48 hour intravenous	140mg/kg, followed by 70mg/kg every 4 hours x 12	980
21 hour oral	150mg/kg over one hour, followed by 50mg/kg over 4 hours and 100mg/kg for 16 hours	300
72 hour oral	140mg/kg, followed by 70mg/kg every 4 hours x 17	53.2-133
36 hour oral	140mg/kg, followed by 70mg/kg every 4 hours x 9	30.8-77

With respect to adverse events, including anaphylactoid reactions when receiving IV formulations, more common side effects include nausea and vomiting when taken orally.<sup>37</sup> Anaphylactoid reactions are generally attributed to infusion rate. While they have been reported to occur in as little as 0% of patients to as many as 48%, they are generally minor and easily managed.<sup>38</sup> In most cases NAC infusion can be continued and completed following treatment of the reaction and administration of diphenhydramine.<sup>39-41</sup> Also important, is the established safety of repeated or chronic NAC use. Oral NAC is often used in the treatment of chronic obstructive pulmonary disease (COPD) and is used safely for extended periods of time ranging from 22 weeks to 6 months. Chronic use of NAC in these patients resulted in minimal side effects, of which the most common were gastrointestinal, and in all cases NAC therapy remained uninterrupted.<sup>42</sup> These characteristics make NAC not only a promising choice for kidney protection during IFO therapy but also the most readily available for immediate use.

### Supporting Evidence

Prophylaxis is defined as prevention of disease, while treatment is defined as remedy of disease. We present below evidence for NAC use, both as prophylaxis and treatment, for IFO-induced nephrotoxicity. We reiterate here, that we choose

to discuss NAC rather than other treatment options, which have also successfully protected against IFO-induced nephrotoxicity in animal models, because we believe that NAC is currently the most clinically relevant choice. This is not to suggest that the other agents may not be equally effective or even more potent than NAC, as a direct comparison of the chemicals has never been done. We do however argue that the lack of information of the safe use of these chemicals in children severely hinders their ability to be used in a clinical setting in the near future, until appropriate safety data is collected. The availability of this information for NAC, allows it to be used in a more immediate manner, allowing for prevention/treatment of IFO-nephrotoxicity sooner than with the other treatments. Should one of these other treatments be deemed superior to NAC and have adequate safety data, a re-evaluation of the best treatment for IFO-induced nephrotoxicity should be done.

### Evidence supporting NAC for prophylaxis

There is large body of evidence to date to support the clinical use of NAC to prevent IFO-induced nephrotoxicity. NAC has been efficacious in protecting against IFO-induced renal toxicity in both cell and rodent models.<sup>17,25</sup> LLCPK-1, porcine renal proximal tubule cells, treated with IFO have depleted levels of GSH and significant cell death. Treatment with NAC partially protects

against GSH depletion, and fully protects against decreased cell viability.<sup>25</sup> NAC also displays similar protective effects in a rodent model of nephrotoxicity. In these animals, IFO resulted in depletion of GSH, reduced GSH-S-transferase activity and increases in products of lipid peroxidation. IFO also resulted in morphological damage to tubules and glomeruli, increased levels of serum creatinine and increased urinary excretion of  $\beta$ 2-microglobulin and magnesium. With co-administration of NAC, rats were protected against all parameters of early stages of Fanconi syndrome. Lipid peroxidation increases, as measured by malondialdehyde and 4-hydroxyalkenal, and decreased GSH-S-transferase activity were both restored to control levels. However, in contrast to the *in vitro* model, full rather than partial protection against GSH depletion was seen.<sup>17</sup> Morphological damage including distorted tubules and degenerated glomeruli, as well as interstitial inflammation and oedema, seen with IFO treatment, was not present in NAC treated group. Our group has also done translational work demonstrating that the 21-hour IV dose of NAC used in children for acetaminophen overdose, provides similar systemic exposure when compared to our therapeutically effective rodent model, which as discussed above is protected at early stages of IFO-induced Fanconi syndrome. This suggests that the 21-hour IV dose of NAC should also be sufficient in providing renal protection<sup>43</sup> supporting the choice of 21-hour IV protocol over other oral protocols.

While studies of efficacy are critical to the use of NAC clinically, just as important is work assessing the effects of NAC on the antineoplastic ability of IFO. Both *in vitro* and *in vivo* work exists which shows no evidence that NAC interferes the chemotherapeutic effects of IFO. In two relevant cancer cell lines, rhabdomyosarcoma and neuroblastoma, IFO mustard treated cancer cells retained their ability to kill with both the addition of NAC and NAC + MESNA combination.<sup>44</sup> The addition of MESNA, routinely administered with IFO for uroprotection, was included to ensure that a combination of these chemoprotectants would also not interfere with IFO mustard efficacy. Furthermore, in a mouse

xenograft model, where mice were implanted with Ewing's sarcoma tumours, treatment with NAC and IFO retained the same ability to inhibit tumour growth as IFO alone treated mice, when both were compared to control. While not significant, NAC + IFO treated mice had smaller tumour volumes than mice treated with IFO alone. These studies suggest that ability of IFO to retain its alkylating properties against tumour cells, even in the presence of NAC.<sup>45</sup> Further supporting these findings is work which suggests that the addition of NAC to IFO treatment does not affect IFO pharmacokinetic parameters such as plasma half life, area under the curve, and plasma clearance.<sup>46</sup>

### **Evidence Supporting NAC for Treatment**

While the previous evidence suggests a prophylactic strategy, case reports, collected from circumstances in which treating physicians deemed NAC intervention a necessity following presentation of nephrotoxicity, also provide evidence that NAC can be used not only for prevention but treatment as well.

The most convincing support for the clinical use of NAC in children suffering from renal dysfunction are two case reports which have already been described in the literature, in addition to the third described below, of children who received NAC during, or just following, IFO containing chemotherapy regimens after demonstrating signs of renal dysfunction. The first case report describes a 10-year-old female who presented with primitive neuroectodermal tumour of the Ewing's sarcoma family and acute renal failure. Following unsuccessful surgery, she was treated with IFO ( $3\text{g}/\text{m}^2$ ), vincristine ( $1.5\text{mg}/\text{m}^2$ ), dactinomycin ( $1.5\text{mg}/\text{m}^2$ ), and MESNA on day 1, and IFO ( $3\text{g}/\text{m}^2$ ) and MESNA only on days 2 and 3, followed by dialysis on each day. She was also given the 21-hour IV dose of NAC on days 1 and 2. AUC's of NAC calculated for these two days were similar to AUC's observed in children treated with this dose of NAC for acetaminophen overdose. Following treatment this child had no clinical or laboratory signs of renal damage and she showed all signs of tumour lysis. The second case report describes a 15-year-old male who had recurrence of mixed germ cell testicular cancer.

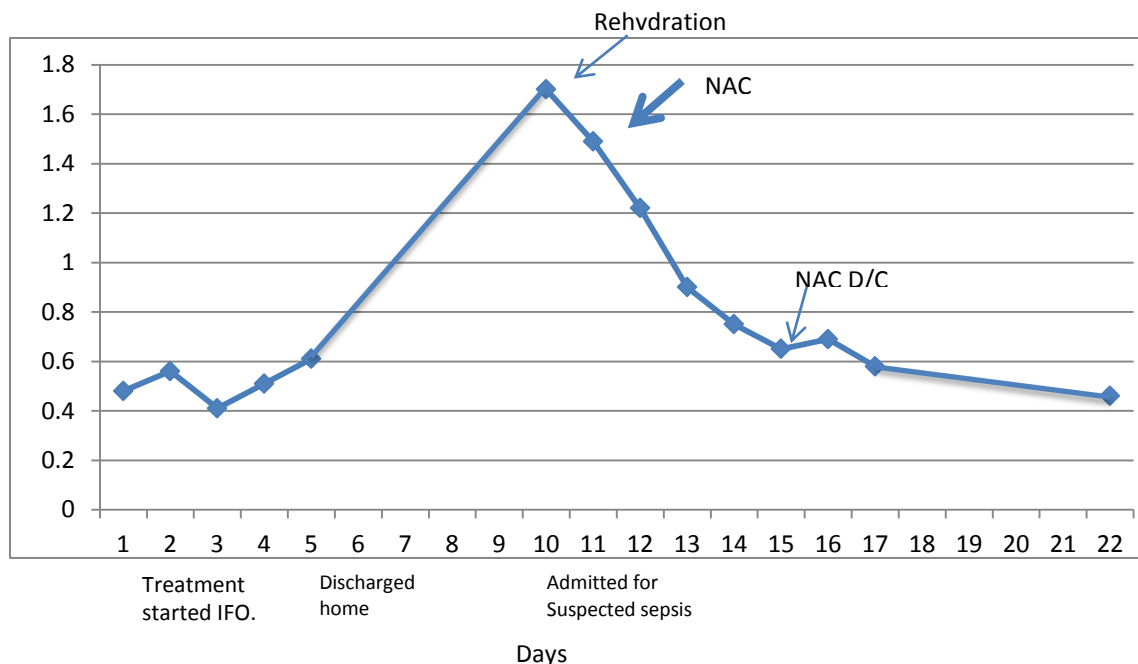
He had elevated levels of serum creatinine (1.2-1.6mg/dl), which remained high following his chemotherapy regimen of cisplatin, etoposide and bleomycin. Following an abdominal relapse, he was treated with a protocol including Paclitaxel 257 mg, carboplatin 653 mg, IFO 3400 mg, and MESNA 684 mg on day 1, and IFO 3400 mg and MESNA only on days 2-5. The patient's serum creatinine steadily rose following treatment to a peak of 2.25mg/dl after the end of therapy. NAC was started 2 days following the end of the chemotherapy protocol at a dose of 600mg BID and was given for 5 days. Following treatment, serum creatinine declined to 1.12mg/dl, levels which were lower than observed creatinine levels at the start of treatment.<sup>45</sup>

### Case Report

A 4-year-old girl was diagnosed with poorly differentiated epithelial Wilms tumor of favorable

histology in April 2010. The tumor was stage 3 due to periaortic node involvement. She received radiation and AREN0532 protocol treatment. In May 2012 she had a relapse surrounding the pulmonary artery, which was confirmed by biopsy. She was started on ICE (Ifosfamide /Carboplatin /Etoposide) protocol and Topotecan/cyclophosphamide therapy for recurrent Wilms tumor. She received four cycles of treatment with ICE, which included 5 days of 1.8g/m<sup>2</sup> of IFO admixed with MESNA 360 mg/m<sup>2</sup> over 2 hours daily for 5 days. During the 4<sup>th</sup> cycle, her serum creatinine remained in the range of 0.4-0.6 mg/dl during the ICE administration (day 1-5) but steadily began to increase following discharge on day 6 to a peak of 1.7mg/dl on day 10, when she was admitted to hospital for suspected sepsis (Figure 2).

**FIG. 2** Serum Creatinine. Serum creatinine levels of 4 year old suffering from Wilms tumor.



Following admission, antibiotics (meropenem and vancomycin) and IV hydration were started. NAC was started on day 11 and was continued for 5 days at a dose of 1g IV per day. Following NAC administration, serum creatinine

levels began to fall and within 1 week were within the normal ranges. Although suspected sepsis could have resulted in renal injury, and therefore its treatment in renal improvement, sepsis was ruled out as blood and urine cultures were

negative. This would indicate the presence and treatment of sepsis was not responsible for changes in renal function. With respect to hydration status, following rehydration the patient did show slight improvement in serum creatinine, however her levels were still abnormally high suggesting kidney injury could not be ruled out. After starting NAC, there was a steep decrease in creatinine values and clinical improvement, improvements which were not seen with rehydration. This would suggest improvements were due at least in part to NAC therapy, as renal dysfunction is multifactorial. Although her condition improved, the decision was made to withhold the 5<sup>th</sup> cycle of ICE. She continues her chemotherapy now with topotecan and cyclophosphamide only; all evidence to date suggests successful treatment of her cancer. She does not have any evidence of metastatic disease and her renal function remains within normal limits.

Currently there is no available approved drug to treat or prevent nephrotoxicity caused by IFO. There is however a good body of evidence, presented above, which suggests both the safe and effective use of NAC for treatment and prevention purposes. While a RCT is most certainly necessary to determine its effectiveness, we believe there is sufficient evidence to use NAC in cases where nephrotoxicity is already present. This evidence includes 3 case reports of children who were successfully treated with NAC for nephrotoxicity which presented during treatment, and whose chemotherapy was successful. Given that there are no alternative options, we believe it is irresponsible not to provide these children with the best possible chance they have to restore their renal function, especially in consideration of the minimal risk associated with NAC therapy and the potential enormous benefits. While we understand physicians may be reluctant to treat every child who requires IFO with NAC as prophylaxis, we believe that until an RCT is carried out, the use of NAC is justified if and when nephrotoxicity is present. Following an RCT evaluating NAC given as standard adjuvant to IFO therapy, much in the same way MESNA is given for uroprotection, we would suggest NAC may be more appropriately used and accepted for prophylaxis.

### **Clinical Protocol Recommendations**

The following guidelines have been developed with input from scientists, clinical pharmacologists and practicing physicians including nephrologists and paediatric oncologists. This section outlines the basic steps and considerations when treating kidney toxicity associated with IFO treatment.

#### ***Who should be treated? Grading nephrotoxicity***

Adolescents and children who present to oncology with cancer requiring treatment with IFO should have baseline kidney function assessed. Both glomerular and tubular function should be assessed by measurements of serum creatinine, electrolytes, phosphate, bicarbonate, calcium magnesium and pH, and urinary glucose and protein. Patients should also have renal function assessed immediately following each IFO containing cycle and immediately before each subsequent cycle begins. Follow up after completion of therapy should occur at 1 week, 3 months and 1 year.

Patient declines of renal function can be measured one of two ways:

1. Using the following five criteria described by Lobstein *et al.*<sup>47</sup> with modifications, to defined abnormal renal function:

- 1) Hypophosphatemia (<2 SD for age)
- 2) Hypocarbica together with metabolic acidosis (bicarbonate<18mEq/L together with pH<7.32)
- 3) Glycosuria (any amount)
- 4) Proteinuria (1.0 g/L or greater)
- 5) Measured or estimated glomerular filtration rate (GFR) and/or creatinine clearance (CrCl) are < 80 ml/min/1.73m<sup>2</sup>.\*

\*measured by isotopic nuclear GFR measurement, measured by creatinine clearance, estimated by creatinine-based equations (such as modified Schwartz formula), estimated by cystatin C-based equations or others.

*Each criterion is to be considered only if it appears as normal in the baseline renal function assessment and became abnormal following the start of IFO and only if it appeared as abnormal at least twice.*

The patient can be classified in one of four categories based on their degree of nephrotoxicity (Table 3).



**TABLE 3** Degree of nephrotoxicity based on Lobstein *et al.*<sup>47</sup> criteria.

<i>Degree of Nephrotoxicity</i>	<i># of Abnormal Criteria Met</i>
Non-nephrotoxic	None
Mildly nephrotoxic	1
Moderately nephrotoxic	2-3
Severely nephrotoxic	4-5

**OR**

As estimations of GFR by creatinine are often underestimated when patient creatinine levels are not in steady state, renal injury can be assessed according to pRIFLE criteria<sup>48</sup> (Table 4).

**TABLE 4** pRIFLE criteria.

	<i>Estimated CCL</i>	<i>Urine Output</i>
<b>Risk</b>	eCCL decrease by 25%	<0.5 ml/kg/h for 8 h
<b>Injury</b>	eCCL decrease by 50%	0.5 ml/kg/h for 16 h
<b>Failure</b>	eCCL decrease by 75% or eCCL <35 ml/min/1.73 m	<0.3 ml/kg/h for 24 h or anuric for 12 h
<b>Loss</b>	Persistent failure >4 weeks	
<b>Endstage</b>	End-stage renal disease stage (persistent failure >3months)	

Any patient categorized as mildly, moderately or severely nephrotoxic, OR who meets any pRIFLE criteria of should be treated with NAC.

***How should n-acetylcysteine be given?***

While both oral and IV NAC are approved protocols (for acetaminophen overdose) the use of IV NAC is recommended for the indication of renal protection for several reasons. Oral NAC has a low oral bioavailability of 4-10%<sup>49</sup>; therefore, a greater systemic dose can be achieved with IV NAC, even when total oral dose is much higher (Table 2). Furthermore, oral NAC has a high rate of nausea and vomiting as a side effect making it

difficult to know what dose, if any at all, was administered.<sup>37</sup> However, most importantly, the 21-hour IV dose, which can be given safely, provides the highest systemic dose, therefore assuring the patient has the highest level of renal protection.

As IFO cycles can range for 2-5 days<sup>50</sup>, it is recommended that NAC be given in the 21-hour IV dose on all days following IFO administration. While no studies exist using repeated administration of the 21-hour IV protocol, as discussed above, oral NAC is routinely given daily for up to 6 months without any serious adverse events.<sup>42</sup> The 21-hour IV protocol should be administered as follows:

*For patients over 40kg<sup>51</sup> (Table 5)*

**TABLE 5** 21-hour intravenous protocol of NAC.

Infusion	Dose	Volume of D5W	Time
1	150 mg/kg	200mL	15-60 minutes
2	50 mg/kg	500mL	4 hours
3	100 mg/kg	1000mL	16 hours

*For patients under 40kg<sup>52</sup> (Table 6):*

**TABLE 6** Dilution of 21-hour IV NAC protocol for patients under 40kg.

Infusion	Dose
1	0.75 ml/kg of NAC 200 mg/ml in 3 ml/kg of D5W with maximum of 200 ml of D5W administered over 1h
2	0.25 ml/kg of NAC 200 mg/ml in 10 ml/kg of D5W with maximum of 500 ml of D5W administered over 4h
3	0.5 ml/kg of NAC 200 mg/ml in 20 ml/kg of D5W with maximum of 1000 ml of D5W administered over 16h

For patients under 40kg the 200mg/mL solution of NAC should be diluted to 40mg/mL with D5W to avoid excessive free water leading to hyponatremia and seizures (Table 6). Renal function should be measured each day following IV NAC and 1 week following completion of treatment. IFO treatment can be continued with special attention being paid to monitoring for changes in renal function. Concomitant NAC treatment should be considered in all future IFO therapy as a preventative measure.

#### ***Measurement of tumour response***

Tumour response should be evaluated according to Jurgens *et al.*<sup>4</sup>

Tumours should be assessed for response with X-ray and/or computerized axial tomography at the end of treatment and will be classified as follows:

1. Complete remission: Lack of measureable evidence of disease
2. Partial remission: regression of more than 50% of tumour size
3. Non-responder: regression of less than 50% of tumour size and progressive disease

#### **Considerations of NAC usage**

Several considerations should be given when using NAC treatment for IFO-induced renal toxicity.

#### ***Dose and Route of Administration***

IV NAC is the preferred treatment option as it is the standard protocol used by most and because it provides a higher systemic exposure, therefore ensuring the highest NAC dose possible. However, there may also be circumstances in which administration of IV NAC is either not practical or not possible. Under such circumstances we would recommend the use of oral NAC as opposed to no treatment at all. Our second case report suggests that the systemic doses achieved with oral NAC can be sufficient in providing renal protection. In such circumstances we recommend the use of 600mg BID in order to provide the patient with a minimum amount of renal protection. However, we again re-iterate, IV NAC is the preferred treatment option as it is the standard protocol used by most and because it

provides a higher systemic exposure, therefore ensuring the highest NAC dose possible.

#### ***Adverse Drug Reaction***

As previously discussed, there exists the potential for adverse drug reactions (ADR's) when using NAC, most commonly anaphylactoid reactions when administration is IV. Following presentation of such a reaction, we recommend following the guidelines published by Bailey *et al.*<sup>41</sup> These guidelines are based on a 6-year retrospective case series and a literature review, and were evaluated prospectively in a poison control centre. Following an anaphylactoid reaction, they recommend IV administration of diphenhydramine 1 mg/kg (maximum 50mg) and suggest reassessing the need for NAC. If NAC is deemed necessary, it may be restarted if the patient has no symptoms 1 hour after treatment of ADR.<sup>41</sup>

#### ***Other***

IFO is commonly given in combination therapy either as part of the ICE protocol including IFO, carboplatin and etoposide as well in combination with etoposide alone. It is important to be aware that work exploring the effects of NAC on both these chemotherapeutic agents has been assessed in animal models. These studies demonstrated that NAC had no effect on the antineoplastic effects of either carboplatin or etoposide.<sup>53</sup> Second, while the ideal patient treated with NAC would present only suffering from nephrotoxicity caused by IFO and would be treated with IV NAC during their IFO cycle, paediatric oncology is far from ideal. Patients may present with declining renal function as a result of previous treatment with nephrotoxic drugs, such as platinum or methotrexate. Under these circumstances, treatment with NAC is still recommended. As demonstrated in two of the case reports, a patient may present with some degree of declining renal function prior to any treatment with IFO. In both cases improvement of renal function was observed even when the primary renal insult may not have been IFO. Furthermore, renal dysfunction may develop following the completion of all IFO cycles; therefore, preventing the administration of NAC during the IFO cycle as recommended above. As evidenced

in 2 of the described cases, NAC also provided renal protection even after the IFO cycle was completed, suggesting children will still benefit from NAC therapy even when administration is delayed. We would therefore still recommend that patients with delayed onset of nephrotoxicity be administered a least one course of the 21-hour IV dose of NAC.

### Future Directions

The ultimate goal of NAC therapy would be to provide patients with renal protection, much in the way that MESNA is currently always given alongside IFO; or at a very minimum to susceptible individuals once the means of identifying them becomes available. The future direction of NAC therapy includes a RCT designed to assess the effectiveness of NAC as a prophylactic strategy for IFO-induced nephrotoxicity. In the meantime, NAC rescue therapy is the most promising strategy available to patients and is an important consideration in the maintenance of the health and well being of the patient.

### Acknowledgements

This study was supported by grants from the Canadian Institutes Health Research (CIHR) to GK, LH and MJR, and from the Pediatric Oncology Group of Ontario (POGO) to LH.

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