BC Cancer Protocol Summary for Therapy of Multiple Myeloma using Carfilzomib, Dexamethasone and Isatuximab with or without Cyclophosphamide

Protocol Code	*UMYISACARD*
Tumour Group	*Myeloma*
Contact Physician	*Dr. Christopher Venner*

ELIGIBILITY:

Patients must have:

- Relapsed/refractory multiple myeloma,
- Previously received at least one prior line of therapy, and
- BC Cancer "Compassionate Access Program" request approval prior to treatment

Notes:

- Patients on active treatment with MYCARDEX who do not have proven progression may switch to UMYISACARD if all other eligibility criteria are met
- Patients are eligible for only one line of anti-CD38 monoclonal antibody therapy (e.g. daratumumab or isatuximab). Re-use of anti CD-38 monoclonal antibody therapy can only be considered if not refractory to use in a prior line.
- Cyclophosphamide may be added per physician discretion to increase response

EXCLUSIONS:

Patients must not have:

- Prior progression on daratumumab-containing regimen, or
- Refractoriness to carfilzomib*,

*does not include patients previously exposed or refractory to bortezomib and ixazomib

CAUTIONS:

- CrCl less than 15 mL/minute (monitor renal function closely in patients with CrCl less than 30 mL/min)
- History of congestive heart failure
- Uncontrolled hypertension
- Platelet count less than 30×10^9/L
- ANC less than 1.0×10^9/L. Consider giving filgrastim
- Total bilirubin greater than 2 x ULN, ALT greater than 3 x ULN

TESTS:

- Baseline (required before first treatment): Red Blood Cell phenotype and Group and Screen pre-isatuximab (mark on requisition ”patient to start isatuximab”)
- Baseline (required before first treatment): CBC & Diff, creatinine, sodium, potassium, urea, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, phosphate, LDH, random glucose
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2): serum protein electrophoresis ***and*** serum free light chain levels, immunoglobulin panel (IgA, IgG, IgM), HCAb, HBsAg, HBsAb, HBcoreAb, beta-2 microglobulin
- Every 4 weeks (required, but results do not have to be available to proceed with treatment): serum protein electrophoresis ***and*** serum free light chains
- Every 4 weeks (optional, results not mandatory but encouraged prior to each cycle): urine protein electrophoresis, immunoglobulin panel (IgA, IgG, IgM), beta-2 microglobulin
- Every 4 weeks: CBC & Diff, creatinine, urea, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, phosphate, LDH, random glucose
- Days 8, 15, 22 (optional if pre-cycle cytopenias, hypercalcemia, hepatic or renal dysfunction, or steroid-induced diabetes is a concern. Results do not have to be available to proceed with treatment. Provider to review results, no dose modifications indicated for mid-cycle bloodwork): CBC & Diff, creatinine, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, phosphate, random glucose
- If clinically indicated: HBV viral load (see protocol SCHBV)

PREMEDICATIONS:

30 minutes prior to isatuximab infusion:

- dexamethasone* (see Treatment table, below)
- acetaminophen 650 mg PO prior to each isatuximab infusion, and then Q4H PRN during the IV infusion if the infusion exceeds 4 hours.
- loratadine 10mg PO (preferred) or diphenhydrAMINE 50 mg PO/IV prior to each isatuximab, then:
  - If using loratadine: give diphenhydrAMINE 50 mg IV Q4H PRN allergic reaction
  - If using diphenhydrAMINE: repeat diphenhydrAMINE 50 mg IV Q4H PRN allergic reaction
- Optional, recommended prior to first dose of isatuximab, and prior to subsequent doses for patients who experience reaction: famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible with diphenhydrAMINE, if using)
- montelukast 10 mg PO prior to each isatuximab dose in Cycle 1, then optional for Cycle 2 onwards
- **If no reaction after 4 consecutive doses of isatuximab, may discontinue acetaminophen, loratadine/diphenhydrAMINE, famotidine and montelukast**. Dexamethasone continues per Treatment table, below
- * predniSONE may be used instead of dexamethasone as the therapeutic steroid. A minimum of 100 mg of predniSONE prior to each isatuximab dose is recommended for cycle 1. After cycle 1, a lower dose of predniSONE may be used and administered prior to each isatuximab dose.
- If there is a contraindication to high-dose steroid, a minimum of 100 mg hydrocortisone is required prior to each isatuximab dose for cycle 1 to prevent infusion-related reactions with isatuximab. See OTHER OPTIONS FOR STEROID DOSING, below

- The therapeutic dose of steroid is used as the premedication steroid to reduce the risk of reactions. The therapeutic steroid dose should be administered prior to isatuximab

SUPPORTIVE MEDICATIONS:

- Very high risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per SCHBV.
- Antiviral prophylaxis against reactivation of varicella-zoster virus (VZV) is recommended prior to initiating isatuximab and carfilzomib. Patients should take valACYclovir 500 mg PO daily.
- Oral proton-pump inhibitor or H_2 antagonist for the duration of treatment with dexamethasone may be considered
- If recurrent nausea is noted, consider:
    - Ondansetron 8 mg PO TID prn nausea the day of and the day after carfilzomib
    - Olanzapine 2.5 mg PO HS the evening before and the evening of carfilzomib

PREHYDRATION:

- Optional IV prehydration with 250 mL NS IV over 30 minutes prior to carfilzomib can be considered, especially on days without isatuximab if there are concerns with renal impairment. Hydration must be used with caution given the risk of transient cardiac contractility impairment and fluid overload.

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
dexamethasone	40 mg* once weekly on Days 1, 8, 15, and 22	PO (preferred, or IV) ▪ Give 30 minutes prior to isatuximab ▪ Patient to self-administer on days without isatuximab. Morning may be preferred.
isatuximab	Cycle 1: 10 mg/kg on Days 1, 8, 15, and 22 Cycle 2 and subsequent: 10 mg/kg on Days 1 and 15	IV in 250 mL NS (use 0.2 micron in-line filter) If reaction** at any time during infusion, follow instructions per SCDRUGRX
		Cycle 1 Day 1: Start at 25 mL/hour; if no reactions after 60 minutes, increase rate by 25 mL/hour every 30 minutes until maximum 150 mL/hour
		Cycle 1 Day 8: if no reaction to Cycle 1 Day 1, or reaction is Grade 2*** or less: Start at 50 mL/hour; if no reaction after 30 minutes, increase rate by 50 mL/hour for 30 minutes, then by 100 mL/hour until maximum 200 mL/hour OR If reaction on Cycle 1 Day 1 is Grade 3*** : Start at 25 mL/hour; if no reactions** after 60 minutes, increase by 25 mL/hour every 30 minutes until maximum 150 mL/hour (slow infusion)
		Cycle 1 Day 15 and Day 22 and subsequent infusions: if no reaction to previous infusion, or reaction is Grade 2*** or less: Infuse over 30 minutes OR If reaction in previous infusion is Grade 3*** : Start at 100 mL/hour; if no reactions** after 60 minutes, increase by 50 mL/hour every 60 minutes until maximum 200 mL/hour (slow infusion)
carfilzomib	Cycle 1: 20 mg/m^2 on Day 1 then 70 mg/m^2 on Days 8 and 15 Cycle 2 and subsequent: 70 mg/m^2 on Days 1, 8, 15 (cap BSA at 2.2)	IV in 100 mL D5W over 30 minutes†
OPTIONAL cyclophosphamide¥	500 mg once weekly on Days 1, 8, 15 and 22 *OR* 50 mg once every 2 days	PO, in the morning may be preferred

* Dexamethasone dose may vary dependent on tolerability and co-morbidities. For older patients i.e. 75 years of age or older, the starting dose of dexamethasone should be 20 mg PO weekly. See also: Other options for steroid dosing, below

** If BP falls to less than 80/50 mmHg or pulse increases to greater than 120 or if flushing, dyspnea, chills, rash, pruritus, vomiting, chest pain, throat tightness, cough, wheezing, or any other new acute discomfort occurs, stop isatuximab infusion and page physician. See Infusion Reaction section in protocol for when to resume infusion and rate.

*** For grading of infusion-related reaction, see Appendix: Infusion Related Reaction

¥ cyclophosphamide may be added per physician discretion to increase response.

† Infusion time remains consistent throughout protocol regardless of any dose modifications

For cycle 6 and onwards, may order a maximum of 3 cycles at a time (i.e. return to clinic in 12 weeks)

Repeat every 28 days until disease progression or unacceptable toxicity.

For additional information on isatuximab infusion rates, see Appendix: Isatuximab infusion rate titration table.

Vitals monitoring and Observation:

Isatuximab:

For infusion on Cycle 1, Day 1:

- Vital signs immediately before the start of the infusion, then every 30 minutes x 4, then every 1 to 2 hours until the end of the infusion. Vital signs post infusion at 30 minutes after the end of the infusion. Patient may leave when infusion is complete and patient is stable for 30 minutes.

For subsequent infusions i.e. Cycle 1, Day 8 and beyond:

- Vital signs immediately before the start and at the end of the infusion, and as needed. Vital signs not required after 4 treatments with no infusion reaction. Patient may leave when infusion is complete.

Carfilzomib:

- Vital signs prior to EACH carfilzomib infusion
- For Cycle 1 only, observe patient for 30 minutes following EACH carfilzomib infusion

Post-Carfilzomib Hydration:

- Optional IV post-hydration with 250 mL NS IV over 30 minutes after carfilzomib can be considered, especially on days without isatuximab if there are concerns with renal impairment. Hydration must be used with caution given the risk of transient cardiac contractility impairment and fluid overload.

OTHER OPTIONS FOR STEROID DOSING

- Can be used (but may result in lower efficacy). Dose must be adjusted based upon toxicity and patient tolerance. Some examples included below:

Option A: dexamethasone 20 mg PO once weekly (or dexamethasone 4 to 40 mg PO once weekly based on toxicity and patient tolerance)
Option B: predniSONE may be substituted for patient or physician preference, in a variety of regimens based upon toxicity and patient tolerance. (e.g. predniSONE 10 to 100 mg PO once weekly)
Option C: No dexamethasone/predniSONE. High-dose steroids may need to be avoided in certain patients who are intolerant or have difficulty with side-effects. It is expected that the response will be inferior than with high-dose steroids. High-dose steroids may be added for non-response. In cycle 1, hydrocortisone 100 mg IV should be considered prior to each isatuximab dose for prevention of IRR with isatuximab.

DOSE MODIFICATIONS:

For isatuximab: No specific dose modifications for isatuximab. Manage adverse reactions with treatment delays as indicated.

For carfilzomib:

Carfilzomib Dose Levels:

Drug	Dose Level 0	Dose Level -1	Dose Level -2	Dose level -3	Dose level -4
carfilzomib	70 mg/m^2	56 mg/m^2	45 mg/m^2	36 mg/m^2	27mg/m^2

1. Infusion-related reactions (IRRs): Isatuximab

- Refer to SCDRUGRX protocol for management guidelines.

Rate Adjustment for Isatuximab Infusion-Related Reactions:

Infusion reactions	Rate Adjustment
If BP falls to less than 80/50 mmHg or pulse increases to greater than 120 or if flushing, dyspnea, chills, rash, pruritus, vomiting, chest pain, throat tightness, cough, wheezing, or any other new acute discomfort, stop infusion and page physician	**Initial occurrence:** After recovery of symptoms, restart infusion at HALF the rate at which the infusion reactions occurred. If symptoms do not recur after 30 minutes, continue with escalation of infusion rates as per Treatment table, above. **Subsequent occurrence:** If the infusion must be stopped a second time, restart after recovery of symptoms, at HALF the rate at which the infusion reactions occurred and continue at that rate without further escalation

Infusion Rate when resuming isatuximab infusion after Grade 1 or greater symptoms are resolved:

Infusion Rate when Reaction Occurred (mL/hour)	Maximum Infusion Rate when Resuming Infusion (mL/hour)
25	13
50	25
75	38
100	50
125	63
150	75
175	88
200	100

2. **Hematological (based on pre-cycle lab work):**

- **Microangiopathy and thrombotic thrombocytopenic purpura is a rare but serious hematologic toxicity. If the clinical picture is suggestive, carfilzomib should be stopped immediately and a hemolytic work up should be initiated: CBC & Diff, platelets, peripheral smear, LDH, total and direct bilirubin, haptoglobin, DAT, creatinine, urea**

ANC (x10^9/L) on Day 1		**Platelets (x10^9/L)** on Day 1	**Carfilzomib Dose**	**Isatuximab Dose**	**Cyclophosphamide Dose (if using)**
Greater than or equal to 0.5	and	Greater than or equal to 50	Maintain dose level	100%	100%
0.5 to 0.99	and	30 to 49	Notify provider. Proceed but consider dose reduction by one dose level for low platelets.	100%	Delay until recovery
Less than 0.5†	or	Less than 30*	May proceed but consider decrease by one dose level if felt to be treatment related.		
Reoccurrence of less than 0.5†	or	Reoccurrence of less than 30*	For recurrence of ANC less than 0.5, may proceed but consider decrease by one dose level if felt to be treatment related Delay until platelets greater than or equal to 30, then consider decreasing by one dose level		

* follow hematology weekly and consider arrangements for transfusion support as required.

† Consider weekly filgrastim if clinically indicated and filgrastim is available. Filgrastim is not covered as a benefit drug by BC Cancer.

3. Non-hematological: carfilzomib and isatuximab

Toxicity During Treatment	Carfilzomib Dose	Isatuximab Dose
Renal*: Serum creatinine greater than or equal to 2 × baseline, or creatinine clearance less than 15 mL/min	Delay and decrease by one dose level when renal function has recovered to within 25% of baseline; dose may be escalated to previous dose at physician's discretion	100% No adjustment required in mild to severe renal impairment. No data in patients requiring hemodialysis
Febrile neutropenia	Delay and if ANC returns to baseline Grade and fever resolves, resume at same dose level	Delay until recovery and fever resolves, then proceed at 100%
Any Grade 3 or 4 non-hematological toxicity	Delay and consider decreasing by one dose level when toxicity has resolved to less than or equal to Grade 2 or baseline; dose may be escalated to previous dose at physician's discretion	Discontinue for Grade 4 infusion-related reaction. For all other non-hematological toxicities, proceed at 100% per physician discretion

* for patients receiving dialysis carfilzomib should be administered after the dialysis procedure

Non-hematological: cyclophosphamide

- Hepatic impairment: no dose reduction is necessary.
- Renal failure: dose reduction is necessary per table, below. Physician may consider giving full dose of cyclophosphamide irrespective of renal function if deemed to be of benefit.
- For patients on hemodialysis, give dose after dialysis.

Creatinine clearance (mL/min)	Cyclophosphamide Dose
Greater than or equal to 10	100 %
Less than 10	75 %

Calculated creatinine clearance = $\frac{N \times (140 - Age) \times weight\ (kg)}{Serum\ Creatinine\ (micromols/L)}$

N = 1.04 (Females) and 1.23 (Males)

PRECAUTIONS:

1. **Infusion- related reactions** to isatuximab are reported in up to 46% of patients. Most IRRs occur during the first cycle of isatuximab treatment, with the majority of reactions resolving on the same day. Symptoms include hypertension, dyspnea, bronchospasm, tachycardia, cough, dyspnea, nasal congestion, vomiting, nausea, and chills.
   To minimize the risk and severity of reaction, premedication with an antipyretic, H2 antagonist, antihistamine, and corticosteroid is recommended. When dexamethasone is prescribed as part of combination therapy, additional dexamethasone premedication may not be required. Permanently discontinue isatuximab if a Grade 4 or higher infusion-related reaction occurs, or if symptoms do not improve or recur after infusion interruption.

   Infusion-related reactions to carfilzomib are rare but can occur. Must be differentiated from fluid overload and congestive heart failure. Reactions can occur immediately following or within 24 hours of carfilzomib infusion. Symptoms may include: fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, and/or angina.

   For management of infusion-related reactions, see infusion-related reactions section in protocol, above, and BC Cancer Protocol SCDRUGRX: Management of Infusion-Related Reactions to Systemic Therapy Agents.
2. **Interference with cross-matching and red blood cell antibody screening** occurs due to drug binding to CD38 on red blood cells (RBC) resulting in a positive Indirect Antiglobulin Test (Coombs test). This interference may persist for up to 6 months post last isatuximab treatment. Inform blood bank that a patient has received isatuximab. Type and screen patients prior to starting isatuximab.
3. **Interference with determination of myeloma response** as isatuximab (a human IgG kappa monoclonal antibody) may be detected on serum protein electrophoresis and immunofixation assays which monitor for endogenous M-protein. Interference with these assays by isatuximab may affect the determination of complete response and disease progression in some patients with IgG kappa myeloma protein.
4. **Cardiac Toxicities:** New onset or worsening of pre-existing cardiac failure (e.g., pulmonary edema, decreased ejection fraction, congestive heart failure) is the main concern with carfilzomib. The mechanism of action is transient effects on myocardial contractility. It is reversible and can respond to standard CHF management often not necessitating discontinuation of therapy. Also reported are myocardial ischemia and infarction. Patients at high risk of cardiac complications include; those who are age 75 years or older, prior history of heart failure, recent myocardial infarction, conduction abnormalities, angina or presence of concomitant AL amyloidosis. Although adequate hydration is required prior to cycle 1, **monitor patients for volume overload and tailor fluid requirements as necessary in patients with pre-existing or at high risk of cardiac failure**. During treatment, monitor patients for clinical signs and symptoms of cardiac failure/ischemia. Withhold carfilzomib until recovery for Grade 3 or 4 cardiac adverse events. Carfilzomib may be restarted at a reduced dose following risk/benefit assessment. Following reconstitution, each mL of carfilzomib contains 0.3 mmols (7 mg) of sodium. This should be taken into consideration for patients on a controlled sodium diet.
5. **Hypertension** including hypertensive crisis has occurred with carfilzomib; hypertension should be well-controlled prior to initiation of treatment.

6. **Hemorrhage**, related to hematologic toxicity, both serious and fatal, including gastrointestinal, pulmonary and intracranial hemorrhage as well as serious cases of epistaxis may occur. Carfilzomib dose reduction or temporary discontinuation may be required following signs of blood loss.
7. **Hematologic** toxicities including neutropenia, febrile neutropenia, thrombocytopenia, lymphocytopenia and anemia are reported during treatment with isatuximab. Infections including upper respiratory tract infections, pneumonia, and urinary tract infections are reported and occur even in the absence of neutropenia. Patients with neutropenia should be closely monitored for signs of infection and promptly treated.
8. **Hepatotoxicity:** Hepatic failure, including fatal cases, have been reported in multiple myeloma patients treated with carfilzomib. Hold treatment upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose of carfilzomib may be considered.
9. **Renal Toxicity** occurs in up to 10% of carfilzomib patients and may require dose reduction, interruption, or therapy discontinuation. The risk of renal failure may be greater in patients with a reduced creatinine clearance at baseline. Ensure patient is adequately hydrated to mitigate the risk of renal toxicity. **Must monitor for thrombotic microangiopathy as noted above.** See Dose Modifications, above.
10. **Pulmonary toxicities** including Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease, such as pneumonitis and interstitial lung disease have been reported with carfilzomib. Some of these events have been fatal. Hold carfilzomib until these events resolve; consider the benefits and risks when deciding if treatment should be re-initiated.
11. **Posterior Reversible Encephalopathy Syndrome (PRES)** cases have been reported with carfilzomib. Symptoms include seizure, headache, lethargy, confusion, blindness, altered consciousness, and/or other visual and neurological disturbances, along with hypertension. Hold treatment if suspected and evaluate by neuro-radiological imaging.
12. **Hepatitis B Reactivation**: See SCHBV protocol for more details.
13. **Need for irradiated blood products:** Patients receiving an autologous stem cell transplant require irradiated blood products from 7 days prior to collection to 3 months post-transplant (6 months if total body irradiation conditioning) to eliminate the risk of potentially life-threatening transfusion-related graft-versus-host-disease. All other myeloma patients do not require irradiated blood products.

Call Dr. Christopher Venner or tumour group delegate at 604-877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Moreau P, Dimopoulos MA, Mikhael J, et al; IKEMA study group. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. Lancet. 2021 Jun 19;397(10292):2361-2371.
2. Moreau P, Mateos MV, Berenson JR, et al. Once weekly versus twice weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (A.R.R.O.W.): interim analysis results of a randomised, phase 3 study. Lancet Oncol. 2018 Jul;19(7):953-964.
3. CADTH Reimbursement Review. Provisional Funding Algorithm. Multiple Myeloma. November 2022.
4. Isatuximab (Sarclisa) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies 2022; 2(2): 1-19.
5. Georgiopoulos G, Makris N, Laina A, et al. Cardiovascular Toxicity of Proteasome Inhibitors: Underlying Mechanisms and Management Strategies: *JACC: CardioOncology* State-of-the-Art Review. JACC CardioOncol. 2023 Feb 21;5(1):1-21.

Appendix:

Isatuximab Infusion Rate Titration Table

Isatuximab – UMYISACARD

Cycle 1 Day 1:

Isatuximab 10 mg/kg in 250 mL NS Total Volume – refer to Pharmacy Label		
TITRATION RATE	**DURATION**	**VOLUME TO BE INFUSED (VTBI)**
25 mL/h	**60 minutes**	**25 mL**
50 mL/h	**30 minutes**	**25 mL**
75 mL/h	**30 minutes**	**38 mL**
100 mL/h	**30 minutes**	**50 mL**
125 mL/h	**30 minutes**	**63 mL**
150 mL/h	**To Be Determined***	**To Be Determined***

*Refer to Total Volume on Pharmacy label and adjust duration and VTBI as needed

Cycle 1 Day 8:

Isatuximab 10 mg/kg in 250 mL NS Total Volume – refer to Pharmacy Label		
TITRATION RATE	**DURATION**	**VOLUME TO BE INFUSED (VTBI)**
50 mL/h	**30 minutes**	**25 mL**
100 mL/h	**30 minutes**	**50 mL**
200 mL/h	**To Be Determined***	**To Be Determined***

*Refer to Total Volume on Pharmacy label and adjust duration and VTBI as needed

Cycle 1 Day 8 (Slow infusion)

Isatuximab 10 mg/kg in 250 mL NS Total Volume – refer to Pharmacy Label		
TITRATION RATE	**DURATION**	**VOLUME TO BE INFUSED (VTBI)**
25 mL/h	**60 minutes**	**25 mL**
50 mL/h	**30 minutes**	**25 mL**
75 mL/h	**30 minutes**	**38 mL**
100 mL/h	**30 minutes**	**50 mL**
125 mL/h	**30 minutes**	**63 mL**
150 mL/h	**To Be Determined***	**To Be Determined***

*Refer to Total Volume on Pharmacy label and adjust duration and VTBI as needed

Cycle 1 Day 15 and onwards

Isatuximab 10 mg/kg in 250 mL NS Total Volume – refer to Pharmacy Label	
DURATION	**VOLUME TO BE INFUSED (VTBI)**
30 minutes	**250 mL***

*Refer to Total Volume on Pharmacy label and adjust VTBI as needed

Cycle 1 Day 15 and onwards (Slow infusion)

Isatuximab 10 mg/kg in 250 mL NS Total Volume – refer to Pharmacy Label		
TITRATION RATE	**DURATION**	**VOLUME TO BE INFUSED (VTBI)**
100 mL/h	**60 minutes**	**100 mL**
150 mL/h	**60 minutes**	**150 mL**
200 mL/h	**To Be Determined***	**To Be Determined***

*Refer to Total Volume on Pharmacy label and adjust duration and VTBI as needed

Appendix: Infusion Related Reaction

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDS, narcotics, iv fluids); prophylactic medications indicated for less than or equal to 24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and /or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death

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