Hypersensitivity & Infusion Reaction Management Guide

SCC PHARMACY
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Reaction Management

General Signs and Symptoms of Reactions

The most common signs and symptoms are cutaneous (e.g., sudden onset of generalized urticaria, angioedema, flushing, and pruritus). However, 10-20% of patients have no skin findings. Danger signs: Rapid progression of symptoms, respiratory distress (e.g., stridor, wheezing, dyspnea, increased work of breathing, persistent cough, cyanosis), vomiting, abdominal pain, hypotension, dysrhythmia, chest pain, collapse.

Infusion Reactions

These is common with taxanes, rituximab, bleomycin, daratumumab, PEGylated liposomal doxorubicin and daunorubicin, trastuzumab, immunotherapy (list), brentuximab, ofatumumab, panitumumab.

Related to the administration of the chemotherapy, the agent may or may not have an allergic component. Infusion reactions may affect any organ system in the body. Most are mild in severity, although severe and even fatal reactions occur. The most common signs and symptoms of infusion reactions are:

- Flushing
- Itching
- Alterations in heart rate and blood pressure
- Dyspnea or chest discomfort
- Back or abdominal pain
- Fever and/or shaking chills
- Nausea, vomiting, and/or diarrhea
- Various types of skin rashes
- Throat tightening
- Hypoxia
- Seizures
- Dizziness and/or syncope

Anaphylaxis Reactions

These are common with platinum agents, asparaginase, etoposide, cetuximab, alemtuzumab. Reactions usually occur during or within a few hours of drug infusion. Although they occur most commonly with the first or second drug administration, infusion reactions are unpredictable and can occur at any time despite preventive measures (especially with platinum agents).
The most **common signs and symptoms of anaphylaxis** caused by intravenously administered medications are the following:

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUTANEOUS SYMPTOMS</td>
<td>Flushing, itching, urticaria, and/or angioedema (usually of face, eyelids, or lips)</td>
</tr>
<tr>
<td>RESPIRATORY SYMPTOMS</td>
<td>Repetitive cough, sudden nasal congestion, shortness of breath, chest tightness, wheeze, sensation of throat closure or choking, and/or change in voice quality (due to laryngeal edema), hypoxia</td>
</tr>
<tr>
<td>CARDIOVASCULAR SYMPTOMS</td>
<td>Faintness, tachycardia (or less often bradycardia), hypotension, hypertension and/or loss of consciousness</td>
</tr>
<tr>
<td>GASTROINTESTINAL SYMPTOMS</td>
<td>Nausea, vomiting, abdominal cramping, and/or diarrhea</td>
</tr>
<tr>
<td>NEUROMUSCULAR SYMPTOMS</td>
<td>Sense of impending doom, tunnel vision, dizziness, and/or seizure, severe back, chest, pelvic pain</td>
</tr>
</tbody>
</table>

Although there is overlap between the clinical features of anaphylaxis and those of infusion reactions, certain **signs and symptoms are highly suggestive of anaphylaxis**, and they should be specifically sought out when evaluating a patient with an infusion reaction: *urticaria, repetitive cough, wheeze, throat tightness/change in voice, and hypotension*.

These stereotypical signs and symptoms result from the release of mediators from mast cells and basophils. In contrast, *fever and prominent muscular pain are NOT features of anaphylaxis*, and the presence of these signs and symptoms suggests the reaction is an infusion reaction.

It is **critical to undress the patient and examine the skin carefully during reactions** to fully appreciate skin findings, especially urticaria. The neck, trunk, extremities, abdomen, and axillae are the sites where urticaria often appears first.
Grading of Reactions

Infusion Reactions

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild transient reaction; infusion interruption not indicated; intervention not indicated</td>
</tr>
<tr>
<td>2</td>
<td>Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics [opioids], (intravenous fluids); prophylactic medication indicated for less than or equal to 24 hours</td>
</tr>
<tr>
<td>3</td>
<td>Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>

* Infusion-related reaction is characterized by adverse reaction to the infusion of pharmacological or biological substances
* NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events;
  NSAIDs: nonsteroidal anti-inflammatory drugs.

Anaphylactic Reactions

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension</td>
</tr>
<tr>
<td>2</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>3</td>
<td>Death</td>
</tr>
</tbody>
</table>

* Anaphylaxis is characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death.
Patients with mild signs or symptoms of anaphylaxis should not be re-exposed to the causative agent until they have been evaluated by the attending physician. In particular, these patients should NOT be considered candidates for additional premedication and an attempt at drug re-administration using a slower rate of infusion unless specified by the prescribing physician. Desensitization protocols should only be attempted if the drug cannot be substituted for a clinically equivalent option.

**Immediate steps**

1. Stop the infusion  
2. Maintain i.v. access  
3. ABCs: Airway, Breathing, Circulation  
4. Assess level of consciousness  
5. Vital signs  
6. If ↓ blood pressure → Trendelenburg position  
7. Oxygen if needed

**If further measures needed, EMSA to be called.**

**Treatment of mild to moderate reactions**

- Mild to moderate infusion reactions (i.e., National Cancer Institute [NCI] Grade 1, Grade 2) and infusion reactions that do not involve symptoms of anaphylaxis can usually be managed with temporary interruption of the infusion and symptom management. All the necessary medications are in the infusion reaction bags; these are available on each nursing unit. Refer to Paclitaxel and Rituximab Protocols for patients that appropriate for re-challenge on the titration protocol.

**Re-challenge**

- **Alert an attending** before re-challenge attempt.

### NCI CTCAE V5.0 Allergic Reaction

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Allergic reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Systemic intervention not indicated</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Oral intervention indicated</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death</td>
</tr>
</tbody>
</table>

*Allergic reactions are characterized by adverse local or general responses from exposure to an allergen. NOTE: If related to a drug infusion, use the grading scheme for infusion-related reaction.*
After all symptoms have resolved, re-challenge with a reduced infusion rate and additional premedication is usually successful.

Following a severe infusion reaction (NCI Grade 3 or higher), re-challenge is usually discouraged. This is particularly true if the SIR included any symptoms suggestive of an allergic reaction, such as urticaria or angioedema

H1/H2 antagonists: diphenhydramine 50 mg i.v. plus famotidine 20 mg i.v.

Corticosteroids equivalent dose to 125 mg of i.v. (methyl) prednisolone once. May be repeated in 4-6 hours if needed.

Acute management

Reactions with any features of anaphylaxis or severe infusion reactions (NCI Grade 3 or higher) require discontinuation of the drug infusion and immediate treatment with epinephrine (see dose below) and antihistamines.

The first and most important treatment in anaphylaxis is epinephrine.

- There are NO absolute contraindications to epinephrine in the setting of anaphylaxis.
- Airway: Immediate intubation if evidence of impending airway obstruction from angioedema. Delay may lead to complete obstruction.
  - Intubation can be difficult and should be performed by the most experienced clinician available. EMSA should be called immediately if an experienced clinician is not available.
- Promptly and simultaneously, give IM epinephrine (1 mg/mL preparation): Give epinephrine 0.3 to 0.5 mg intramuscularly, preferably in the mid-outer thigh.
- Can repeat every 5 to 15 minutes (or more frequently), as needed.
- If epinephrine is injected promptly IM, most patients respond to one, two, or at most, three doses. After second dose, physician to be called. Use discretion on inpatient EMSA being called and admission/observation for the patient.

Normal saline rapid bolus Treat hypotension with rapid infusion of 1 to 2 liters IV. Repeat, as needed. Massive fluid shifts with severe loss of intravascular volume can occur.

Albuterol (salbutamol): For bronchospasm resistant to IM epinephrine, give 2.5 to 5 mg of albuterol in 3 mL saline via nebulizer. Repeat, as needed.

Restart infusion at 50% rate and titrate to tolerance (If no Grade 3 or 4)

For patients who have recurrent SIRs despite premedication, desensitization protocols have allowed for continued use of the drug in some cases.

Adjunctive therapies

- H1 antihistamine*: Give diphenhydramine 50 mg IV (for relief of urticaria and itching only).
- H2 antihistamine*: Give famotidine 20 mg IV.
- Glucocorticoid*: Give methylprednisolone 125 mg IV.
Monitoring: Continuous noninvasive hemodynamic monitoring and pulse oximetry monitoring should be performed. Urine output should be monitored in patients receiving IV fluid. Resuscitation for severe hypotension or shock.

Documentation of Infusion Reaction

<table>
<thead>
<tr>
<th>How To Document An Infusion Reaction (IR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRE-INFUSION ASSESSMENT</strong></td>
</tr>
<tr>
<td>➢ Drug</td>
</tr>
<tr>
<td>➢ Number of cycles</td>
</tr>
<tr>
<td>➢ Reintroduction of treatment (Yes/No)</td>
</tr>
<tr>
<td>➢ Relevant medical history/allergy/atopy</td>
</tr>
<tr>
<td>➢ Concomitant medication</td>
</tr>
<tr>
<td>➢ Oral premedication correctly taken</td>
</tr>
<tr>
<td>➢ Infusion rate</td>
</tr>
<tr>
<td>➢ Premedication</td>
</tr>
<tr>
<td>➢ Timing of symptom onset</td>
</tr>
<tr>
<td>➢ Vital signs</td>
</tr>
<tr>
<td>➢ Symptoms/signs</td>
</tr>
<tr>
<td>➢ Standard grading (CTCAE)</td>
</tr>
</tbody>
</table>

**RELEVANT INFORMATION OF THE IR EVENT**

**MANAGEMENT**

➢ Intervention
➢ Time to symptom resolution
➢ Patient response Reintroduction (Yes/No)
➢ Rate reintroduction

References

CTCAE, Common Terminology Criteria for Adverse Events

Pager Instructions

Coverage Begins March 1, 2019
Coverage Ends: TBD

1. **All APPS must be hospital credentialed**, as the infusion center is now hospital based.

2. APP Coverage will be scheduled. This schedule will be shared on a monthly basis.

3. **Coverage begins at 8:00 a.m. and ends at 5:00 p.m.** Infusion Center hours are 7:00 a.m. – 6:00 p.m. The incident two physician will take the call before and after hours.

4. APPs are expected to **physically carry a pager, remain in the building and available at all times** during your date of coverage.

5. **The assigned pager will be picked up and dropped off from the front desk in infusion on the third floor.**

6. **If you are unavailable on one of the days you are scheduled:**
   a. Please find someone to cover your shift at least 24 hours in advance.
   b. Notify Nike Miller, Nikesia-Miller@ouhsc.edu, so that calendar can be updated.
   c. Please be generous and accommodating when coverage needs to be switched.

7. Director of Pharmacy will provide training on management of reactions.
   a. **If you are unable to attend, you will be required to complete an online training.**

8. **Meet RNs at the round table** (patient snack table) in between both sections when responding to a page.
   a. Contact Rizan Mohsin rizan-mohsin@ouhsc.edu if you have issues accessing the training

9. Copy and paste [https://intranet.stephensongynecancercenter.org/Resources/Infusion-Policies](https://intranet.stephensongynecancercenter.org/Resources/Infusion-Policies) into your browser. Login using your credentials and click on “Hypersensitivity training” to access the presentation at any time.
   a. Contact Rizan Mohsin rizan-mohsin@ouhsc.edu if you have issues accessing the training.