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# Integrating Best Evidence to Solve the Puzzle of Managing Hypersensitivity Reactions

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## Objective

- Identify one positive patient and staff outcome from using evidence-based practices to manage infusion reactions

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## Disclosures

- No conflicts of interest to disclose

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# Background

- Many Drugs with High Risks of Reactions
  - ❑Antibiotics (esp. PCN and Sulfas)
  - ❑NSAIDS
  - ❑Chemotherapy
  - ❑Biotherapy/monoclonal agents
- Oncology Staff with Increased Risks

Image from: www.drugdiscovery.com


Image from: www.fourstarplastics.com

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**Figure 19. Immediate Hypersensitivity Reactions: Predicted Risk of Chemotherapy**

**High Potential**
- L-Asparaginase
- Taxanes
  - Paclitaxel
  - Docetaxel
- Platinum compounds
  - Cisplatin
  - Carboplatin
  - Oxaliplatin
- Epipodophyllotoxins
  - Etoposide
  - Teniposide

**Occasional Potential**
- Anthracyclines
  - Doxorubicin
  - Daunorubicin
  - Idarubicin
  - Epirubicin
- Mercaptopurine
- Azathioprine

**Rare Potential**
- Bleomycin
- Chlorambucil and melphalan
- Cyclophosphamide and ifosfamide
- Cytarabine and fludarabine
- Dacarbazine
- Dactinomycin
- 5-Fluorouracil
- Hydroxyurea
- Methotrexate
- Polyethylene glycol-modified *E. coli* asparaginase
- Vincristine and vinblastine

*Note.* From "Chemotherapy-Induced Hypersensitivity Reactions," by B.H. Gobel, 2005, *Oncology Nursing Forum, 32*, p. 1029. doi:10.1188/05.ONF.1027-1035. Copyright 2005 by Oncology Nursing Society. Reprinted with permission.

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**Figure 20. Biotherapy Drugs Associated With Hypersensitivity Reactions and Cytokine-Release Syndromes**

**Interferon**
- Interferon alfa
- Interferon beta (1A and 1B)
- Interferon gamma

**Interleukin**
- Aldesleukin
- Denileukin diftitox

**Kinase Inhibitor**
- Temsirolimus

**Monoclonal Antibodies**
- Murine
  - Ibritumomab tiuxetan
  - Tositumomab
- Chimeric
  - Brentuximab
  - Cetuximab
  - Rituximab
- Humanized
  - Alemtuzumab
  - Bevacizumab
  - Gemtuzumab ozogamicin
  - Trastuzumab
- Fully human
  - Ipilimumab
  - Ofatumumab
  - Panitumumab

*Note.* Based on information from Bristol-Myers Squibb Co., 2013; GlaxoSmithKline, 2011; Gobel, 2007; Lenz, 2007; Seattle Genetics, Inc., 2012; Wyeth Pharmaceuticals, 2012.

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# Background

- Rituximab (Rituxan) Most Frequent Reaction
- Reactions Range from Mild to Severe
- Requires Standard Protocol & Medications
- Documentation and Follow-up

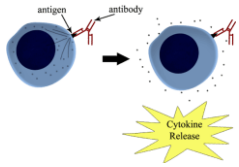


Image from: https://www.researchgate.net/figure/Antibody-activation-and-cytokine-release-Antibodies-can-bind-antigens-resulting-in_fig4_221925519

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# Definitions

| Anaphylaxis | Hypersensitivity | Cytokine Release |
|---|---|---|
| • IgE Mediated<br>• 5-10 minutes<br>• Delayed<br>• Often Uriticarial | • Typical Type 1<br>• Multiple Infusions<br>• Local or Generalized | • Monoclonals<br>• 30-120 min<br>• Grade 1-2<br>• Antihistamine & Restart |

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**Table 16. Grading Criteria for Allergic Reactions, Anaphylaxis, and Cytokine-Release Syndrome**

| Adverse Event | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|
| Allergic reaction | Transient flushing or rash, drug fever < 38°C (< 100.4°F); intervention not indicated | Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics); prophylactic medications indicated for ≤ 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 (e.g., renal impairment, pulmonary infiltrates) | Life-threatening consequences; urgent intervention indicated | Death |
| Anaphylaxis | – | – | Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension | Life-threatening consequences; urgent intervention indicated | Death |
| Cytokine-release syndrome | Mild 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 ≤ 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 (e.g., renal impairment, pulmonary infiltrates) | Life-threatening consequences; pressor or ventilatory support indicated | Death |

IV—intravenous; NSAIDs—nonsteroidal anti-inflammatory drugs

*Note.* From *Common Terminology Criteria for Adverse Events* [v.4.03], by the National Cancer Institute Cancer Therapy Evaluation Program, 2010. Retrieved from http://ws.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

## Significance

- Needs Assessment:
  - ❑Lack of Knowledge
  - ❑Inconsistent Charting/Grading
  - ❑Inconsistent Reaction Management
  - ❑Poor Patient Outcomes
  - ❑Out of Date Order Sets
  - ❑Lacked Nursing Autonomy

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## Evidence Evaluation

- No Albuterol
- Epinephrine Under Utilized
- Demerol Not Supported
- No Grading Scale
- Dosages Random
- Decadron First-Line
- Rationales Missing

Image from: www.clipart-library.com

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## Purpose/objectives

1. Increase staff knowledge of infusion reaction signs/symptoms and management
2. Develop appropriate documentation process and fields
3. Update medication order set to align with the latest evidence

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## Project Team

**Inter-professional taskforce including:**
Nursing, Pharmacy, Physicians, Respiratory Therapists, and IT departments led by the Oncology CNS

Image from: www.clipart-library.com

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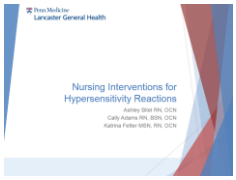
## Interventions

- Education
- Pre and Post Test
- Algorithm
- Chart Audits
- Real-Time Feedback

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## Nursing Management of Infusion Reactions

| | |
|---|---|
| Signs of Cytokine Release Syndrome (fever, chills, hypotension, tachycardia, headache, tongue/throat swelling, dyspnea) | • Administer Diphenhydramine 50mg IV<br>• Administer Dexamethasone 4mg IV to prevent delayed reaction<br>• Consider Demerol (high risk med with minimal evidence to support) |
| Bronchial Constriction (Dyspnea, Wheezing, Stridor) | • Epinephrine 0.3mg IM in thigh |
| Shortness of breath, tachypnea, or decreased oxygen saturation | • Oxygen at 6-10 L/min by face mask<br>• Albuterol 2.5mg by inhalation |
| Hypotension (>30% decrease in SBP from baseline) | • Epinephrine 0.3mg IM into thigh OR IV bolus 0.5-1mL<br>• Normal Saline IV 500mL fluid bolus over 10 minutes, then as ordered |
| Hives, itching, flushing, swollen lips or tongue | • Diphenhydramine 25-50mg IVP<br>• Famotidine 20mg IV OR Ranitidine 50mg IV |
| Prevention of delayed reaction (limited evidence) | • Dexamethasone 10-20mg IV<br>• Methylprednisone 30-50mg IV<br>• Hydrocortisone 100-500mg IV |

## Order Set Med Updates

- Faster Bolus
- Increased Decadron
- Increased Oxygen
- Removed Ativan

- Decreased Demerol
- Added Pepcid
- Added Albuterol


Image from: www.addictionsearch.com

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## Order Set Updates

- Indications Clear
- Order/Rationale for Administration
- Demerol for Rigors only as Last Resort
- Myths about Epinephrine

Image from: www.epipen.ca


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**Hypersensitivity Infusion Reaction Orders [524]**

**Medications**

**Hypersensitivity/Infusion Reaction Orders**

Hypersensitivity/ infusion-reaction symptoms include any adverse symptom or physical sign during an infusion that may be considered potentially life threatening: Cough, wheezing, shortness of breath, chest tightness/pain, hypotension/hypertension, angioedema (swelling of mucous membranes and skin), increased mucous production, urticaria/hives, flushing, fever, chills/rigors, nausea/vomiting and generalized restlessness/anxiousness.

| | |
|---|---|
| ☑ Monitor for signs of reaction | Routine, UNTIL DISCONTINUED, Starting today For Until specified, If patient shows first sign of reaction then STOP infusion immediately and initiate reaction orders immediately. Hypersensitivity/ infusion-reaction symptoms include any adverse symptom or physical sign during an infusion that may be considered potentially life threatening: cough, wheezing, shortness of breath, chest tightness/pain, hypotension/hypertension, angioedema (swelling of mucous membranes and skin), increased mucous production, urticaria/hives, flushing, fever, chills/rigors, nausea/vomiting and generalized restlessness/anxiousness. |
| ☑ NaCl 0.9% bolus | 500 mL, Intravenous, for 31 Minutes, ONCE PRN, For hypotension caused by hypersensitivity/infusion reaction, For 1 Doses<br>Run wide open through a piggy-backed line |
| ☑ Apply Nasal Cannula or Mask (2-4 LPM) to Maintain Sp02 greater or equal to 92% | Routine, PRN<br>Liters per minute: 2 LPM<br>Titrate to Keep O2 Sats: |
| ☑ diphenhydrAMINE (BENADRYL) injection | 50 mg, Intravenous, ONCE PRN, Itching, for hypersensitivity / infusion reaction OR shivers/rigors, Starting today, For 1 Doses<br>Administer first. |
| ☑ famotidine (PEPCID) | 20 mg, Intravenous, ONCE PRN, Heartburn, for hypersensitivity/infusion reaction, For 1 Doses<br>Administer immediately after diphenhydramine. |
| ☑ dexamethasone (DECADRON) injection | 10 mg, Intravenous, ONCE PRN, hypersensitivity reaction, For 1 Doses |

| | |
|---|---|
| ☑ meperidine (DEMEROL) injection | 12.5 mg, Intravenous, ONCE PRN, Shivers, For shivers/rigors, Starting today, For 1 Doses<br>Give if shivers/rigors not controlled by diphenhydramine. |
| ☑ EPINEPHrine (ADRENALIN) injection | 0.3 mg, Intramuscular, ONCE PRN, Anaphylaxis, Starting today, For 1 Doses<br>For anaphylaxis, dyspnea, wheezing, stridor, or hypotension not improved after 10 minutes of NaCl bolus at 999 mL/hr. |
| ☑ albuterol (PROVENTIL) nebulizer solution | 2.5 mg, Nebulization, ONCE PRN, Wheezing, Shortness of breath, tachypnea, or decreased oxygen saturation, For 1 Doses |

## Documentation

- Added Validated Grading Scale
- Guidelines for Provider Communication
- Updated Medications to Match Orders
- Developed Messaging in EMR
- Post-Reaction Documentation

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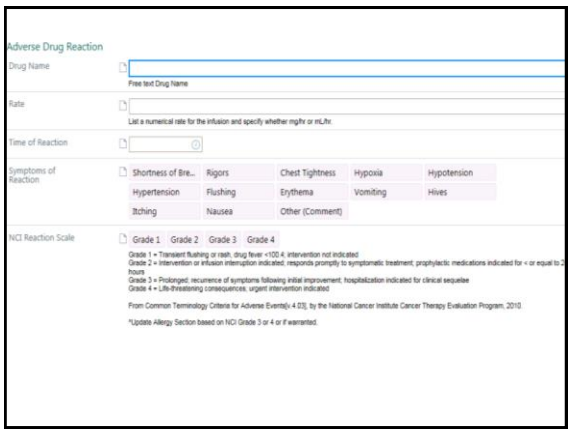

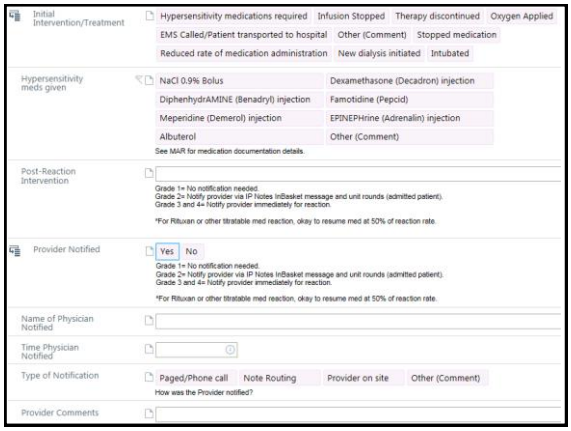

Initial Intervention/Treatment
Hypersensitivity medications required | Infusion Stopped | Therapy discontinued | Oxygen Applied
EMS Called/Patient transported to hospital | Other (Comment) | Stopped medication
Reduced rate of medication administration | New dialysis initiated | Intubated

Hypersensitivity meds given
NaCl 0.9% Bolus | Dexamethasone (Decadron) injection
DiphenhydrAMINE (Benadryl) injection | Famotidine (Pepcid)
Meperidine (Demerol) injection | EPINEPHrine (Adrenalin) injection
Albuterol | Other (Comment)
See MAR for medication documentation details.

Post-Reaction Intervention
Grade 1= No notification needed.
Grade 2= Notify provider via IP Notes InBasket message and unit rounds (admitted patient).
Grade 3 and 4= Notify provider immediately for reaction.
*For Rituxan or other titratable med reaction, okay to resume med at 50% of reaction rate.

Provider Notified
Yes | No
Grade 1= No notification needed.
Grade 2= Notify provider via IP Notes InBasket message and unit rounds (admitted patient).
Grade 3 and 4= Notify provider immediately for reaction.
*For Rituxan or other titratable med reaction, okay to resume med at 50% of reaction rate.

Name of Physician Notified

Time Physician Notified

Type of Notification
Paged/Phone call | Note Routing | Provider on site | Other (Comment)
How was the Provider notified?

Provider Comments

## Interventions

- Direct Observations
- Monthly Report Run
- Data Tracked
- Sharing Trends
- Ongoing Evaluations

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## Outcomes

- Improved Test Scores
- Subjective Feedback
- Enhanced Response to Reactions
- Ongoing Opportunities

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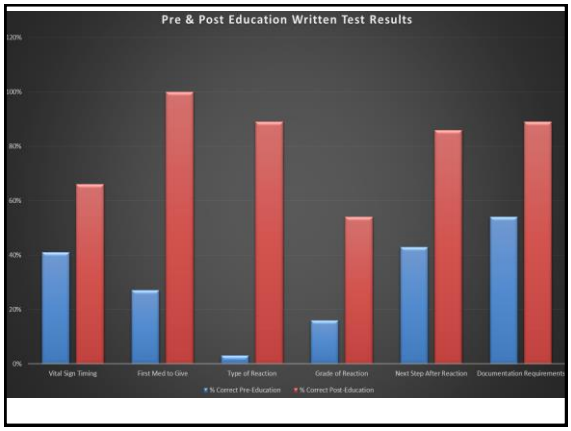


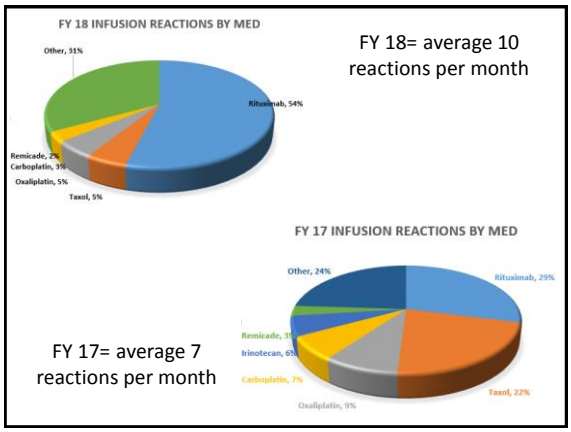


## Discussion/Next Steps

- Monthly Review of Reactions
- Identify Trends & Educate
- Biannual Report Out at Formulary Committee
- CNS Rounding with Feedback on Adherence
- CNS Available for Consultation

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## Opportunities

- Education Documentation-Start Tracking
- Post-Reaction Documentation (missing 50%)
- Missing a Med or Wrong First-Line Med (12%)
- Incorrect Grading (19%)


Image from: www.clipart-library.com

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## Questions?

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