When it comes to emergency management of hypersensitivity infusion reactions, many oncology nurses have a general knowledge but not the ability to apply immediate pharmacologic interventions. Don’t stop at by-the-books knowledge—make sure you’re prepared for the rapid recognition, management, and treatment of these complications. In this session, you’ll cover the pathophysiology and etiology of an infusion reaction, preventive and therapeutic pharmacological management, how to incorporate the CTCEA grading criteria to guide nursing interventions, and how to perform a comprehensive nursing risk assessment. Speakers will walk you through an evidence-based, nurse-driven procedure within a large healthcare system, helping you to visualize the outcomes of time-sensitive assessment and management.

Content Outline:
I. Pathophysiology/etiology of an infusion reaction
   A. Hypersensitivity/anaphylaxis immune responses
   B. Cytokine release syndrome
      1. Chemotherapy/biotherapy associated with high risk for infusion reaction
   2. Comprehensive nursing risk assessment
      a. Prophylaxis, premedication (antipyretics, antihistamines, steroids)
      b. Therapeutic action of epinephrine in anaphylaxis
II. Time-sensitive nursing management of infusion reaction
   A. Failure mode effect analysis
   B. The development of an evidence-based nurse-driven policy and procedure
      1. Inclusion of CTCEA grading criteria to guide nursing interventions
      2. Collaboration of pharmacy, physicians, and nursing
         a. Implementation of policy and procedures
         b. Evaluation of the outcomes

Bibliography:


Lexi-Comp OnlineTM, Lexi-Drugs OnlineTM, Hudson, Ohio: Lexi-Comp, Inc.; February 20, 2011.


Pichler, W.J. (2006). Adverse side-effects to biological agents. [Research Support, Non-U.S. Gov’t].


Complement

- More than 30 proteins that can recognize and bind to foreign molecules
- Complement activation releases other proteins and enzymes which enhance inflammatory processes
- Once activated, complement proteins coat foreign substances and allows them to be more visible to macrophages and mast cells
- Releases anaphylatoxins which stimulate an inflammatory response

Mast Cells

- Are considered “first responders” to a stimulus
- Can live for up to a year
- Do not circulate
- Found throughout the body (high concentrations in epithelial and mucosal tissues) and are specialized in each location
- Complement (e.g., C3a, C4a, C5a)
- Cytokines (IL-1β, IL-3, IL-6, IL-9, IL-10, IL-11, GMCSF)
- IgE and IgG
- Neuropeptides (e.g., substance P)

Mast Cells Contain:

- Adhesion molecules (allows non-specific attachment to foreign molecules)
- Protease Granules
  - Trypsin (generates complement C3a, enhances respiratory effects of histamine, and recruits inflammatory cells)
  - Chymase (converts angiotensin II to angiotensin I) enhances histamine, and stimulates IL-4 production
- Additional granules:
  - Carboxypeptidase
  - Cathespins G
- Heparin
- Histamine

Degranulation occurs within seconds to minutes, although not all substances are released at once

Mast Cells Produce:

- Vasoactive mediators and cytokines
  - Prostaglandins (e.g., PGD2)
  - Leukotrienes (LTC4, LTD4, LTE4)
  - Cox2
  - IL 3, IL-4, IL-5, IL6, IL-8, SCF, TNFα
- Lipid-derived Mediators (from arachidonic acid)
**Basophils**
- Found in the circulatory system
- Lifespan of several days
- Activated by IL-3, IL-5, IL-18, IL-33, C3a and C5a, IgE and and thymic stromal lymphopoietin (TSLP)
- In animal models: IL-3 produces urticaria, Nv/V/d and edema
- Contain granules (tryptase, chymase)
- Produce IL-4, IL-13, leukotriene LTC4, platelet activating factor, and histamine
- Express CD40L (TNF family), chemokine CCR3
- Interact with T-cells and IgE

**Newly Formed Mediators**
- Leukotrienes:
  - CysLT1 and CysLT4 increase vascular permeability
  - CysLT1 and CysLT4 increase vascular permeability and bronchoconstrictive
- Platelet Activating Factor (PAF):
  - Increases vascular permeability
  - Causes bronchoconstriction
  - Causes degradation of white cells
- Prostaglandin D2 (PGD2):
  - Acts on receptors on smooth muscle cells
  - Prostaglandins
  - Bronchoconstriction, vasoconstriction, smooth muscle constriction

**Cytokines**
- Chemical messenger proteins or glycoproteins
- Activate immune cells
- Stimulate the production of:
  - Additional cytokines (e.g., TNF-a, IFN-y)
  - Endothelial leukocyte adhesion molecule 1
  - Vascular cell adhesion molecules
  - Cause the release of:
    - Prostaglandins
    - Leukotrienes
    - Proteases

**Immune Reactions**
**Initial drug exposure or cross-reactivity**
- Production of antigen-specific IgE
- Mast cells sensitized

**Subsequent exposure causes mast cell degranulation**
(begins non-immune HSR sequence)

**Paclitaxel**
- Formulated in Cremophor EL® (CrEL) and ethanol (1:1)
- CrEL directly activates complement C3a, C5b, and SC5b-9
- Most reactions occur with 1st or 2nd dose, usually within first 10 minutes
- Similar reaction rate with 1hr vs. 3hr infusion
- Manufacturer recommended premedication:
  - H1 Antagonist
  - Steroid
  - Diphenhydramine

**Docetaxel**
- Highly insoluble in sterile water
- Formulated with Tween® 80 [Polysorbate 80]
- Mixture of esters of sorbitol and polyethylene glycol
- Used in lotions, cosmetics, suppositories, oral and IV medications
- Less data than for CrEL, but also believed to activate complement
**Docetaxel**
- Most reactions occur with 1st or 2nd dose, usually within a few minutes of starting the infusion
- Manufacturer recommended premedication:
  - Oral steroid (e.g., dexamethasone)
  - No data on use of antihistamines
  - Severe reactions have been reported despite premedication

**Etoposide**
- Etoposide contains Tween® 80 (46%-51%)¹
- Tween® 80 content: Example BSA 2.0 (50mg/M²)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tween® 80</th>
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<tbody>
<tr>
<td>Etoposide</td>
<td>520mg</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>1300mg</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>800mg</td>
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</table>

- Etoposide phosphate (no Tween® 80): 3%²
- No manufacturer recommended premeds

**PEGylated Liposomal Doxorubicin**
- Liposomes can activate complement [C3a and C5a]¹
- Pegylation may enhance liposomal HSR¹
- Tachyphylaxis observed in animal models¹
- When given together, may decrease incidence of carboplatin HSR¹
- No manufacturer recommended premeds
- Start infusion at 1mg/min¹

**Platinum Agents HSRs**
- Occur with subsequent doses
- Most to least frequent:
  1. Carboplatin
  2. Cisplatin
  3. Oxaliplatin
- Antihistamines do not prevent HSR
- Patients may be responsive to desensitization protocols

<table>
<thead>
<tr>
<th>Carboplatin Cycle</th>
<th>Risk of HSR (%)</th>
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<tbody>
<tr>
<td>1-3</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>6.5</td>
</tr>
<tr>
<td>≥7</td>
<td>27</td>
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**L-asparaginase**
- Derived from either *Escherichia-coli* or *Erwina chrysanthemi* – both are highly antigenic and can produce anti-asparaginase antibodies
- PEGylated *Escherichia-coli* product has replaced “native” version (discontinued 12/2012) [note most HSR data is for native version]
- HSR may be IgG, IgM, or CARPA and occur after 1st dose (within 1 hour)
- Increased risk with number of doses and/or IV route

**L-asparaginase**
- Fewer reactions using IM route
- Additional risk factors include prior exposure, and a time interval of a > week between doses
- Cross-reactivity with GCSF (E.coli)
- Patients who react to *Escherichia-coli* form can be switched to *Erwina chrysanthemi*
- Desensitization can be useful if reactions occur
Monoclonal Antibodies

- Interaction of Fab portion with the antigen target results in release of TNF-α and IL-6.
- Sensitization to non-human proteins can ↑ HSR risk.
- Antibody development to murine portion (HAMA) typically results in clearance of the mAb, rendering the therapy ineffective.
- Although less common, fully human mAbs can also elicit antibodies (HAMA).
- Commonly caused by cytokine mechanisms (non-immune).
- Less commonly caused by Type I-IV “immune” (pre-existing or subsequently developed antibodies).

Rituximab

- Variable domain targets CD20 antigen on B cells.
- Constant domain recruits immune cells resulting in complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC).
- Severe reactions common with 1st infusion, occurring 30-120 minutes after initiating.
- Serum IL-6 and TNF-α levels peak at 90 minutes.
- HSR severity is related to lymphocyte count.
- Manufacturer recommends premedication with acetaminophen and antihistamine (add steroid for RA).

Rituximab Administration

- 1st dose:
  - Titrated, starting at 50mg/hr
  - Subsequent doses:
    - Titrated, starting at 100mg/hr OR
    - Accelerated 90 minute rate for NHL: (20% of dose over 30 minutes, then remainder over 60 minutes).

Cetuximab

- Chimeric mAb (from mouse plasmacytoma).
- Anti-epidermal growth factor receptor (EGFR) that mediates antibody-dependent cellular cytotoxicity (ADCC).
- Reactions can be IgE and/or cytokine mediated.
- Manufacturer recommends premedication with H1 antagonist (for 1st dose).
- 90% of “severe” reactions occur with 1st dose, despite premedication.
- Premedication with antihistamines and steroid may not prevent HSR.
- Higher percentage of 1st dose HSRs in South and southeastern US.

Cetuximab

- Pre-existing cross-linked IgE antibodies for galactose-α-1,3-galactose are associated with significantly worse HSRs (particularly 1st dose).

Summary

- HSRs can be non-immune or immune mediated.
- Mast cells, complement and cytokines are involved.
- Reactions can be due to:
  - The diluent (e.g., paclitaxel).
  - Direct antibody formation (e.g., cetuximab).
  - Secondary cytokine release (e.g., rituximab).
  - Components of murine protein (e.g., cetuximab).
- Premedication will not always prevent an HSR.

Chung et al. study (n=75)

<table>
<thead>
<tr>
<th>Categories</th>
<th>Percentages</th>
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<tr>
<td>HSR positive</td>
<td>83% (25)</td>
</tr>
<tr>
<td>Antibody positive</td>
<td>92% (17)</td>
</tr>
<tr>
<td>Antibody negative</td>
<td>17% (8)</td>
</tr>
</tbody>
</table>
Failure Mode Effect Analysis (FMEA)

- Ongoing quality improvement process employed to examine processes to determine points of potential failure and what their effect would be – before any error actually happens.
- A proactive risk management tool used to look more carefully and systematically at vulnerable areas or processes.
- Shared Governance: Chemotherapy Council
  - Goal to Improve Chemotherapy Administration Safety
    - Nurses indicated a learning need for further instruction on how to manage hypersensitivity
    - Research was needed to establish the most evidenced based practice for IV and oral chemotherapy administration.

FMEA Prevention Action Plan

- Pharmacy team
  - Developed medication alerts
  - Reminded pharmacy and nursing to pre-medicate for hypersensitivity
- Immediate Nursing Education
  - Underlying pathophysiology of an infusion reaction
  - Review of anaphylaxis prophylaxis
  - Premeds as per protocol NOT acceptable as an order
  - Comprehensive Nursing Risk Assessment
  - Management of Cytokine Release Syndrome (CRS)

Nursing Education

- Assessment of Current Knowledge
- Prompted the development of a system-wide educational plan.
- During the process of determining which algorithm to employ, we discovered nurses working in the inpatient and outpatient oncology setting had the general knowledge of emergency management of hypersensitivity infusion reactions, but not the ability to apply immediate pharmacological interventions.

Literature Review: Revealing a Solution

- Early recognition and treatment with Epinephrine to prevent progression to life threatening respiratory and/or cardiovascular event including shock.
- Even mild systemic reactions are best treated immediately with epinephrine, as this appears to prevent progression to more severe symptoms more effectively.
- "There are NO absolute contraindications to epinephrine use in anaphylaxis!"
- "Reluctance to administer epinephrine due to fear of adverse cardiac effects should be countered by the awareness that the heart is a target organ in anaphylaxis".
- "The risk of death due to inadequately treated anaphylaxis usually outweighs other concerns".
  (Simons, Camargo, 2012).

Development of a Nurse Driven Policy

- Analyzed the literature to decide upon the most common criteria for managing adverse effects.
- Planned to implement a nurse-driven protocol which permitted the administration of epinephrine based on clinical judgment and established guidelines using the CTCAE Criteria.

Common Terminology Criteria for Adverse Events (CTCAE)

- Descriptive terminology which can be utilized for adverse Event (AE) reporting
- Broken down into categories with a broad classification of AEs based on anatomy and/ or pathophysiology
- Within each category, AEs are listed accompanied by their descriptions of severity (Grade)
  - Grade 1 Mild AE
  - Grade 2 Moderate AE
  - Grade 3 Severe AE
  - Grade 4 Life-threatening or disabling AE

CTCAE Grading to Guide Intervention

**Grade 1 Signs and Symptoms**
- Transient flushing
- Rash
- Mild itching
- Mild anxiety
- Mild disorientation

**Interventions**
- Closely monitor patient
- No infusion interruption necessary

**Grade 2 Signs and Symptoms**
- Fever
- Rash
- Arthralgia
- Noisy breathing, but causing no respiratory distress
- Shortness of breath with minimal exertion
- Intense itching, or moderate disorientation

**Interventions**
- Stop chemotherapy/biotherapy infusion immediately and disconnect chemotherapy/biotherapy line to avoid further administration of drug
- Call physician and treat as ordered

**Grade 3 Signs and Symptoms**
- Severe arthralgia
- Extensive rash
- Symptomatic bronchospasm with or without urticaria
- Hypotension
- Angioedema
- Shortness of breath with stridor
- Decrease in oxygen saturation
- Respiratory distress at rest
- Rash covering 30% of the body with intense or widespread itching
- Severe disorientation, or severe hallucinations

**Grade 3 Interventions**
- Call Rapid Response Team (RRT)
- Initiate Hypersensitivity and Anaphylaxis Standing Order for Chemotherapy and Biotherapy which include administration of IM epinephrine.

**Grade 4 Signs and Symptoms**
- Severe cardiac or respiratory compromise requiring life threatening urgent intervention such as ventilator support, intubation, tracheostomy or intubation

**Interventions**
- Call Code
- Document administration of Epinephrine and ADE in electronic tracking system

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**Hypersensitivity and Anaphylaxis Standing Orders for Chemotherapy and Biologic Therapy in Oncology:**
- Stop chemotherapy/biotherapy infusion immediately.
- Disconnect chemotherapy/biotherapy line to avoid further administration of drug.
- Assess airway, breathing, circulation, and cognitive function.
- For grade 1 or 2 signs or symptoms, call physician and treat as ordered.
- For grade 3 or 4 signs and symptoms (bronchospasm, with or without urticaria; allergy-related edema/angioedema; hypotension, altered mental status):
  - Call Rapid Response Team.
  - Initiate Hypersensitivity and Anaphylaxis Standing Order for Chemotherapy and Biotherapy.

**Assess Airway**
- Not obstructed → Continue close monitoring.
- Obstructed → Administer Epinephrine a 0.3mg IM auto-injector.
- Establish airway.
- Vomiting patients need to be placed on the side.
- Obtain vital signs every 2-3 min until patient is stable.
- CPR if pulse is absent

a. IM Epinephrine (1mg/mL, 1:1000 preparation): Give epinephrine 0.3 mg intramuscularly, preferably in the mid-anterolateral thigh; can repeat every 5 minutes as needed (may give sooner than 5 min if clinically warranted).

b. B. Oxygen therapy at the first sign of compromise: administer 100% O2 via non-rebreather mask accompanied by continuous oxygen saturation monitoring.

**Assess Breathing**

- No wheezing or stridor → Continue close observation
- Bronchospasm, stridor, O2 sat less than 88% → Administer Epinephrine 0.3mg IM
  - Rescue breathing if absence of breath
  - Administer 100% O2 via non-rebreather mask accompanied by continuous O2 sat monitoring
  - Obtain vital signs every 2-5 minutes until patient is stable
  - CPR if pulse absent

**Assess Cognitive Function**

- Normal cognitive function → Continue close observation
- Altered cognitive function → Administer epinephrine 0.3mg IM autoinjector
  - If patient is unconscious, assess airway again
  - Obtain vital signs every 2-5 minutes until patient is stable
  - CPR if pulse is absent

**Barriers Encountered**

- Physician resistance
  - “How will the nurse differentiate between an anaphylaxis and choking?”
  - “Why did you send my patient to the emergency room?”
  - “What about the cardiac side effects?”
  - “How are you going to track its effectiveness?”
- Nursing resistance
  - “How will I know when to give the epinephrine?”

**The Barriers Continue**

- Identified as first specialty to have a nurse driven protocol for an emergent situation
- Needed approval from multiple system wide committees
- Required a method to track effectiveness
- Mandated education on how to document infusion reactions as ADE’s.
- Resulted in a revision in the Chemotherapy Order form
  - Delayed implementation of protocol 7 months
  - Concerns of not having official order after policy went “live”

**A Pyramid of System-wide Committees Needed for Approval**

**The Hypersensitivity and Anaphylaxis Policy**

- Identify the risk factors involved with infusion therapy
- Ensure recommended prophylactic medical measures are provided prior to infusion.
- Administer premedication prior to administration of infusion with antipyretics, antihistamines, or steroids.
- Document the infusion reaction in electronic reporting system as an Adverse Drug Event.
- Review the patient allergy history and other associated risk factors for hypersensitivity reaction including previous exposure to chemotherapy or biotherapy.
The Hypersensitivity and Anaphylaxis Policy

- Obtain and record baseline vital signs including baseline pulse oximetry.
- Ensure that emergency equipment is readily available at bedside (inpatient setting) or chair (outpatient setting).
- Instruct patient on hypersensitivity symptoms and to report symptom.
- Document education in the medical records.

Implementing the Protocol

- System-wide approval for implementation on the oncology units.
- Pharmacy consulted about supplying the epinephrine to the medication dispensing system at each campus.
  - In the form of a unit dose
  - Eliminated the potential for an inaccurate amount of drug to be administered during a time-sensitive situation

Educating the Staff

- Significant change in practice.
- Through the use of simulation.
- Time sensitive outcomes may be met when all the standard components of simulation are included, such as preparation, pre-brief, the simulation, and debrief (Muehlbauer, Parr, & Perkins, 2013).

Evaluating Patient Data and Outcomes 2012

- Clinical manifestations of Grade 3 hypersensitivity develops.
- Infusion Stopped. Alerted Rapid Response Team.
- Administered diphendramine, corticosteroids
- Patient monitored in the Emergency Room until stable, or admitted for telemetry observation
- ED visit $1300.00
- ICU Bed Charge $1200.00
- Intubation Charge $3343.00
- Average cost of wasting Chemotherapy drugs $100.00-$30,000

Evaluating Patient Data and Outcomes 2013

- Clinical manifestations of Grade 3 Hypersensitivity develops.
- Alert Rapid Response Team, follow protocol
- Administer Epinephrine 0.3mg. IM Auto-injector
- Cost of Epinephrine Auto-Injector $150.00
- 8 patients treated successfully with protocol
- 6 of 8 patients able to be discharged after completing chemotherapy
- 10 patients eligible for protocol did not receive epinephrine
- 2 of 8 patients were admitted for 23 hour observation
- ED visit $1300.00
- ICU Bed Charge $1200.00
- Intubation Charge $3343.00
- Average daily cost $12,000 with care
- Average cost of wasting Chemotherapy drugs $100.00-$30,000

The Journey Continues

- Not all RNs comfortable with algorithm
- Physician reluctance persists
- Developing a Fact Sheet handout for patient education and management of delayed or recurrent reactions at home
- Working with physician colleagues in ordering Epinephrine Auto Injector post discharge for delayed reaction
- Continuing to monitor outcomes and coach and mentor physicians & nurses to achieve compliance with the algorithm
Hypersensitivity and anaphylaxis nursing protocol for chemotherapy and biologics in inpatient and outpatient oncology:

1. **Grade 1** Hypersensitivity closely monitor patient. 
   Signs and Symptoms include: as transient flushing or rash, mild itching, mild anxiety, or mild disorientation. 
   **No infusion interruption necessary.**

2. **Grade 2.** Stop chemotherapy/biotherapy infusion immediately and Disconnect chemotherapy /biotherapy line to avoid further administration of drug. **Call physician and treat as ordered.**
   Signs and Symptoms include as fever, rash, arthralgia, noisy breathing but causing no respiratory distress, shortness of breath with minimal exertion, intense itching, or moderate disorientation.

3. **Grade 3** signs and symptoms severe arthralgia, extensive rash, symptomatic bronchospasm with or without urticaria, hypotension, allergy related edema (angioedema), shortness of breath with stridor, decrease in oxygen saturation, respiratory distress at rest, rash covering 30% of the body with intense or widespread itching, sever disorientation, or severe hallucinations ;
   a. Call Rapid Response Team.
   b. Initiate Hypersensitivity and Anaphylaxis Standing Order for Chemotherapy and Biotherapy which include administration of IM epinephrine. ( see protocol)

4. **Grade 4** Call Code. Signs and Symptoms include: severe cardiac or respiratory compromise requiring life threatening urgent intervention such as ventilator support, intubation, tracheostomy or intubation.

5. **Document Administration of Epinephrine on RRT form and Document ADR in Carelink**
If signs and symptoms of a hypersensitivity reaction are present, stop infusion and maintain vascular access.

Assess Airway
- Obstructed:
  - Administer epinephrine^a 0.3 mg IM autoinjector
  - Establish Airway
- Not obstructed:
  - Continue close observation

Assess Breathing
- Bronchospasm or stridor or oxygen saturation < 90%:
  - Administer epinephrine^a
- No wheezing or stridor:
  - Continue close observation

Assess Circulation
- Hypotensive (SBP < 90 mmHg or > 30% decrease from baseline) or tachycardic:
  - Administer epinephrine^a 0.3 mg IM autoinjector
- Normotensive:
  - Continue close observation

Assess Cognitive Function
- Altered cognitive function:
  - Administer epinephrine^a 0.3 mg IM autoinjector
- Normal cognitive function:
  - Continue close observation

Tilt head, lift chin to open airway
Obtain vital signs every 2–5 minutes until patient is stable
Cardiopulmonary resuscitation if pulse is absent

Rescue breathing if absence of breath occurs
Obtain vital signs every 2–5 minutes until patient is stable
Cardiopulmonary resuscitation if pulse is absent

Place patient in recumbent position and elevate lower extremity
Obtain vital signs every 2–5 minutes until patient is stable
Cardiopulmonary resuscitation if pulse is absent

Vomiting patients may need to be placed on side

Obtain vital signs every 2–5 minutes until patient is stable
Cardiopulmonary resuscitation if pulse is absent

If patient is unconscious, assess airway again
Obtain vital signs every 2–5 minutes until patient is stable
Cardiopulmonary resuscitation if pulse is absent

Cardiopulmonary resuscitation if pulse is absent

Rapid infusion of 1 L normal saline wide open rate

Obtain vital signs every 2–5 minutes until patient is stable


References:


Lexi-Comp OnlineTM, Lexi-Drugs OnlineTM, Hudson, Ohio: Lexi-Comp, Inc.; February 20, 2011.


