48TH ANNUAL ONS Congress | Rejuvenate. Refocus. Revitalize.

Infusion-Related Reaction Management

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Disclosures

We have no relevant financial relationships with ineligible companies* to disclose.

*An ineligible company is one whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used on or by patients.

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Session Objectives

- Describe the pathophysiology and management of infusion-related reactions
- Develop an appropriate plan for monitoring and treating infusion-related reactions

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What is an Infusion-Related Reaction (IRR)?

- Many terms used to describe infusion-related reactions
  - Hypersensitivity reaction (HSR)
  - Cytokine reaction
  - Anaphylaxis
- Reactions are mediated by the immune system
  - IgE
    - Lowest serum concentration, shortest half-life in the serum
    - Involves mast cells, eosinophils, and basophils
    - IgE + allergen= Histamine release within first 5 minutes
  - IgG and IgM
    - Complement activation and infiltration of neutrophils
    - Cytokines, activation of macrophages and T-cells

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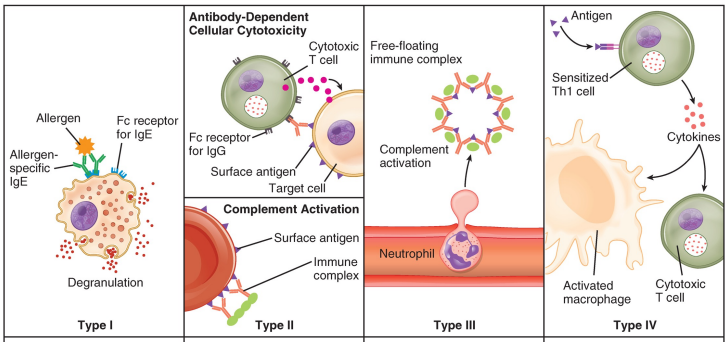
Hypersensitivity Reaction Classification



IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
IgE is bound to mast cells via its Fc portion. When an allergen binds to these antibodies, crosslinking of IgE induces degranulation.	Cells are destroyed by bound antibody, either by activation of complement or by a cytotoxic T cell with an Fc receptor for the antibody (ADCC)	Antigen–antibody complexes are deposited in tissues, causing activation of complement, which attracts neutrophils to the site	Th1 cells secrete cytokines, which activate macrophages and cytotoxic T cells and can cause macrophage accumulation at the site
Causes localized and systemic anaphylaxis, seasonal allergies including hay fever, food allergies such as those to shellfish and peanuts, hives, and eczema	Red blood cells destroyed by complement and antibody during a transfusion of mismatched blood type or during erythroblastosis fetalis	Most common forms of immune complex disease are seen in glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus	Most common forms are contact dermatitis, tuberculin reaction, autoimmune diseases such as diabetes mellitus type I, multiple sclerosis, and rheumatoid arthritis

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Common risk factors

- Age-related factors
- Concomitant diseases
- Severe atopic disease
- Concurrent medications
- Allergy profile

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Proactive prevention measures

- Prior to drug administration, ask patient about medical background
- Check for history of previous infusion-related reactions in allergy profile and previous nursing notes
- Ensure patient has taken appropriate premedication(s) if applicable
- Be aware of potential risk of reaction with each drug and when reaction is most likely to happen
- Promptly recognize symptoms and intervene

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Common Terminology Criteria for Adverse Events (CTCAE) Reaction types and Definitions

Reaction Type	Definition
Infusion-related reaction	A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances
Cytokine release syndrome	A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia cause by the release of cytokines
Anaphylaxis	A disorder 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

Adapted from NCI CTCAE Version 5.0 (2017).

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CTCAE Grading

Reaction Type	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion-related reaction	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 medication 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	Life-threatening consequences; urgent intervention indicated	Death
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to <40% 02	Hypotension managed with one pressor; hypoxia requiring ≥40% 02	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

Adapted from NCI CTCAE Version 5.0 (2017).

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Management of Infusion-Related Reaction

- Stop the administration of the medication
- Summon additional help to assist with reaction
- Maintain intravenous (IV) access
- Assess airway, breathing, circulation (ABCs) and patient's level of consciousness
- Follow institution policies on management of reaction
- Notify provider

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Medications used for IRR management

Pharmacologic Category	Example(s)	Rationale
Antihistamines	H1 antagonist- Diphenhydramine H2 antagonist- Famotidine	Control cutaneous and cardiovascular manifestations associated with degranulation of mast cells and basophils
Corticosteroid	Methylprednisolone	Prevent biphasic reactions- not critical in management of anaphylaxis
Antipyretic	Acetaminophen	Treat symptoms including fever
Alpha-/Beta- Agonist	Epinephrine	Mainstay for anaphylaxis treatment in patients experiencing hypotension or cardiac arrest
Beta2 Agonist	Albuterol	Respiratory symptoms, bronchospasm, wheezing
Gas	Oxygen	Respiratory distress, decreased pulse oximetry
Opioid Analgesic	Meperidine	Control rigors and chills
Parenteral Electrolyte Supplement	Normal saline	Hypotension management- fluid resuscitation

Olsen et al, 2019.

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Characteristics and management of IRRs

Drug	Incidence	Timing of Reaction	Signs and Symptoms	Prophylaxis	Management of IRs
Anthracyclines	7-11%	Early (usually first infusion)	Chest pain, pruritus, syncope, flushing, chills, fever, angioedema, rash, hypotension, tachycardia, nausea/vomiting, headache, back pain	Stop or Decrease infusion rate, premedication not routine	Stop or decrease infusion rate, treat symptoms, consider desensitization
Asparaginase	60% (10% severe HSR)	Several doses, within 1 hr of admin	Pruritus, dyspnea, rash, urticaria, abdominal pain, bronchospasm, hypotension, angioedema, laryngospasm	Corticosteroids, antihistamines	Consider switch to PEGylated formulation
Bleomycin	1%	Immediate or delayed for hrs, usually after 1st or 2nd dose	Hypotension, mental confusion, fever, chills, wheezing	Consider smaller or decreased doses early in treatment	Stop or decrease infusion rate, treat symptoms, consider desensitization
Etoposide	1-3% (severe)	After 1st dose	Hypotension, fever, chills, urticaria, bronchospasm, angioedema, chest discomfort	Slow infusion over 30-60 min. Premedicate with corticosteroids and antihistamines	Stop or decrease infusion rate, treat symptoms, consider desensitization

Adapted from Rosello et al., 2017.

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Characteristics and management of IRRs

Drug	Incidence	Timing of Reaction	Signs and Symptoms	Prophylaxis	Management of IRs
CARBOplatin	12%	Variable, increased risk with cumulative doses, 6+ courses	Rash, itching, erythema, abdominal cramps, facial edema, bronchospasm, hypotension, tachycardia, dyspnea, chest pain	Corticosteroids, H1/H2 blockers not routinely recommended. Premedication may not prevent IR	Stop or decrease infusion rate, treat symptoms, consider desensitization
OXALIplatin	1-25%	Within 60 min of starting infusion (typically 5-10 min); 7-8th course	Sweating, watering, pruritus, rash, back or chest pain, laryngospasm, dyspnea, fever, urticaria, bronchospasm, hypotension	Corticosteroids, H1/H2 blockers not routinely recommended. Premedication may not prevent IR	Stop or decrease infusion rate, treat symptoms, consider desensitization
DOCEtaxel	2% (severe)	1st or 2nd dose, within first 10 minutes	Hypotension, dyspnea, bronchospasm, urticaria, skin reactions, angioedema, flushing, pruritus, tachycardia, chest or back pain	PO dexamethasone 8mg BID for 3 days (starting 24 hr prior to infusion)	Stop or decrease infusion rate, treat symptoms, consider desensitization
PACLitaxel	2-4% (severe)	1st or 2nd dose, within first 10 minutes	Flushing, skin reactions, dyspnea, hypotension, tachycardia, bronchospasm, angioedema, urticaria	Premedicate with IV dexamethasone, H1 and H2 blocker 30 minutes prior	Stop or decrease infusion rate, treat symptoms, consider desensitization

Adapted from Rosello et al., 2017.

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Characteristics and management of IRRs

Drug	Type of antibody	Mechanism of action	Incidence	Signs and symptoms	Prophylaxis	Management
Rituximab	Chimeric	Anti-CD20	77% on first infusion, 10% severe	Fever, chills, dyspnea, hypotension, nausea, rhinitis, urticaria, pruritus, asthenia, angioedema, bronchospasm	Slow initial rate recommended. Premedication: antipyretic and H1 blocker	Stop or decrease infusion rate, treat symptoms. Grade 3/4: consider resuming and 50% previous rate
Infliximab	Chimeric	TNF-alpha	18%, 1% severe	Varies	Slow initial rate recommended. Premedication: antipyretic and H1 blocker	Stop or decrease infusion rate, treat symptoms. Grade 3/4: consider resuming and 50% previous rate
Blinatumomab	Bispecific T-cell engaging	Anti-CD19/CD3	44-67%*	Pyrexia, asthenia, headache, hypotension, nausea, disseminated intravascular coagulation, capillary leak syndrome	Dexamethasone IV 1 hr prior to infusion, antipyretic	Stop or decrease infusion rate, treat symptoms. Consider dose escalation if no previous toxicity. Grade 4: Permanently discontinue
Pembrolizumab	Humanized	Anti-PD1	1-5%	Pyrexia, chills	Premedication with antipyretic or antihistamine considered	Grade 1/2: Stop or decrease infusion rate Grade 3/4: Permanently discontinue

* Serious reactions (0.5%) with median onset of a cytokine release syndrome event 2 days

Adapted from Rosello et al., 2017; Galvao, V.R. et al., 2015.

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Potential Reaction Symptoms

Body System	Symptoms
Cutaneous	Itching, redness/flushing, urticaria, rash
Respiratory	Shortness of breath, wheezing, stridor, throat tightening, tachypnea, decreased oxygen saturation
Cardiovascular	Chest pain/tightness, hyper/hypotension, tachycardia
Gastrointestinal	Nausea, vomiting, cramping
Other	Fever, rigors, lower back pain

Adapted information from Olsen et al., 2019; Shimabukaro-Vornhage et al., 2018.

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Case Study #1

- Today is C1D1 of Paclitaxel/Carboplatin/Nivolumab for C.M. who was recently diagnosed with NSCLC. Paclitaxel premeds include:
  - H1- Diphenhydramine 50mgIV
  - H2- Famotidine 20mg IV
  - Corticosteroid- Dexamethasone 20mg IV
- Approximately 10 mins. into the Paclitaxel infusion C.M. complains of severe back pain and feeling warm. Upon approaching the patient, you notice her face is bright red and she's holding her lower back
  - Consider what type/grade of reaction is C.M. experiencing
  - Consider possible interventions

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Case Study #2

- T.G. was recently diagnosed with Diffuse Large B-Cell Lymphoma (DLBCL). She will be starting R-EPOCH and comes to the infusion area for C1D1 Rituximab. Premeds include:
  - H1- Diphenhydramine 50mg IV
  - Acetaminophen 500mg PO
- You titrate the Rituximab from 100mg/hr to 150mg/hr- 10 mins. later the patient begins to complain of chills and is visibly shaking

  - Consider what type/grade of reaction is T.G. experiencing
  - Consider possible interventions

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Case Study #3

- K.D. was recently diagnosed with iron-deficiency anemia. He arrives to the infusion area today for Iron Sucrose (Venofer) 400mg
- Approximately 2 hour into his infusion, K.D. puts his call bell on and says, “something is not right”. He begins to cough, complains of chest tightness and states that his lips and tongue feel tingly and swollen
- Upon assessment his vital signs are: 78/50, 120, 97.9, 26, 86% on room air. You hear audible wheezes throughout his lungs and note lip and tongue swelling

  - Consider what type/grade of reaction is K.D. experiencing
  - Consider possible interventions

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Case Study #4

- R.K. has a history of stage 3 ovarian cancer and was previously treated with 6 cycles of Paclitaxel/Carboplatin. Unfortunately, patient has had a recurrence and will be starting treatment again with Paclitaxel 175 mg/m2 & Carboplatin AUC 6
- Pt receives Paclitaxel without incident. Approximately 20 mins. into the Carboplatin infusion, patient complains of hives to her torso, red and itchy palms, and lower back pain
    - Consider what type/grade of reaction is R.K. experiencing
    - Consider possible interventions

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Guidelines and literature

- National Comprehensive Cancer Network (NCCN)- GYN
- Oncology Nursing Society (ONS)
- European Society for Medical Oncology (ESMO)
- American Society of Clinical Oncology (ASCO)
- American College of Physicians (ACP)- Allergy and Immunology

- Still limited

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Best Practices

- Follow your hospital's policy and procedure for reaction management
- Advocate for standing orders and nurse-driven protocols for emergency management of acute IRRs
- Know your drugs prior to hanging them
- Be prepared and ready to manage a reaction
- Counsel patient and family on signs and symptoms of reaction (including delayed reactions)- report immediately!

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Best Practices (continued)

- Document the reaction, interventions, and who was notified
- Reassure the patient and family
- Recognize risk factors for developing an anaphylactic reaction
- Accurate allergy labeling and reporting
- Consider pre-built titrations/desensitization in EMR for common IR-causing agents
  - Take-home medication panel for pre-medications 24-48 hours prior to infusion

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Next steps after IRR

- Physician discretion and patient preference to continue
- Depending on the drug and severity of reaction:
  - Rechallenge
  - Slow the rate of infusion
  - Desensitization
    - Give total dose of drug in small increments and different concentrations over long period of time
    - Involves multiple doses of pre-meds
  - Consult with allergist to confirm true drug allergy
  - Discontinue and discuss new drug regimen

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Final thoughts

- Need for randomized controlled trials to investigate preventive and management algorithms

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Key Takeaways

- Know your drugs
- Know your facility's protocol for IRR management

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Resources

- ONS Chemotherapy and immunotherapy guidelines and recommendations for practice
- NCCN Guidelines: Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer.

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