Prevention and handling of acute allergic and infusion reactions in oncology

Markus Joerger MD PhD

Medical Oncology&Clinical Pharmacology

Cantonal Hospital St.Gallen (Switzerland)

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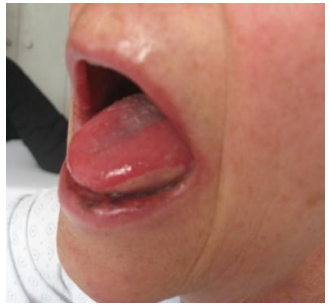
OVERVIEW

- mechanism and definition
  - immune-type hypersensitivity reaction (HSR)
  - symptoms of acute infusion reaction (AIR)
  - clinical significance of AIR
- chemotherapy
- monoclonal antibodies (mAb)
- management of AIR
- what to do after AIR occurred

not covered: AIR to contrast agents, blood products

Infusion-related Adverse Drug Reactions (ADR)

- intolerance (type A)
  - predictable ADR at normal doses due to the pharmacological activity of the drug
- idiosynkrasie (type B)
  - unpredictable ADR due to individual predisposition, e.g. enzyme defect

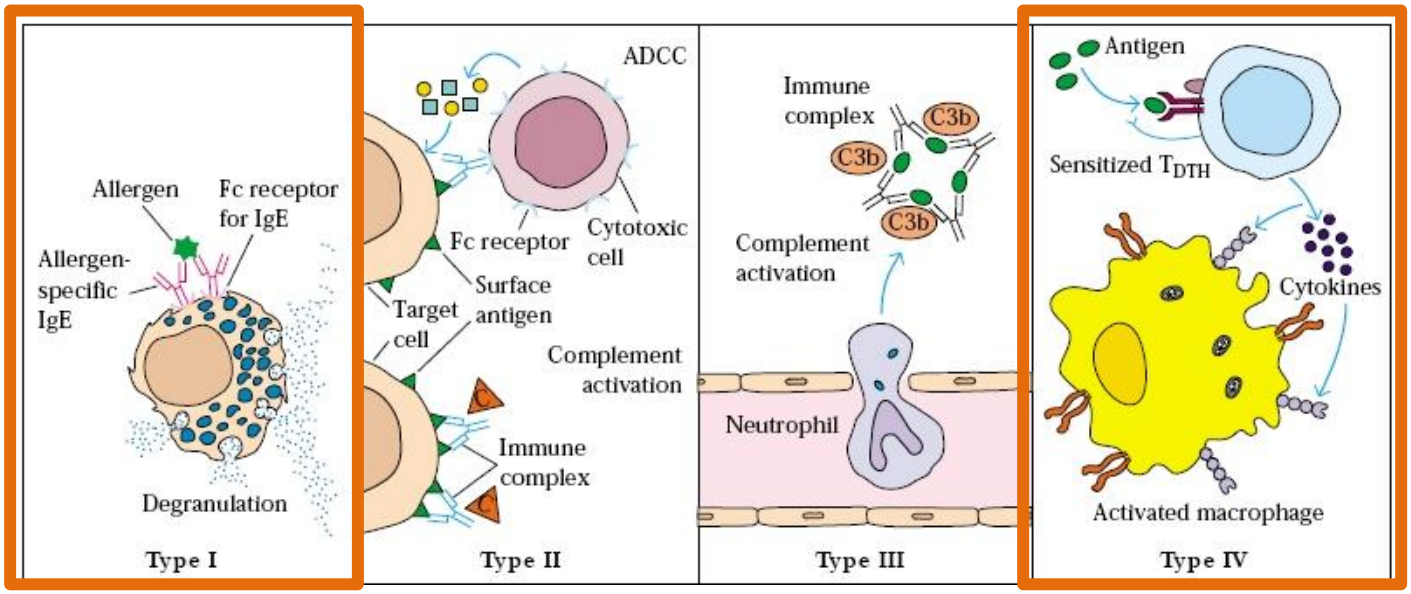


- HSR/AIR
  - “drug allergy” and “pseudo-allergy”
  - one of four immune-type reactions
  - “anaphylaxis” and “anaphylactoid”

Four Immune-type HSR (Gell&Coombs)

- type 1: IgE-mediated
- type 2: IgG-mediated cytotoxicity
- type 3: Immuncomplex-mediated
- type 4: T Cell-mediated, cytokines, complement

only with mAb

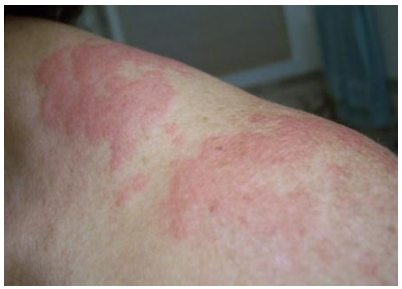


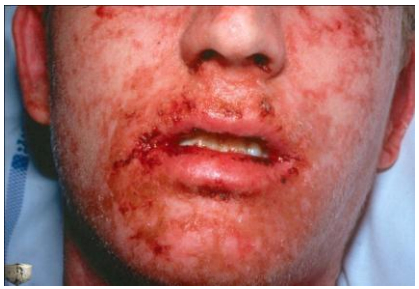
HSR: immediate/non-immediate

- definition by: European Network for Drug Allergy

I. immediate Reaction after <1 hour of exposure
   - urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, overt anaphylaxis

II. nonimmediate Reaction after >1 hour of exposure
   - cutaneous symptoms, maculopapular eruptions, vasculitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, eosinophilia





Spectrum of acute HSR

GRADING OF HYPERSENSIVITY REACTIONS
Common Terminology Criteria for Adverse Events (CTCAE) v4.0

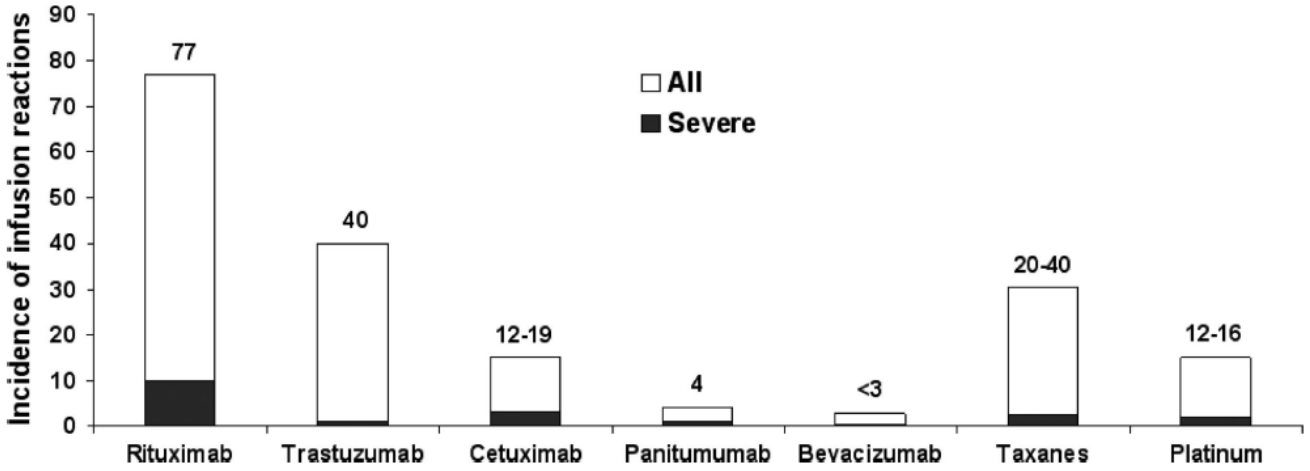
Grade 0 (no reaction)	No reaction
Grade 1 (mild)	Local reaction only Transient flushing or rash Drug fever <38°C (<100.4°F)
Grade 2 (moderate)	Flushing Mild bronchospasm Rash, urticaria, dyspnea Drug fever ≥38°C (≥100.4°F)
Grade 3 (severe)	Moderate bronchospasm, Severe local reaction (>10mm or lasting >24 hours) Serum sickness Allergy-related edema/angioedema Hypotension
Grade 4 (life-threatening)	Anaphylaxis
Grade 5	Death

Anaphylaxis/Anaphylactoid Reaction: Oncologic Emergency!

- anaphylaxis (HSR)
  - systemic, immediate, IgE-mediated
- anaphylactoid reaction (AIR)
  - unspecific degranulation of mast cells or basophils
- risk factors for HSR
  - repeated administration of the drug ("priming")
  - predisposition = atopy
  - history (or family history) of drug allergy

Clinical Significance of AIR

- every drug infusion may cause (severe) AIR
- skilled personel mandatory
- adequate premedication mandatory



Chung et al, The Oncologist 2008;13:725-32

CHEMOTHERAPY

Platinum Salts: Oxaliplatin

- mild/severe HSR in <25/1% of cases[1]
- after 7-8 cycles, minutes after the start of infusion
- type I (II) reaction [2]
- use H1/H2 blockers, steroids, slow infusion rate[3]
- consider desensitization if oxaliplatin fundamental
- differentiate between acute neurotoxicity and HSR

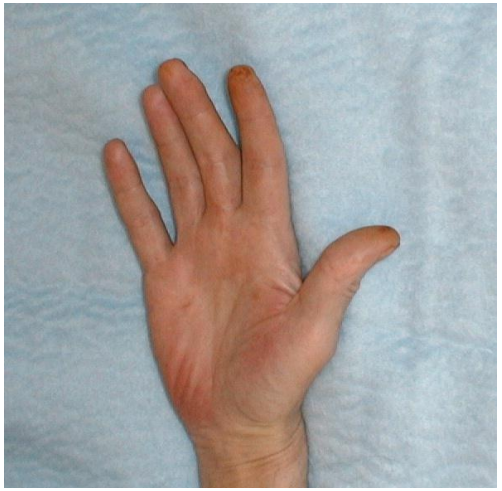
[1]Polyzos et al, Oncoogy 2009;76(1): 36-41.

[2] Syrigou et al, Curr Allergy Asthma Rep 2008;8(1):56-62.

3 Brandi et al, Br. J. Cancer (2003) 89(3):477-481. l

Carboplatin

- mild/severe HSR in 19/2% after 8 cycles [1]
- minutes to days after the start of infusion
- type I (IV) reaction
- use H1/H2 blockers, steroids, slow infusion rate
- switch to cisplatin in severe case (75% success)[2]
- skin tests reliable



[1] *Sliesoraitis et al, Int J Gynecol Cancer 2005;15(1):13-18.*

[2] *Callahan et al, Am J Obstetr Gynecol 2007;977(2): 199.e1-199.e5.*

Cisplatin

- lower incidence of mild (0.4%) and severe HSR (0.8%) [1]
- minutes from the start of infusion
- usually after ≥6 treatment cycles
- type I (IV) reaction
- skin test not reliable
- consider desensitization if cisplatin fundamental [2]

[1]*Sakaeda et al, Int J Med Sci 2011;8(4):332-338.*

[2]*Castels et al, J Allergy Clin Immunol 2008;122(3):574-80.*

Taxanes

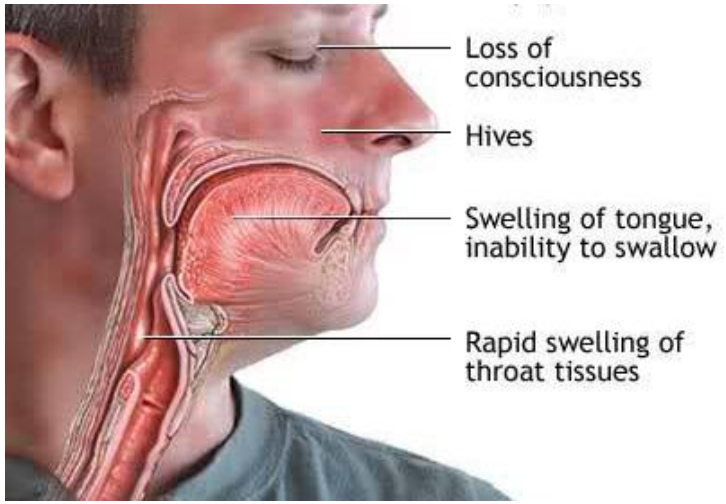
- AIR primarily due to the solvent “cremophor EL” (paclitaxel) and “polysorbate 80” (docetaxel, cabazitaxel)
- solvent-triggered histamine release (not IgE)[1]
- 30%/ ≤4% of patients without/with premedication
- dose- and infusion-rate dependent
- “hits early”: first minutes of infusion, first 2 cycles
- disappears on rechallenge and premedication[2]

[1]*Ardavanis et al, Anti-Cancer Drugs 2004, 15:581–585*

[2]*Demoly et al, Immunol Allergy Clin North Am 2004;24(3):345-56.*

Taxanes: AIR

- symptoms: dyspnea, hypotension, urticaria, erythematous rash, tongue swelling, dysphagia
- differentiate between platinum & taxane AIR when given in combination!
- rapid normalization after discontinuation of the drug



Taxanes: Prevention of AIR

- oral dexamethasone 20mg –12 / –6(2) hours
- i.v. H1 and H2 blocker –30min
- dexamethasone prevention over 3 days for docetaxel
- i.v. dexamethasone 10-20mg –30min also safe[1]
- severe AIR @rechallenge: desensitization or nab-paclitaxel[2]
- cross-reactivity in 90%[2]

[1] *Bookman et al, Annals of Oncology 8: 611-614, 1997*

[2] *Fader et al, Int J Gynecol Cancer 2009;19: 1281Y1283*

[3] *Dizon et al, Gynecol Oncol 2005;100(1):149-51.*

L-Asparaginase

- enzyme from E. coli or Erwinia chrysanthemi
- 40% risk of IgE-mediated HSR (severe in ≤10%)[1]
- risk factors: iv. (im.) application, previous exposure to L-Asp.[2]
- allergic patients have enzyme-neutralizing Ab's [3]
- after HSR occurred:
  - Switch to Erwinia Asparaginase[4]
  - Switch to PEG-Asparaginase (polyethylene glycol)[5]

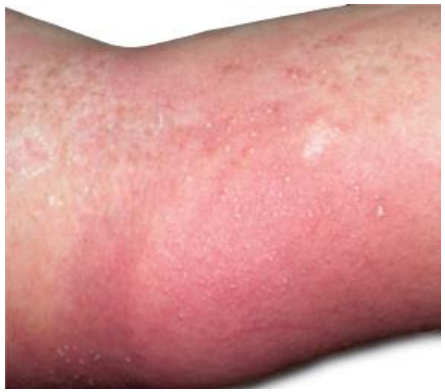
[1]*Narta et al, Crit Rev Oncol Hematol 2007;61(3):208-221.*

[2] *Demoly, Toxicology 2005; 209(2):221-23.*

[3] *Woo et al, Leukemia 1998;12:1527–1533.*

[4] *Vrooman et al, Pediatr Blood Cancer 2010;54:199–205*

[5] *Raetz et al, J Pediatr Hematol Oncol 2010;32:544–563*



Procarbazine

- HSR caused by type I, III or IV reaction
- HSR in 6 to 18% of patients
- symptoms include fever, maculopapular rash, urticaria, toxic epidermal necrolysis [1]
- rechallenge after HSR usually not successful, even with steroid prophylaxis [1]
- no rechallenge

[1]*Weiss, Semin Oncol 1992;19(5):458-77.*

Podophyllotoxins

- AIR primarily due to the solvent “cremophor EL” (teniposide) and “polysorbate 80” (i.v. etoposide)
- AIR to teniposide in 6–41% [1]
- AIR to etoposide less frequent than with teniposide
- importance of adequate premedication and slow infusion
- high cross-reactivity [2]

[1] *Lee et al, Ann Allergy Asthma Immunol 2009;102(3):179-87.*

[2] *Hudson et al, J Clin Oncol 1993;11(6):1080-84.*

Intermediate potential for AIR

- Anthracyclines
  - usually mild cutaneous symptoms
  - HSR may be prevented by low infusion rates
  - desensitization to liposomal doxorubicin is an option [1]
- Methotrexate
  - infrequent, but potentially severe HSR
  - acute pneumonitis after some days following MTX[2]
  - very rare, acute liver failure[3]

[1] *Castells et al, j Allergy Clin Immunol 2008;122(3):574-80.*

[2] *Hlaing et al, Int J Rheumatol 2008;4 (2).*

[3] *Kaito et al, Rinsho Ketsueki 1990; 31:1862-1867.*

MONOCLONAL ANTIBODIES (mAb)

Monoclonal Antibodies (mAb)

- murine with –o– stem

  tositumomab, ibritumomab

- chimera with –xi– stem

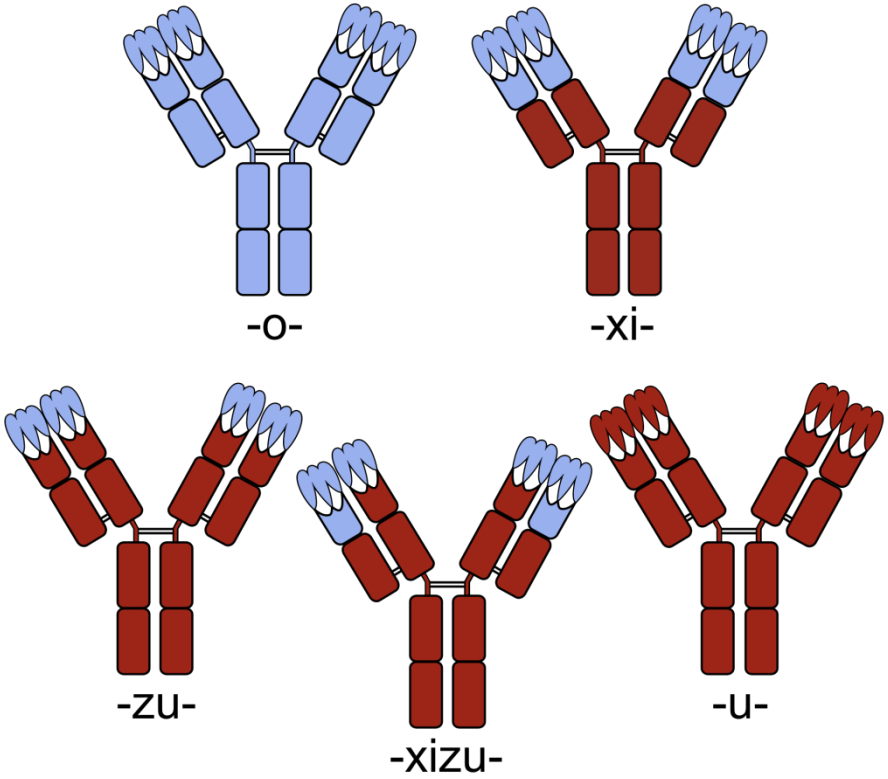
  cetuximab, rituximab

- humanized with –zu– stem

  alemtuzumab, bevacizumab, trastuzumab, pertuzumab, gemtuzumab

- human with –u– stem

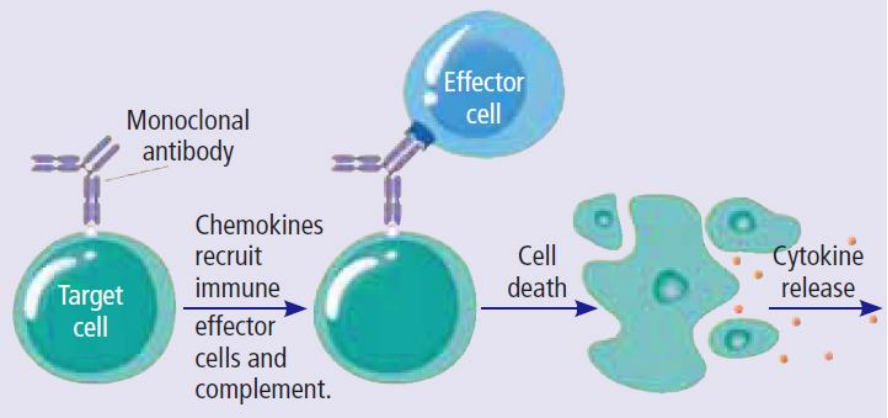
  panitumumab, ipilimumab, denosumab



mAb

- chimeric mAb: >50% human
- humanized mAb: 90% human
- fully humanized mAb: 99% human
- prevalent and induced anti-mouse Ab
- anti-mouse Ab → cytokine release (less prevalent HSR)
- AIR: stop infusion, H1/H2 blockers, restart at slow rate

more prevalent non-allergic type reaction (AIR)



mAb: General Remarks

- most AIR mild
- 2 pathomechanisms:
  - allergic → IgE
  - non-allergic → cytokine-mediated
- severe reactions are IgE-mediated
  - Consider desensitization, avoidance
- rechallenge successful with non-allergic reactions
- paracetamol & H1-blocker usually recommended

  … except bevacizumab, panitumumab

mAb

- NCI grading criteria for cytokine-release infusion reactions [1]

Grade 1	Mild reaction; infusion interruption or intervention not indicated
Grade 2	Infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, steroids, IV fluids)
Grade 3	Prolonged symptoms (not rapidly responsive to symptomatic medication and interruption of infusion); recurrence of symptoms following initial improvement
Grade 4	Life-threatening consequences; vasopressors and/or ventilatory support indicated
Grade 5	DEATH

[1]*National Cancer Institute 2010.*

mAb: Specific Compounds

- rituximab: AIR in 77% @ 1st application (7% severe HSR) [1]
- trastuzumab: AIR in 40% @ 1st application [1]

  ….lower with s.c.-trastuzumab
- alemtuzumab: given s.c. in a fractionated way to avoid AIR
- cetuximab: C-IgE in 0.6-21% of the U.S. population [2]
- bevacizumab&panitumumab: no premedication necessary

[1]Kimby E, Cancer Treat Rev 2005;31(6):456-73.

[2] Chunge et al, N Engl J Med 2008;358:1109-17.

Rituximab: Tumor lysis-type Reaction

- lymphocytes >25G/L, high tumor load
- hypotension and bronchospasm in 10% of pts @1st exposure
- electrolyte abnormalities, renal dysfunction, high LDH
- tumor cell agglutination > cytokine release
- stop infusion, do not restart before careful diagnostics and Tx
- prophylaxis: inpatient 1st exposure, fractionated dosing (100mg), allopurinol, hydration, close monitoring

Byrd JC, J Clin Oncol 17:791-95.

Kimby, CANCER TREATMENT REVIEWS (2005) 31, 456–473.

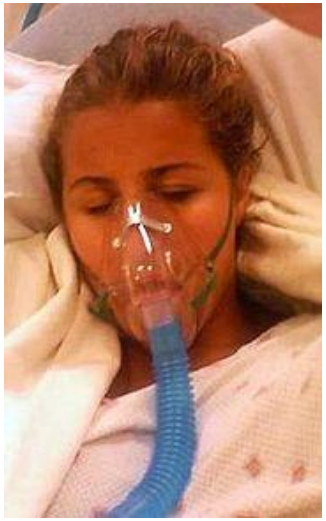
MANAGEMENT OF AIR/HSR

Preparation

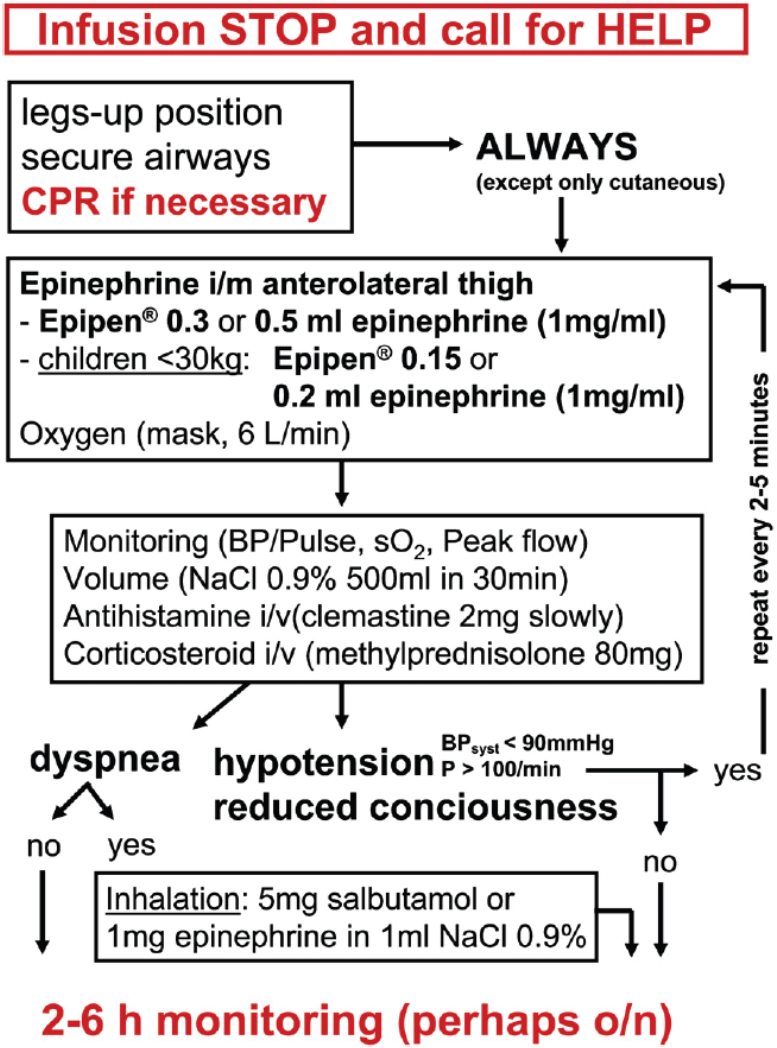
- obtain baseline assessment and vital signs
- assess for risk factors (eg. previous treatment)
- educate patient about potential symptoms of AIR/HSR
- make sure emergency equipment is available
- confirm that patient took premedication

Treatment

- **stop infusion**
- give i.v. volume, keep systolic BP >90mmHg
- supine position (if no vomiting or dyspnea)
- severe: call emergency, epinephrine
- maintain airway, consider O_2
- monitor vital signs q2min until baseline is reached
- documentation



(suspected) Anaphylaxis: Treatment Algorithm



Hausmann et al, Med Clin N Am 94 (2010) 791–804

STRATEGIES AFTER AN AIR/HSR OCCURRED

Specific Compounds

- platinum salts:
  mild-moderate HSR: use H1/H2 blockers, steroids, slow infusion rate,
  severe HSR: desensitize, cautious cross-over
- taxanes, podophyllytoxins:
  intensify premedication, no substitution (except nab-paclitaxel)
- L-Asparaginase:
  switch to Erwinia/PEG-Asparaginase, intensify premedication, desensitize
- procarbazine:
  discontinue
- mAb
  intensify premedication, slow infusion rate
  cetuximab → panitumumab[1]

[1]*Langerak et al ,ClinColorectal Cancer, 2009;8(1): 49-54.*

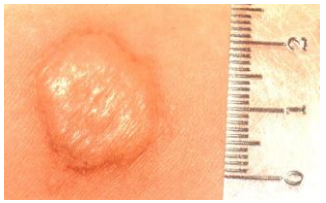
Drug Desensitization

- only with IgE-mediated HSR
- mast cell desensitization* > tolerant state
- reversible process
- presence of trained allergist and nursing staff

*receptor downregulation, exhaustion of mediators, enhanced metabolism or drug efflux

Drug Desensitization: Protocol

- conventional:
  - escalating i.d. doses (e.g. 1→3→10→30→100)
  - increasing i.v. infusion rate



- drug-specific, simplified (e.g. paclitaxel)[1]:
  - 20mg oral dexamethasone –36/ –12/ –2 hrs
  - i.v. dexamethasone, H1 and H2 blocker –30min
  - paclitaxel 2mg/100ml NaCl/30min → 10mg/100ml/30min
  - remaining full dose in 500ml NaCl/3hrs

[1]*Markman et al, J Clin Oncol 2000; 8:102-105.*

CONCLUSIONS

- differentiate between HSR, AIR, intolerance & idiosynkrasie
- intensify premedication in case of solvent/mAb-related AIR
- desensitize or substitute in case of severe IgE-mediated HSR

…..thanks for your kind attention!

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