

Antibiotics and allergy

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Introduction - Drug Allergy



Adverse drug events

Type A

- Pharmacological/toxical properties
- Predictable

Eg: diarrhea during antibiotic therapy

Type B

- Unpredictable/Uncommon
- Not depending on pharmacology

Allergy

→ Immunologic mechanism

Non immunological hypersensitivity

→ Not immune mediated

Gell and Coombs classification

Reactie	Synoniem	Mechanisme	Mediatoren	Vb.
Type 1	Onmiddellijke overgevoeligheid	Medicatie-specifiek IgE ALn	mast cellen basofielen	Anafylaxie
Type 2	AL-gemedieerde cytotoxiche overgevoeligheid	Medicatie-specifiek IgM en IgG ALn	Complement	Cytopenia (hemolytische anemie/trombocytopenie)
Type 3	Immuuncomplex-gemedieerde overgevoeligheid	Medicatie-specifiek IgM en IgG ALn	Complement	Serum sickness
Type 4	Cellulair-gemedieerde overgevoeligheid	Medicatie specifiek T lymfocyten	Lymfokines chemokines	Contactdermatitis, MPE, FDE, morbilliform eruption, photodrug reaction, SJS, TEN

IgE mediated reaction

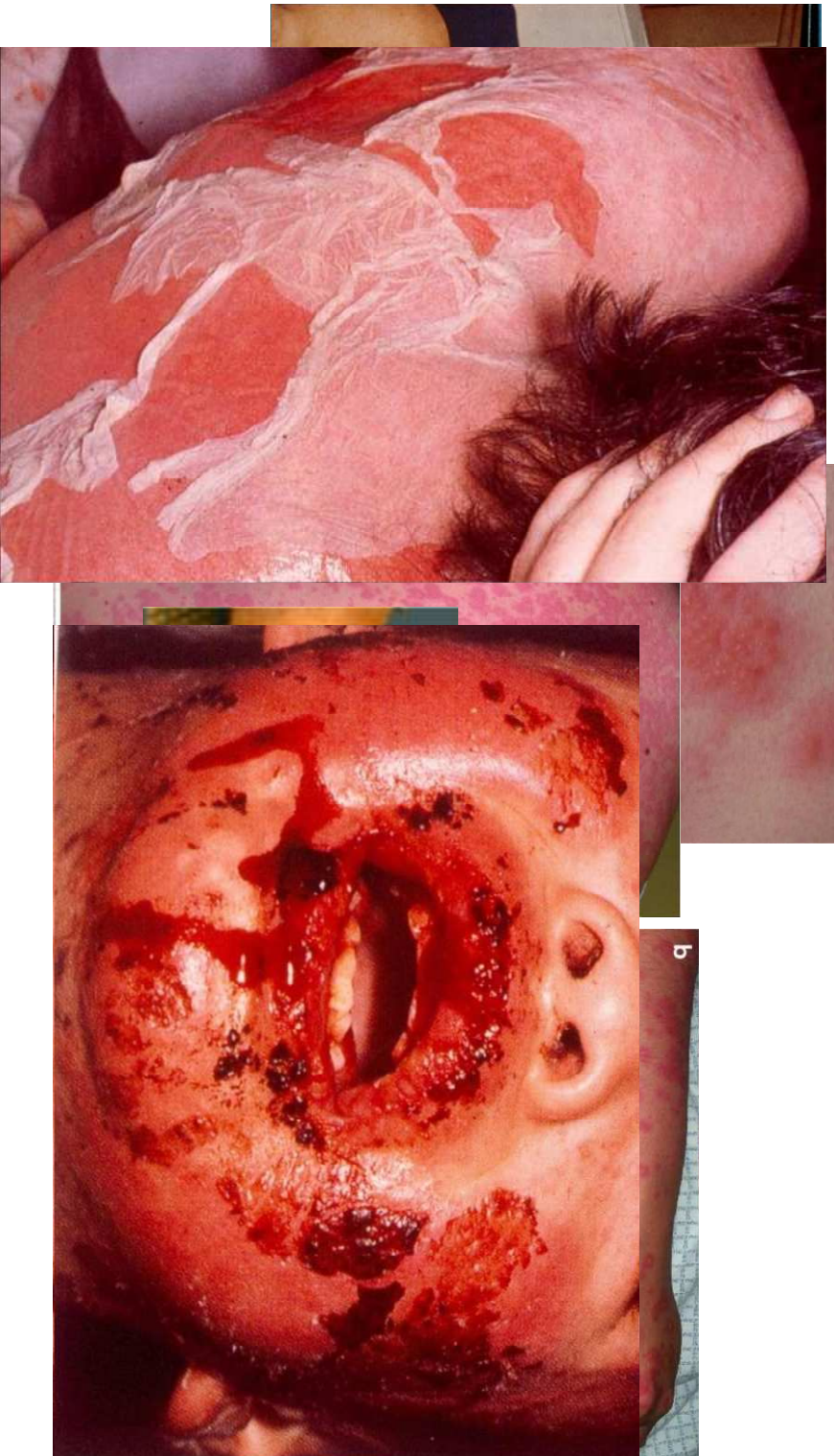


Occuring within 2h after drug intake

IgE mediated – diagnostics

- ▶ Skin prick testing and intradermal testing
- ▶ sIgE measurements
- ▶ Basophil activation test
- ▶ Challenge test

T-cell mediated reactions



Occuring days to weeks after drug intake

T cell mediated - diagnostics

- ▶ Patch testing



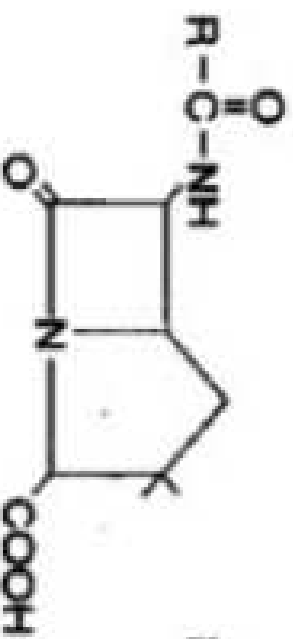
- ▶ Intradermal testing with late readings

Penicillin Allergy - Background

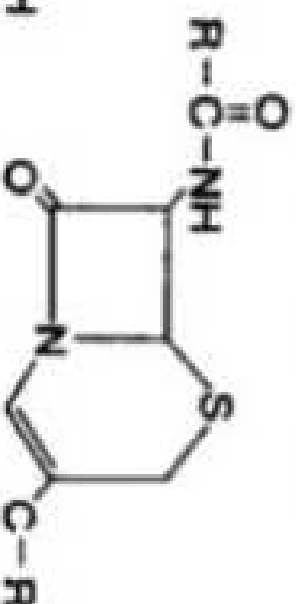


Structure

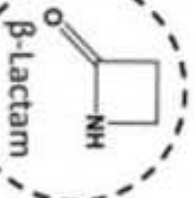
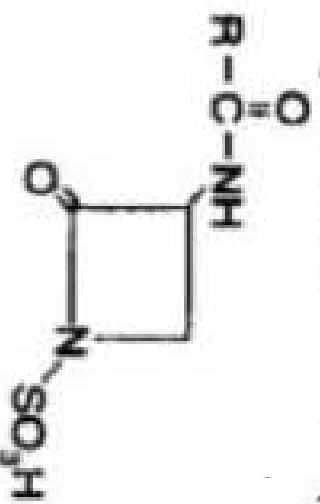
Penicillins



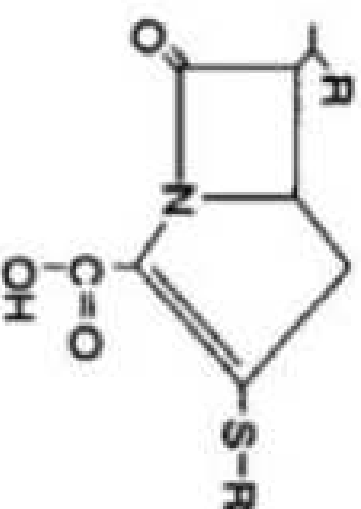
Cephalosporins



Monobactams



Carbapenems



Penicillin allergy: incidence

Self reported incidence: 10% ↔ 90% of them tolerate penicillins

Reasons:

- Reaction histories poorly characterized and very remote
- Symptoms may have been consequence of underlying illness (viral, infectious disease)
- Symptoms may have been consequence of interaction between a penicillin AB and an infectious agent (eg EBV)
- Concomitant intake of other drugs (eg NSAID)
- Loss of penicillin sensitivity over 5 years?

- ▶ Incidence (based on positive skin tests)
 - ▶ Decreasing over the past 2 decades
 - ▶ Anaphylaxis: very rare (0,01% to 0,04% of treated patients)
 - ▶ US: 500 -1000 deaths/year are secondary to penicillin induced anaphylaxis

Consequences Penicillin Allergy Label

- ▶ Increased antimicrobial resistance
- ▶ Increased Clostridium difficile infections
- ▶ Prolonged length of hospital stays
- ▶ Increased intensive care admissions
- ▶ Increased hospital readmissions
- ▶ **Significantly higher costs** (297 dollar could be saved per patient when switched from a non-betalactam to a betalactam AB)

Penicillin Allergy – Diagnostic management



When to evaluate?

YES

- ▶ All patients with a history of possible IgE mediated penicillin allergy
- ▶ Reaction history unclear? → testing is reasonable

NO

- ▶ skin testing as a routine screen in the absence of clinical history
- ▶ patients who never took penicillin but have family history of penicillin allergy
- ▶ Reaction incompatible with allergy?

History taking

- ▶ First intake?
- ▶ Was the drug well tolerated in the past?
- ▶ Did the patient take the same (or similar) drug after the reaction?
- ▶ Timing of reactions? After first intake, or after 3 days into therapy?
- ▶ Delay between last intake and reaction?
- ▶ (Dis)continuation of the drug?
- ▶ When stopped: resolution of symptoms?
- ▶ Exact description of symptoms
- ▶ Treatment?
- ▶ Photo!

slgE measurement

► Low sensitivity (<45%)

β -lactams (updated from Ebo D et al. [87]).

Compound	Reference test	Assay	Sensitivity	Specificity	N	Reference
Various β -lactams	H + ST	CAP-FEIA	BPO + AXO + penil G + AMP: 31.8%	BPO + AXO + penil G + AMP: 88.6%	58	[88]
Various β -lactams	H \pm ST \pm DPT	CAP-FEIA	BPO: 32%	BPO: 98%	129	[89]
			AXO: 43%	AXO: 98%		
			BPO + AXO: 50%	BPO + AXO: 96%		
Various β -lactams	H \pm ST \pm DPT	CAP-FEIA	BPO: 10-68%	BPO: 98%	410	[18]
			AXO: 41-53%	AXO: 95%		
Various β -lactams	H	CAP-FEIA	37.9%	86.7%	58	[90]
Various β -lactams ^a	H \pm ST \pm DPT	CAP-FEIA	0-25% ^b	83.3-100% ^b	45	[14]
		RAST ^b	42.9-75% ^b	66.7-83.3% ^b		
Various β -lactams	H \pm ST	CAP-FEIA	85% ^c	54% ^c	176	[21]
		CAP-FEIA	44% ^d	80% ^d		
Various β -lactams	H \pm ST	CAP-FEIA	66%	52%	293	[22]

H: history, ST: skin test, DPT: drug provocation test, N: number, CAP-FEIA: fluorescence enzyme immunoassay available from Phadia Therapeutics, RAST: radio allergosorbent test, Penil G: penicillin G, AMF: ampicillin, BPO: benzyl penicilloyl, AXO: amoxicillin.

^a Home-made assay.

^b Sensitivity and specificity vary according to clinical manifestations.

^c For threshold 0.10 kUA/L.

^d For threshold 0.35 kUA/L.

Skin testing

Reading after 15-20 minutes

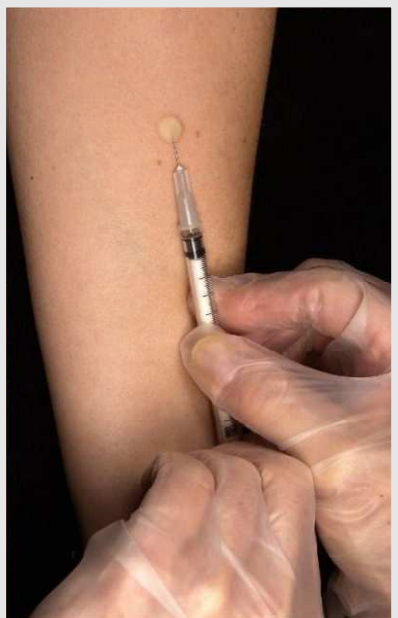
1. Prick testing



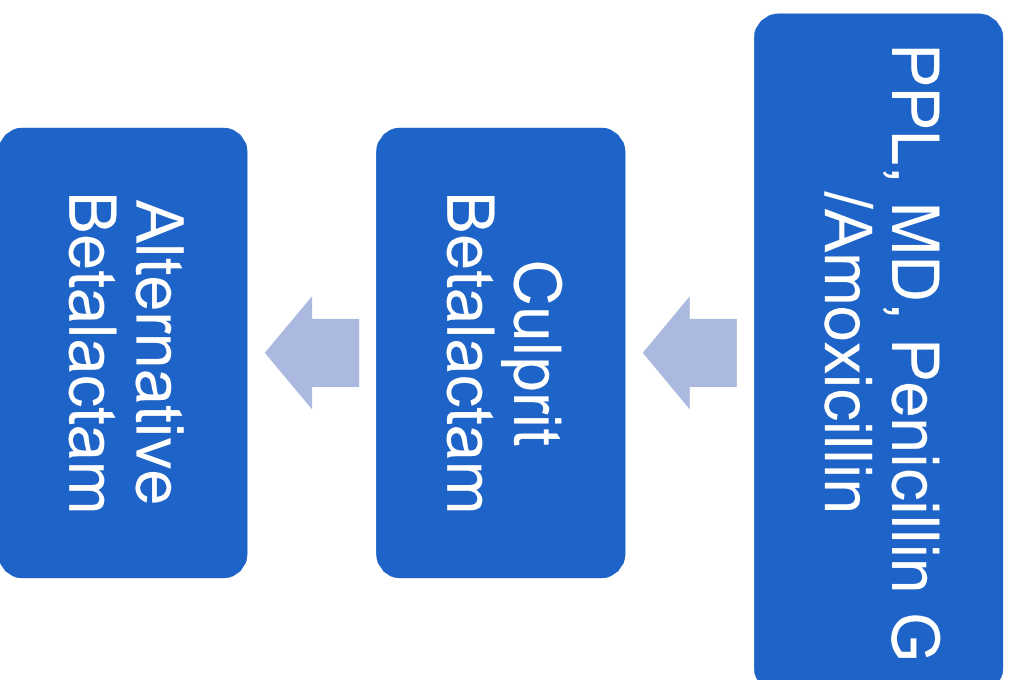
When
negative



2. Intradermal testing



Skin testing



PPV: 50%
NPV: 84%-99% (esp PPL)

Challenge test?

- ▶ When skin testing is negative → despite very high NPV still 52% of patients are reluctant to or advised against taking betalactam antibiotics (by other physicians)

- ▶ Therefore: challenge test is needed!

PROVOCATIE PER OS
CLAMIOXYL (= Amoxicilline)

} Badge van patient(e)

Datum: " "

Aanvragende arts:

Verpleegkundige:

Huidige medicatie:

Huidige klachten:

infus heparineslotje
 monitoring
 hoog risico
 laag risico

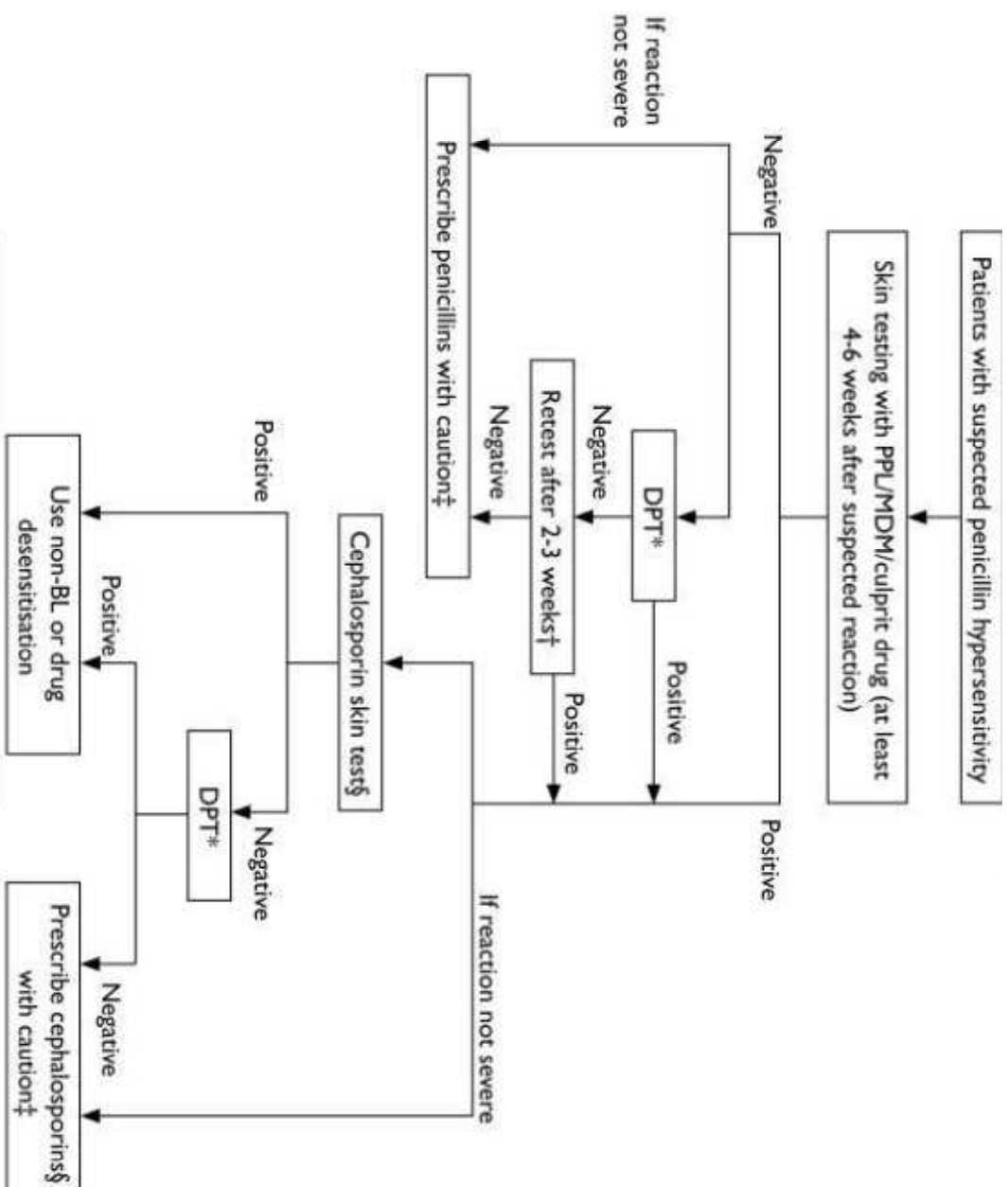
0. neg. controle		papier		erytheem			
1. pos. controle	uur	dosis	bloeddruk	pols/min	sat.	Kliniek:	
T ₀			/				
30'		1 mg	/				
60'		50 mg	/				
90'		100 mg	/				
120'		250 mg	/				
150'		500 mg	/				

Opmerking:

Cross reactivity

- **With other penicillins:** estimated at 10% → probably overestimated
- **With cephalosporines:** also overestimated
 - Cross reactivity is based on R1 side chain, not on the betalactam ring
 - Mostly with 1th and 2nd generation (up to 30%)
 - Rarely with 3th and 4th generation (<0,1%)
- **With monobactams en carbapenems:** practically zero

Diagnostic flowchart



Penicillin Allergy – After diagnosis



Established diagnosis?

- ▶ **Allergy card:**
 - ✓ Culpit drug
 - ✓ Symptoms
 - ✓ Safe alternative
- ▶ Drug allergy **DOES NOT REQUIRE AN EPIPEN** (avoidable allergen!)
- ▶ **Desensibilisation?**
 - ▶ Can be done in specific situations (eg syfillis and penicillin allergy)
 - ▶ CAVE desensitisation : a temporary phenomenon





Vaccination and allergy

Introduction



Adverse reactions after immunization

- ▶ Commonly reported
- ▶ Often results in withholding further immunizations
- ▶ Most often: local reactions and nonimmediate skin eruptions
- ▶ True hypersensitivity: **VERY RARE**



Local reactions



Local reactions



Mild local reaction



Large local reaction



Limb swelling

*Arthus reaction

Local reactions



Subcutaneous nodules
(aluminium containing
vaccines)



Local eczema
(aluminium hydroxide, thiomersal and
formaldehyde)

Local reactions: management

Mechanism	nonspecific inflammation (due to variety of factors, e.g. high content of aluminium hydroxide and/or substances of microbial origin)
Risk?	NOT associated with higher rate of systemic reactions
Allergy work up?	Generally not necessary
	Nodules or eczema-> consider patch testing (preservatives/adjuvants)**
Subsequent injection	Can be given, often well tolerated
Arthus reaction?	Serum vaccine specific IgG or IgM can be measured (if high enough: no additional dose)

Local reactions: prevention?

- ▶ Risks: not well defined
- ▶ Reactogenicity is reduced by
 - ▶ Correct needle length (longer needle ~ lower rate of local reactions)
 - ▶ Injection site (thigh ~ lower rate of local reactions)



Systemic reactions



Systemic reactions



Urticaria/Exanthema



Angioedema

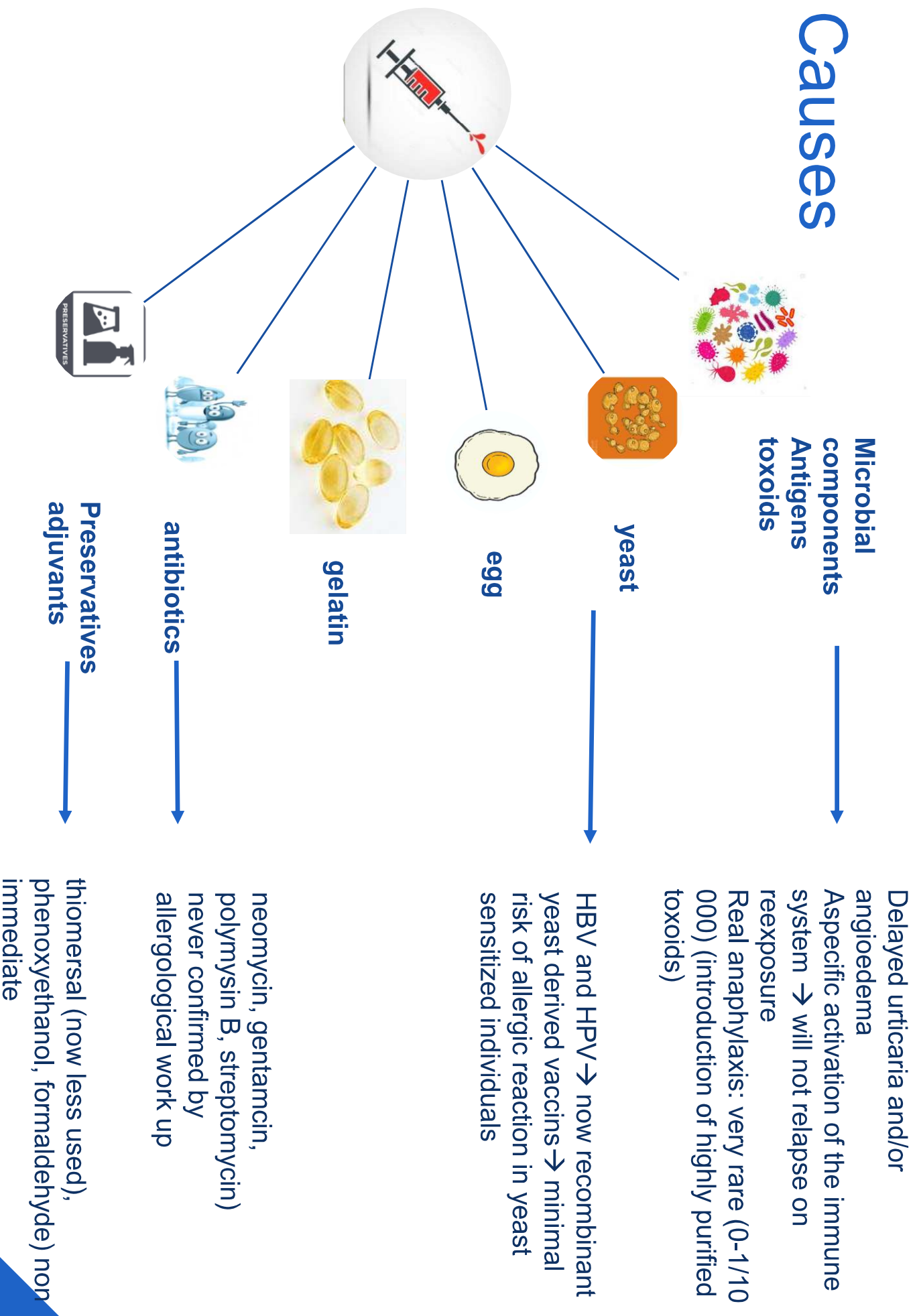


Anaphylaxis

Anaphylaxis: rare

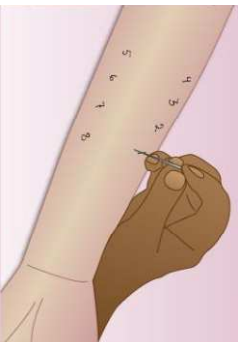
Vaccine	Rate/million doses	Total dosis administered (millions)
Haemophilus influenza b	0	1,14
Hepatitis B	0	1,29
Influenza (TIV)	1,59	8,83
MMR	5,14	0,58
Pertussis (DTP) Pertussis (DTaP)	2,89 2,07	3,12 1,45
Pneumococcal (PCV13)	0	0,74
IPV	1,65	1,22
All vaccines	1,31	25,17

Causes



Systemic reaction - management

- ▶ Clinical history not sufficient
- ▶ Allergological workup:



Prick testing

- Vaccin full dose or 1/10
- Intradermal test 1/100 with culprit vaccin and related vaccins
- If possible skin tests with single components: egg, gelatin, latex, yeast, formaldehyde...

- ▶ Measurement of vaccin antibodies (IgG, IgM) **NOT** IgE
- ▶ When work up confirms hypersensitivity to one of the vaccine components → vaccine can be given in graded doses, or allergen free vaccine can be use

General recommendation

Allergic reaction to previous vaccine dose	Skin test result	Vaccine administration	Precautions
Local reaction	Not needed	Full dose	No observation period
Systemic reaction	Negative	Allergen avoidance*, if possible, split dose	60 min observation, IV line
Systemic reaction	Positive	Allergen avoidance*, If possible, graded doses	60 min observation, monitorin, IV line

*is not: no vaccination, but using allergen free vaccine or a low allergen content vaccine if available

Influenza vaccines in egg allergic patients



Background

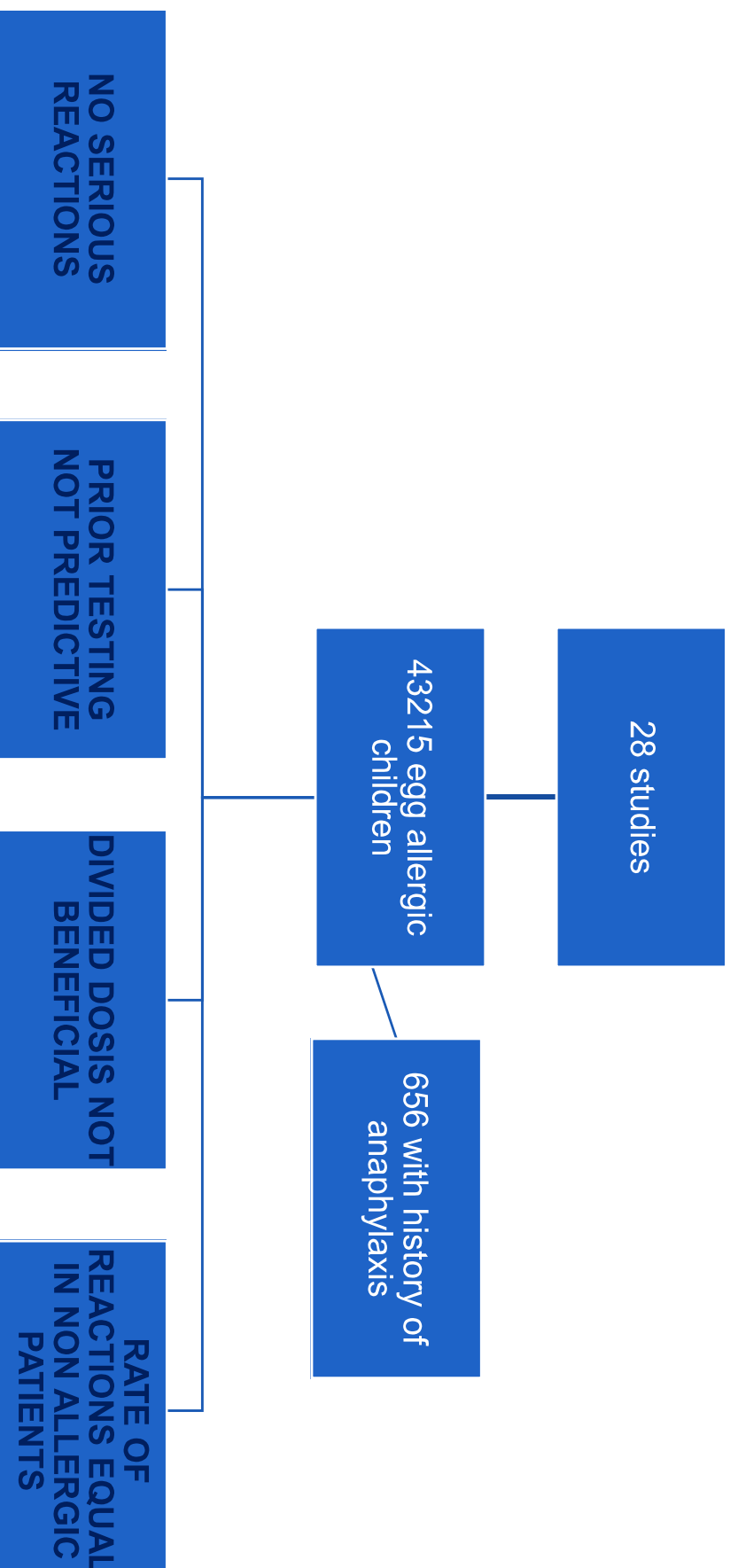
- ▶ Majority is grown in eggs → leaves amount of residual egg protein (ovalbumin) in vaccines
- ▶ Raises possibility of allergic reaction when administered to egg allergic patients
- ▶ Incidence of anaphylaxis after influenza vaccination
 - ▶ VSD 2009-2010: 0,9 per million doses
 - ▶ 1,9 per million doses
 - ▶ VAERS: 0,8 per million doses

Egg protein in influenza vaccines

Lowest dose of egg protein ever reported provoking allergic reaction	130mcg ovalbumin
Package insert statements	< 1 mcg ovalbumin
Measured doses	<0, 12 µg/mL ovalbumin

→ very unlikely to provoke allergic reaction, even in egg allergic children

Literature



Risk of not vaccinating?



- ▶ Vast majority of egg allergic patients: children
- ▶ +- 20 000 hospitalizations and 100 deaths from influenza each year (USA)
- primarily in children that are not vaccinated

Not vaccinating = risk for vaccine preventable morbidity and mortality

Recommendations



- Egg allergic (mild) → full dose, 30 m observation
- Egg allergic (severe) → refer to allergist

2011



- Mild or severe → single dose without prior testing
- Special precautions regarding medical setting and waiting periods after adm of IV to egg allergic recipients beyond those recommended for any vaccine **NOT WARRANTED**

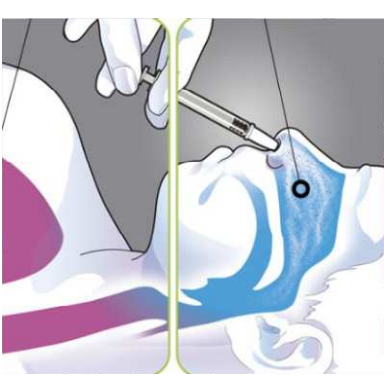
2013



- Manifest egg allergy:
- Low egg (<0,12µg/mL) vaccines
- Non anaphylactic reaction to eggs: standard conditions
- Anaphylactic reaction to eggs: single dose vaccination in hospital setting, 1 h observation period

2017

Live attenuated intranasal vacciin



- ▶ Very low ovalbumine content (<0,24mcg/0,2mL dose)
- ▶ 2015, JACI: 282 children with egg allergy (115 anaphylaxis, 67% astma)
 - ▶ No systemic allergic reactions
 - ▶ 8 with self limiting symptoms
 - ▶ 26 lower respiratory tract symptoms occurring within 72h (not requiring medical intervention beyond routine therapy)

→ LAIV appears to be safe for use in children with egg allergy and is well tolerated in children with asthma or recurrent wheeze.



Newer techniques: Non egg based influenza vaccines

- ▶ Cell cultured based vaccines
 - ▶ Uses seed virus grown in eggs
 - ▶ Could theoretically contain $1 \times 10^{-7} \text{e}$ $\mu\text{g/mL}$ of ovalbumin
 - ▶ Egg allergy not mentioned as precaution or contraindication
- ▶ Recombinant vaccines
 - ▶ Process that does not involve eggs

Key issues

- ▶ Anaphylaxis after vaccination is rare
- ▶ Patients with egg allergy should receive annual influenza vaccination
- ▶ Carefull evaluation of allergic reaction to influenza vacciin may identify culprit allergens to inform more cautious subsequent vaccination