



Praktisk insektgifts-immunterapi VIT

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EAACI guidelines on allergen immunotherapy: Hymenoptera venom allergy

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Insektgifts-immunterapi

- Den eneste behandling, som har potentialet til at kunne forhindre fremtidige anafylaktiske reaktioner, er immunterapi med insektgift (VIT)
- Den dokumenterede kliniske effekt af insektgifts-immunterapi er:

77 - 84% ved behandling med honningbi-gift

91 - 96% ved behandling med hvepse-gift

Insektgifts-immunterapi

I Danmark er de kommercielt tilgængelige allergen-ekstrakter til immunterapi med insektgift:

- Honningbi (*Apis mellifera*)



- Hveps (*Vespula spp.*)



Insektgifts-immunterapi

Danske kommercielle allergen-ekstrakt formuleringer til insektgift-immunterapi:

Vandige ekstrakter:

- **Aquagen[®] SQ** (100.000 SQ-U/ml)
- **Pharmalgen[®]** (120 µg/hætteglas)

Depot-ekstrakter (bundet til aluminiumhydroxid):

- **Alutard[®] SQ** (100, 1.000, 10.000 & 100.000 SQ-U/ml)

Insektgifts-immunterapi

- Vandige ekstrakter anvendes til regimer som:
 - ultra-rush, rush, cluster og konventionel opdosering samt til vedligeholdelses-behandling.
- Aluminium-hydroxid adsorberede ekstrakter anvendes til:
 - konventionel eller cluster opdosering og til vedligeholdelses-behandling

Insektgifts-immunterapi

- Efter en hurtig opdosering med vandigt ekstrakt kan skiftes til vedligeholdelses-behandling med depot-ekstrakt
- Depot-ekstrakt udløses generelt færre lokale bivirkninger - men dette kan være forårsaget af en langsommere opdoseringsfase eller en langsommere frigivelse af allergen fra aluminium-hydroxid

Recommendations for individuals with
venom allergy

Evidence
level

Grade of
recommendation

Strength of recommen-
dation

Other
considerations

Key reference

Assigning levels of evidence and recommendations (Oxford Centre for Evidence-based Medicine)

Level of evidence

Level I	Systematic reviews, meta-analysis, randomized controlled trials
Level II	Two groups, nonrandomized studies (e.g., cohort, case-control)
Level III	One group nonrandomized (e.g., before and after, pretest, and post-test)
Level IV	Descriptive studies that include analysis of outcomes (single-subject design, case series)
Level V	Case reports and expert opinion that include narrative literature, reviews, and consensus statements

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Grades of recommendation

Grade A Consistent level I studies

Grade B Consistent level II or III studies or extrapolations from level I studies

Grade C Level IV studies or extrapolations from level II or III studies

Grade D Level V evidence or troublingly inconsistent or inconclusive studies at any level

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Strength of recommendations

Strong

Evidence from studies at low risk of bias

Moderate

Evidence from studies at moderate risk of bias

Weak

Evidence from studies at high risk of bias

Recommendations for individuals with venom allergy	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
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VIT is recommended in adults and children with detectable sensitization and systemic sting reactions exceeding generalized skin symptoms	I (III for children)	A (B for children)	Strong to moderate for adults based on two low risk of bias SR. ^{1,131} Weak for children based on one high risk of bias CBA ¹⁵ and one high risk of bias RCT study that included children ⁸⁷	Carrying an AAI without VIT negatively impacts on health-related QoL	Dhimi 2017 ¹ Boyle 2012 ¹³¹ Golden 2004 ¹⁵ Hunt 1978 ⁸⁷
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VIT er indiceret til børn og voksne med påvist sensibilisering og systemisk reaktion ud over generaliserede hud-symptomer (respiratoriske og/eller kardiovaskulære symptomer)

Recommendations for individuals with venom allergy	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
VIT is recommended in adult patients with systemic sting reactions confined to generalized skin symptoms if quality of life is impaired	I	A	Strong to moderate based on one low risk of bias SR ¹ and two adult RCTs of moderate risk of bias ^{50,52}	Carrying an AAI without VIT negatively impacts on health-related QoL	Dhami 2017 ¹ Oude Elberink 2002 and 2009 ^{50,52}

VIT anbefales til voksne med systemisk reaktion alene omfattende generaliserede hud-symptomer, hvis livskvaliteten er påvirket

Recommendations for individuals with venom allergy	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
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VIT can be recommended in adults with recurrent, troublesome LLR to reduce the duration and size of future LLR	II	B	Moderate/low based on one open, controlled trial of venom-allergic adults with LLR ¹⁹	Cost/benefit profile should be considered for this indication. No pediatric data	Golden 2009 ¹⁹
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VIT anbefales almindeligvis ikke til personer med store lokalreaktioner

Recommendations for individuals with venom allergy	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key reference
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Two venoms can be administered simultaneously in the left and right arm, respectively. However, in the case of systemic adverse events, VIT should be continued with 30-minute intervals between injections	V	D	Weak based on expert consensus		Expert consensus
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To insektgift-ekstrakter kan administreres simultant i hver sin arm

Samtidig behandling med flere allergen-ekstrakter:

- Der anvendes separat registrering for hvert allergen
- Forskellige allergener må ikke blandes i samme sprøjte
- Findes der indikation for AIT med flere allergener, anbefales det at opdosere med ét allergen ad gangen
- Skønnes samtidig behandling med 2 allergener indiceret, anbefales det at administrere injektioner med mindst 30 minutters interval

Recommendations for individuals with venom allergy	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key reference
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It may be recommended to give injections every 4 weeks in the first year of treatment, every 6 weeks in the second year, and in case of a 5 year treatment every 8 weeks from year 3-5	V	D	Weak based on expert consensus ⁹³		Bonifazi 2005 ⁹³
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Det anbefalede injektions-interval er:

- hver 4. uge det første behandlingsår
- hver 6. uge det andet år
- derefter hver 8. uge

Prevention and treatment of hymenoptera venom allergy:
guidelines for clinical practice

Allergy 2005

F. Bonifazi¹, M. Jutel², B. M. Biló¹,
J. Birnbaum³, U. Muller⁴ and the
EAACI Interest Group on Insect
Venom Hypersensitivity*

- Det generelt anbefalede tidsinterval til vedligeholdelsesbehandling med 100 µg insektgift er 4 uger
- Forlængelse af tidsintervallet mellem injektioner til 4 til 6 uger i løbet af det første behandlingsår giver fortsat effektiv beskyttelse

Recommendations for individuals with venom allergy	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key reference
In the case of lifelong therapy, 12-week intervals may be still safe and effective	II	C	Moderate based on one CCT ⁹⁴ and one CBA ⁹⁵ study		Simioni 2013 ⁹⁴ Goldberg 2001 ⁹⁵

I tilfælde af livslang VIT er 12-ugers tidsinterval sikkert og effektivt

Maintenance venom immunotherapy administered at 3-month intervals is both safe and efficacious

JACI 2001

Arnon Goldberg, MD, and Ronit Confino-Cohen, MD *Kfar Saba, Israel*

- 6 ud af 160 tolererede ikke 12 ugers interval til vedligeholdelsesbehandling
- 44 stikprovokationer blev udført på 46 patienter på vedligeholdelsesbehandling (12 ugers interval)
- Hos 2 (4.5%) af de 44 patienter udvikledes en systemisk reaktion:
 - Grad I hos 1 patient
 - Grad II hos 1 patient

Efficacy of venom immunotherapy given every 3 or 4 months: a prospective comparison with the conventional regimen

Livio Simioni, MD^{*}; Alberto Vianello, MD^{*}; Patrizia Bonadonna, MD[†]; Guido Marcer, MD[‡]; Maurizio Severino, MD[§]; Mauro Pagani, MD[¶]; Luca Morlin, MD[‡]; Mariangiola Crivellaro, MD[‡]; and Giovanni Passalacqua, MD^{||}

Ann Allergy Asthma Immunol 2013

Konventionel vedligeholdelse hver 4 – 6 uge: 110 patienter
Vedligeholdelsesbehandling hver 16. uge: 76 patienter

Behandlingssvigt:

Konventionel vedligeholdelse: 18,5%

Vedligeholdelse hver 4. måned: 6,5%

Total number of re-stings according to maintenance dose interval and protocol

Maintenance dose	Grade of reaction					Total
	None	I	II	III	LLR	
EMD						
3 months	192	4	1	2	6	205
4 months	39	1	0	0	2	42

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It can be recommended to perform VIT for at least 3 years. In patients with severe initial sting reactions, at least a 5-year treatment is recommended	IV	C	Weak based on case series studies ^{98,99,101}		Lerch 1998 ⁹⁹ Golden 1996 ¹⁰¹ Reisman 1993 ⁹⁸
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Det anbefales at give VIT i mindst 3 år. Hos patienter med initial alvorlig stikreaktion anbefales mindst 5 års behandling

Duration of venom immunotherapy: Relationship to the severity of symptoms of initial insect sting anaphylaxis

J Allergy Clin Immunol 1993

Robert E. Reisman, MD *Buffalo, N.Y.*

- Undersøgelse på 113 patienter på vedligeholdelsesbehandling med VIT fra < 1 år til > 5 år med 217 stik i naturen
- Re-stik medførte 15 systemiske reaktioner hos 10 patienter:
 - en re-stik reaktionshyppighed på 9% per stik og 7% per patient

TABLE I. Relationship of the nature of the symptoms of the initial sting reaction to the occurrence of a re-sting reaction after cessation of VIT

Initial sting reaction symptoms	No. of patients	Re-sting reactions (no. of patients)
Mild: Dermal only	25	1 (4%)
Moderate: Dermal plus other non-life-threatening symptoms	41	2 (5%)
Severe: Hypotension, shock, airway edema, loss of consciousness	47	7 (15%)*

* $p = 0.09$; difference between the re-sting reaction rate in the severe group and the combined mild-moderate groups.

TABLE IV. The relationship of the occurrence of a re-sting reaction to duration of VIT

Duration of VIT (yr)	No. of patients	No. of reactions
<1	14	2
1	21	3
2	39	2
3	21	1
4	9	—
5	4	1
>5	5	1

- Resultaterne antyder en sammenhæng mellem sværhedsgraden af den systemiske reaktion og den deraf følgende varighed af VIT
- 2 til 3 år er tilstrækkeligt til patienter med mild til moderat anafylaksi
- Længere varighed anbefales til patienter med sværere symptomer og som fortsætter med at have positive hudtest med insektgift

Long-term protection after stopping venom immunotherapy: Results of re-stings in 200 patients

J Allergy Clin Immunol 1998

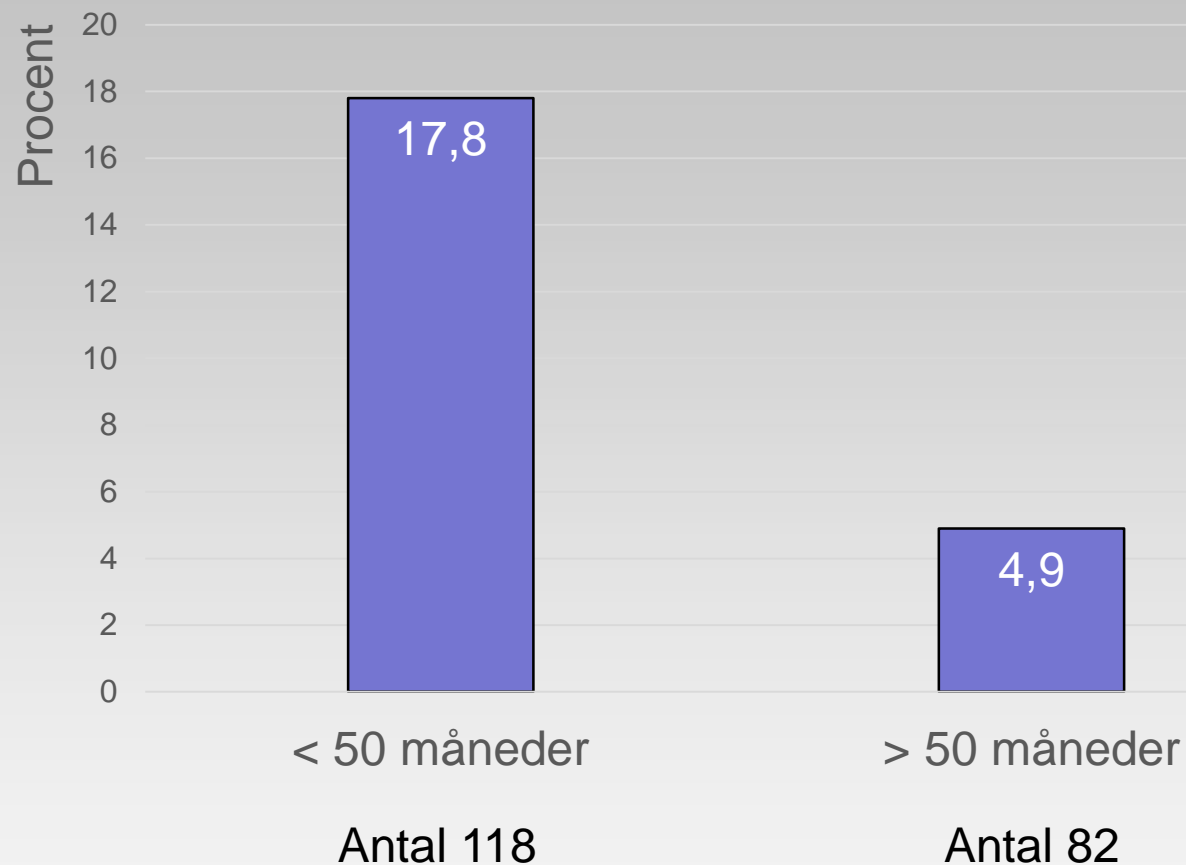
Erika Lerch, MD, and Ulrich R. Müller, MD *Bern, Switzerland*

Re-stik data fra 200 ud af 322 patienter behandlet med VIT i 3 år

Ud af 25 patienter med re-stik-reaktioner var:

- 19 behandlet med bi-gift: behandlingssvigt 15,8%)
- 6 behandlet med hvepsegift: behandlingssvigt 7,5%)

Behandlingssvigt relateret til behandlingsvarighed



VIT af 3 til 5 års varighed sikrer langtidsbeskyttelse hos flertallet af patienter

Men mere end 4 års behandling ser ud til at øge behandlingseffekten

Nevertheless, most of the studies concluded that a minimum of a five-year treatment is superior for long-term effectiveness

Lerch E, Muller UR. Long-term protection after stopping venom immunotherapy: results of re-stings in 200 patients. *J Allergy Clin Immunol.* 1998;101:606-612.

Keating MU, Kagey-Sobotka A, Hamilton RG, Yunginger JW. Clinical and immunologic follow-up of patients who stop venom immunotherapy. *J Allergy Clin Immunol.* 1991;88:339-348.

Golden DB, Kwiterovich KA, Kagey-Sobotka A, Valentine MD, Lichtenstein LM. Discontinuing venom immunotherapy: outcome after five years. *J Allergy Clin Immunol.* 1996;97:579-587.

Golden DB, Kwiterovich KA, Kagey-Sobotka A, Lichtenstein LM. Discontinuing venom immunotherapy: extended observations. *J Allergy Clin Immunol.* 1998;101:298-305.

Recommendations for individuals with venom allergy	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key reference
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Lifelong VIT may be recommended in highly exposed patients with bee venom allergy, patients with very severe initial sting reactions (Muller grade IV or grade III-IV according to Ring & Messmer), and patients with systemic side-effects during VIT as they are major risk factors for relapse	IV	C	Weak based on case series studies ^{8,31,98}		Ruëff 2013 ³¹ ; 2014 ⁸ Reismann 1993 ⁹⁸
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Livslang VIT anbefales til kraftigt udsatte patienter med bi-gift allergi med alvorlig initial reaktion, samt patienter med systemiske reaktioner under VIT

Recommendations for individuals with venom allergy	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key reference
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It may not be recommended to determine venom-specific IgE, IgG levels, BAT response and allergen-blocking capacity to estimate the individual risk for relapse	IV	C	Weak based on case series studies ^{99,100,112}		Lerch 1998 ⁹⁹ Müller 1991 ¹¹² Keating 1991 ¹⁰⁰
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- Hverken absolutte værdier eller ændring af allergen-specifik IgE, IgG, IgG4, histamin-release eller allergenblokerende kapacitet kan bruges som udtryk for klinisk effekt

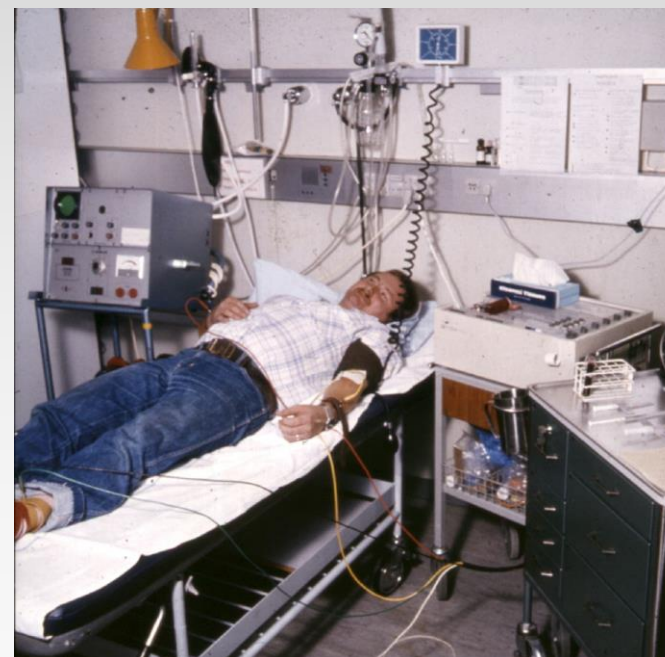
Recommendations for individuals with venom allergy	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key reference
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In adults, a sting challenge can be recommended as the most reliable method to evaluate effectiveness of VIT	IV	C	Weak based on case series studies ^{101,117}		Van Halteren 1997 ¹¹⁷ Golden 1996 ¹⁰¹
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En stikprovokation anbefales som den mest pålidelige metode til at vurdere effekten af VIT

Stik-provokation

- Effekten af behandlingen kan undersøges ved at lade en levende bi eller hveps stikke personen efter immunterapi



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If no sting challenge can be performed, it may be recommended to record outcomes of field stings to evaluate effectiveness of VIT

V

D

Weak based on expert
consensus

Expert consensus

Hvis stik-provokation ikke kan gennemføres giver stik under naturlige forhold også en vis dokumentation for beskyttelse

Fejlkilder:

- Identifikation af insekt
- Stikvarighed



Recommendations for individuals with venom allergy	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key reference
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During and after VIT, AAI cannot be recommended in patients with mild-to-moderate initial sting reactions without risk factors for relapse	V	D	Weak based on expert consensus		Expert consensus
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- Adrenalin autoinjektor anbefales almindeligvis ikke efter at vedligeholdelsesdosis er nået
- Specielt ikke hvis stik-reaktionen har været mild eller hvis patienten har tålt en stikprovokation eller et naturligt stik

Recommendations for individuals with venom allergy	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key reference
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During and after VIT, AAI may be recommended in patients at risk of multiple stings or with risk factors for relapse	V	D	Weak based on expert consensus		Expert consensus
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- Adrenalin autoinjektor kan overvejes efter at vedligeholdelsesdosis er nået hos patienter med svær stikreaktion, samtidig hjertesygdom og ophold langt fra akut lægehjælp



Recommendations for individuals with venom allergy	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key reference
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- Adrenalin autoinjektor kan overvejes efter at vedligeholdelsesdosis er nået hos patienter med svær stikreaktion, samtidig hjertesygdom og ophold langt fra akut lægehjælp
- Adrenalin autoinjektor kan overvejes hos personer med alvorlig indskrænkning af livskvalitet af frygt for fornyet stik

Quality of life

For most patients, and their families, any allergic reaction (regardless of severity) is a frightening experience. Given the effort required to avoid accidental exposures and the inherent uncertainty of success, living with HVA negatively influences QoL

Oude Elberink JN, De Monchy JG, Van Der Heide S, Guyatt GH, Dubois AE. Venom immunotherapy improves health-related quality of life in patients allergic to yellow jacket venom. *J Allergy Clin Immunol.* 2002;110:174-182.

Fischer J, Teufel M, Feidt A, Giel KE, Zipfel S, Biedermann T. Tolerated wasp sting challenge improves health-related quality of life in patients allergic to wasp venom. *J Allergy Clin Immunol.* 2013;132:489-490.

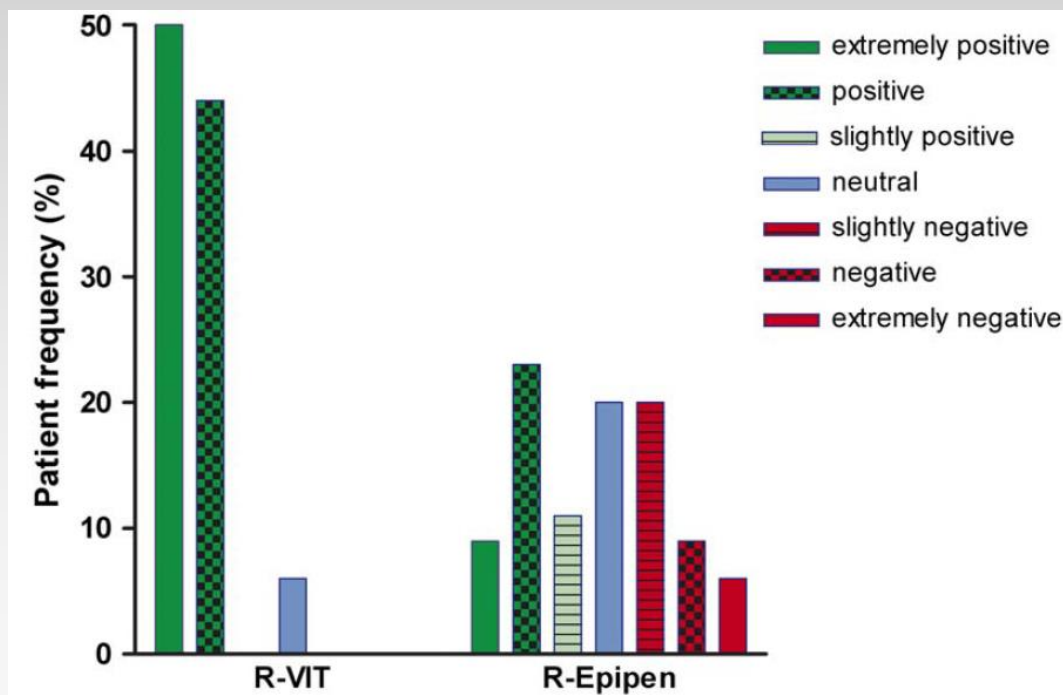
Oude Elberink JN, van der Heide S, Guyatt GH, Dubois AE. Immunotherapy improves health-related quality of life of adult patients with dermal reactions following yellow jacket stings. *Clin Exp Allergy.* 2009;39:883-889.

Oude Elberink JN, van der Heide S, Guyatt GH, Dubois AE. Analysis of the burden of treatment in patients receiving an EpiPen for yellow jacket anaphylaxis. *J Allergy Clin Immunol.* 2006;118:699-704.

Analysis of the burden of treatment in patients receiving an EpiPen for yellow jacket anaphylaxis

JACI 2006

Joanne N. G. Oude Elberink, MD,^a S. van der Heide, MSc, PhD,^a Gordon H. Guyatt, MD,^b and Anthony E. J. Dubois, MD, PhD^a Groningen, The Netherlands, and Hamilton, Ontario, Canada



94 patienter randomiseret til enten VIT eller EpiPen

- 30% er negative overfor EpiPen
- Blandt de 22% som er positive overfor EpiPen finder ca. 60% den besværlig og problematisk

Insektgifts-immunterapi

- Den optimale varighed af VIT hos børn & voksne (3 år vs 5 år eller længere)
- Biomarkører til vurdering af klinisk effekt
- Effekten af VIT på sundheds-relateret livskvalitet sammenlignet med adrenalin autoinjektor
- Omkostnings-effektivitet af VIT