EOSINOPHILE ERKRANKUNGEN DES GASTROINTESTINALTRAKTES

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Gliederung

- Vorbemerkungen
- Einteilung
- Pathophysiologie
- Eosinophile Ösophagitis
  - Symptomatik
  - Diagnostik
  - Assoziierte Erkrankungen
- Eosinophile (Gastro-)Enteritis/-Kolitis
- Behandlung

Allgemeines

- Seit langem bekannt, Erstbeschreibung 1937 durch R Kaijser in Archiv Klin Chir
- Seitdem > 400 Fälle publiziert (meist nur Fallserien/-berichte)
- Erst ab 1990 Talley auch diagnostische Kriterien
  a) Gastrointestinale Symptome
  b) Vorhandensein Gewebseosinophilie
  c) Exklusion anderer Ursachen von Gewebseosinophilie

Intestinal Tract	Eos/hpf
Stomach [44]	>30
Small intestine [44]	>52
Colon [44, 46, 47]	
Right	>100
Transverse and descending	>84
Rectosigmoid	>64

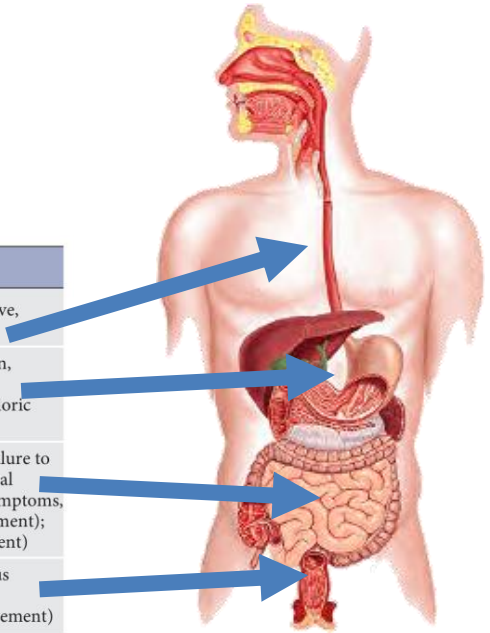
LICARI 2020

Einteilung Eosinophilic GastroIntestinal Diseases

- Bezeichnung umfasst eine **Gruppe**, chronisch inflammatorischer Erkrankungen des Gastrointestinaltraktes
- Klinisch charakterisiert durch Dysfunktion des betroffenden Segmentes
- Histologisch charakterisiert durch **eosinophile Infiltration**
- Ausschluss anderer Ursachen

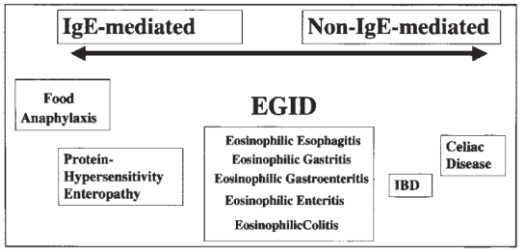
EGID	Clinical symptoms
EoE	Vomiting, GERD-like symptoms, failure to thrive, dysphagia, food impaction
EG	Nausea, vomiting, retrosternal or epigastric pain, dyspepsia, hematemesis/melaena (mucosal involvement); outlet obstruction mimicking pyloric stenosis (muscular involvement)
EGE	Nausea, vomiting, abdominal pain, diarrhea, failure to thrive/weight loss, protein loss or gastrointestinal bleeding (mucosal involvement); obstructive symptoms, intussusception, perforation (muscular involvement); abdominal distention, ascites (serosal involvement)
EC	Abdominal pain, tenesmus, diarrhea with mucus and/or blood (mucosal involvement); volvulus, intussusception, perforation (transmural involvement)

KOUTRI 2018

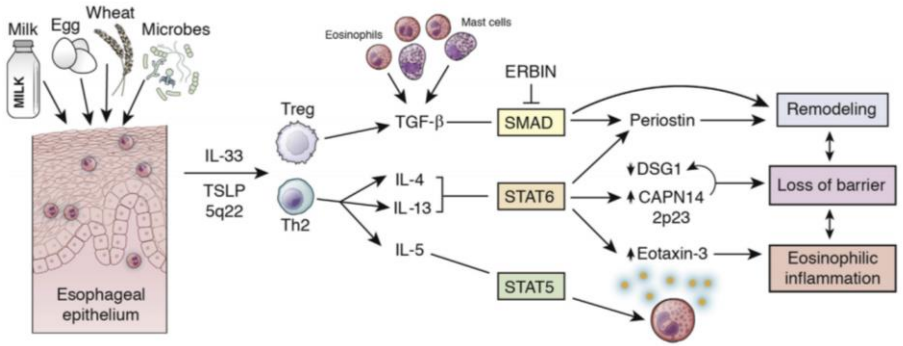


Hintergrund

- Atopische Vorgeschichte in 60% der Fälle (Ekzeme, Asthma, Rhinitis, NM-/Medikamtenallergien)
- Eosinophile normalerweise in Lamina propria der Mukosa vorhanden (Ausnahme Ösophagus)
- Spielen eine bedeutende Rolle in Wirtsabwehr (v.a. gegen Allergene/Parasiten)
- Vor allem degranulierte Eosinophile histologisch bei EGIDs zu erkennen



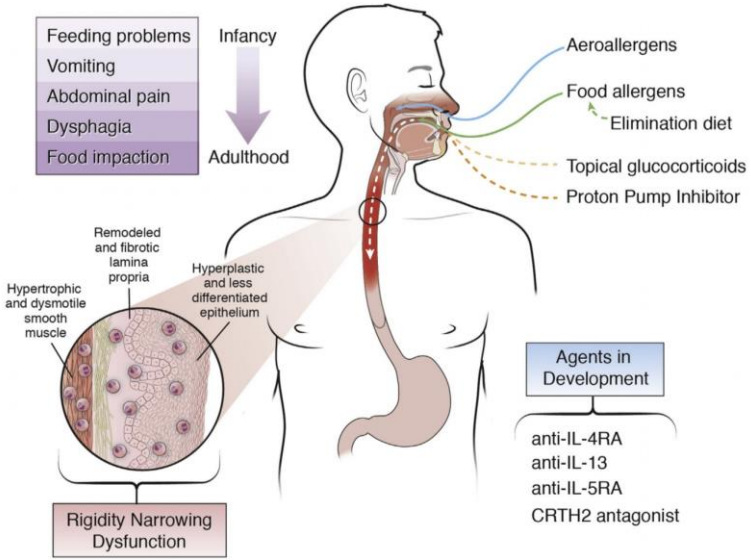
ROTHENBERG 2004



O'SHEA 2018

Eosinophile Ösophagitis

- Inzidenz 5/100.000/Jahr
- Prävalenz ca 30/100.000
- Mehrheitlich Jungen
- Häufig Atopie in der Vorgeschichte
- Aeroallergene oder NM-Allergien
  - Milch
  - Weizen
  - Soja
  - Eier



O'SHEA 2018

Symptomatik

- Wird spezifischer mit dem Alter
- Säuglinge/Kleinkinder
  - Sehr unspezifisch
  - Spucken
  - Ernährungsprobleme
- Kindesalter
  - Erbrechen
  - Bauchschmerzen
- Jugendliche
  - Dysphagie
  - Bolusimpaktation

Table 1. Presenting Symptoms among 103 Pediatric Patients with Eosinophilic Esophagitis.*

Symptom	Median Age (Interquartile Range)	No. (%)
Feeding disorder	2.0 (1.2–6.2)	14 (13.6)
Vomiting	8.1 (3.5–12.3)	27 (26.2)
Abdominal pain	12.0 (9.6–15.2)	27 (26.2)
Dysphagia	13.4 (10.0–16.7)	28 (27.2)
Food impaction	16.8 (13.7–19.6)	7 (6.8)

* Patients may have had more than one symptom, but only the most prominent symptom is included here. The median age varied significantly according to the primary symptom ($P<0.001$ by the Kruskal–Wallis test).

LEE 2004

Diagnostik

- Entsprechend den Empfehlungen der The International Gastrointestinal Eosinophil Researchers (TIGERS)
- Anamnese und Untersuchung mit Fokus auf Wachstum, Ernährung, Schluckakt
- Endoskopie
- Radiographie/Breischluck
- Histopathologie
- Allergische Evaluation
  - Prick Test
  - Serum IgE
  - RAST
  - Patch Test
- Genetik

Ort der Erkrankung	Differentialdiagnosen
Ösophagus	Refluxerkrankung
	Infektionen (Herpes, Candida)
	Achalasie
	Morbus Crohn
	Bindegewebserkrankung
	Hypereosinophilie Syndrom
	Medikamente
	Maligne Erkrankungen
	Zöliakie
Magen	Helicobacter pylori Infektion
	Chronisch Entzündliche Darmerkrankung
	Bindegewebserkrankung
	Hypereosinophilie Syndrom
Dünndarm/Kolon	Infektionen (Parasiten, Amöben, Pilze)
	Chronisch Entzündliche Darmerkrankungen
	Bindegewebserkrankungen
	Vaskulitis
	Maligne Erkrankungen
	Hypereosinophilie Syndrom

Genetik

Genetic risk loci	Genes encoded	Odds ratio for most associated SNP at each locus	Genetic mechanism	Pathogenic mechanism
2p23	*CAPN14*	1.98	Promoter variant leads to genotype-dependent expression of CAPN14, likely involving epigenetic mechanism	CAPN14 is a proteolytic enzyme specific to the esophagus that is induced by IL-13 and involved in epithelial homeostasis and repair
5q22	*TSLP* *WDR36*	0.74	Multiple risk alleles associated with genotype-dependent expression of TSLP	TSLP induces Th2 cell development and activates eosinophils and basophils
11q13	*LRRC32* *EMSY*	2.49	Not yet described	LRRC32 is a TGF-beta binding protein EMSY is involved in transcriptional regulation
12q13	*STAT6*	1.5	Not yet described	STAT6 is a downstream signaling mediator of IL-4Rα and important for Th2 development
19q13	*ANKRD27* *PDCD5* *RGS9BP*	1.6	Not yet described	ANKRD27 inhibits the SNARE complex PDCD5 is involved in apoptotic pathways RGS9BP is not expressed in the esophagus or by immune cells

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Assoziierte Erkrankungen

Mendelian disease associated with EoE	Inheritance	Genetic mutation	Plausible etiologic mechanism
Hyper-IgE syndrome	AD	Deleterious mutations in signal transducer and activator of transcription 3 (*STAT3*)	Dysregulated response to IL-6 and possibly IL-5
Hyper-IgE syndrome	AR	Loss-of-function mutations in dedicator of cytokinesis 8 (DOCK8)	Loss of T cell homeostasis; lack of durable secondary antibody response against specific antigens
Ehlers-Danlos syndrome, hypermobility type	AD	Unknown – other subtypes of Ehlers-Danlos syndrome are caused by mutations in collagen genes	Disrupted joint and skin development; increased activity of transforming growth factor beta (TGF-β) due to altered binding by extracellular matrix
ERBIN deficiency	AD	Loss-of-function mutation in ERBB2-interacting protein (ERBIN)	Increased TGF-β pathway activation in T cells with increased Th2 responses
Loeys-Dietz syndrome (LDS)	AR	Mutations in TGF-β receptors 1 and 2 (*TGFBR1* and *TGFBR2*, respectively)	Enhanced TGF-β signaling
Netherton syndrome	AR	Loss-of-function mutations in skin protease inhibitor, kazal type 5 (*SPINK5*)	Unrestricted protease activity of kallikrein 5 and 7 (KLK5, KLK7)
PTEN hamartoma tumor syndrome (PHTS)	AD	Mutations in phosphatase and tensin homolog (*PTEN*)	Inhibited regulation of the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) signaling pathway
Severe atopy syndrome associated with metabolic wasting (SAM) syndrome	AR	Homozygous mutations in desmoglein 1 (*DSG1*) or desmoplankin (*DSP*)	Disrupted epithelial barrier

AD, autosomal dominant; AR, autosomal recessive; EoE, eosinophilic esophagitis.

O'SHEA 2018

Symptome

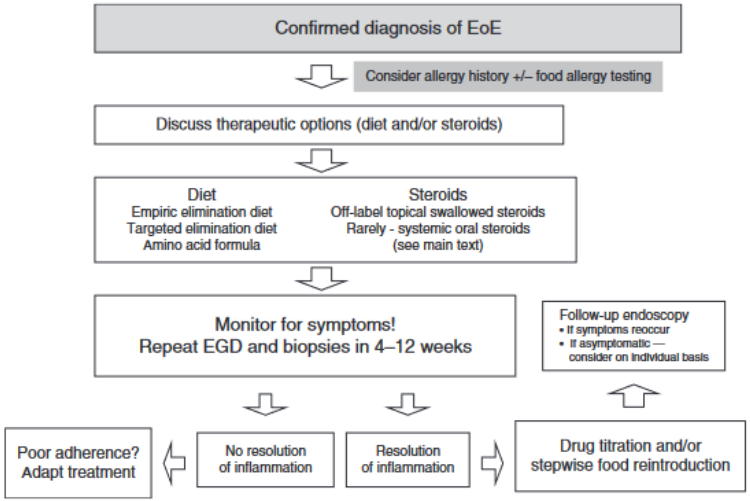
– Unspezifisch gastrointestinal:
  – Bauchschmerzen
  – Völlegefühl
  – Erbrechen
  – Durchfall
  – Malabsorption
– Wachstumsretardierung
– Verzögerte Pubertät

Mucosal Pattern	Muscular Pattern	Serosal Pattern
• Abdominal pain, • Nausea, • Vomiting, • Diarrhea, • Rectal Bleeding, • Anemia, • Protein-losing enteropathy, • Malabsorption, • Weight lose	• Bowel thickening, • Intestinal obstruction	• Eosinophilic ascites

LICARDI 2020 NACH KLEIN 1970

Therapie

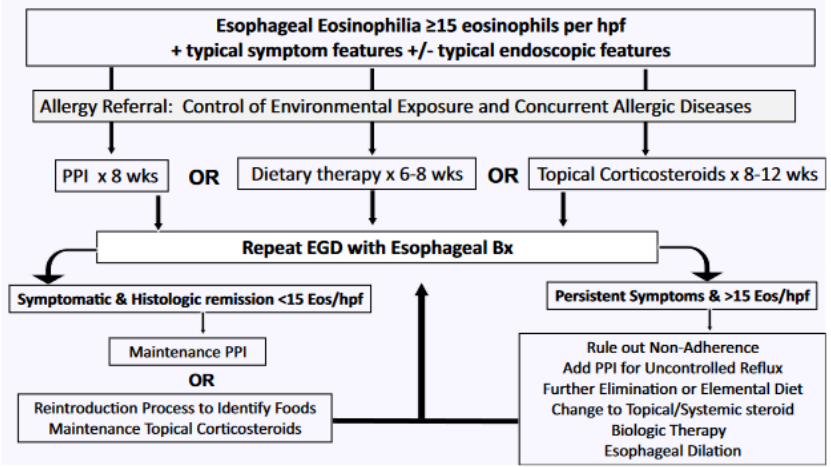
– Therapie nach Prinzipien
  i. Klinische und histologische Remission
  ii. Remission erhalten
  iii. Vermeiden iatrogenen Schadens
– Eliminationsdiäten
  – EEN mit AAF
  – Empirische Eliminationsdiät (EED)
  – Gezielte Eliminationsdiät (TED)



PAPADOPOULOU 2013

Weitere Optionen

- Protonen-Pumpen-Inhibitoren
- Lokale Steroide
- Systemische Steroide
- Ggf Thiopurine/Anti-TNF bei refraktärem Verlauf (Datenbasis schlecht!)
- Neue Medikamente erfolgsversprechend

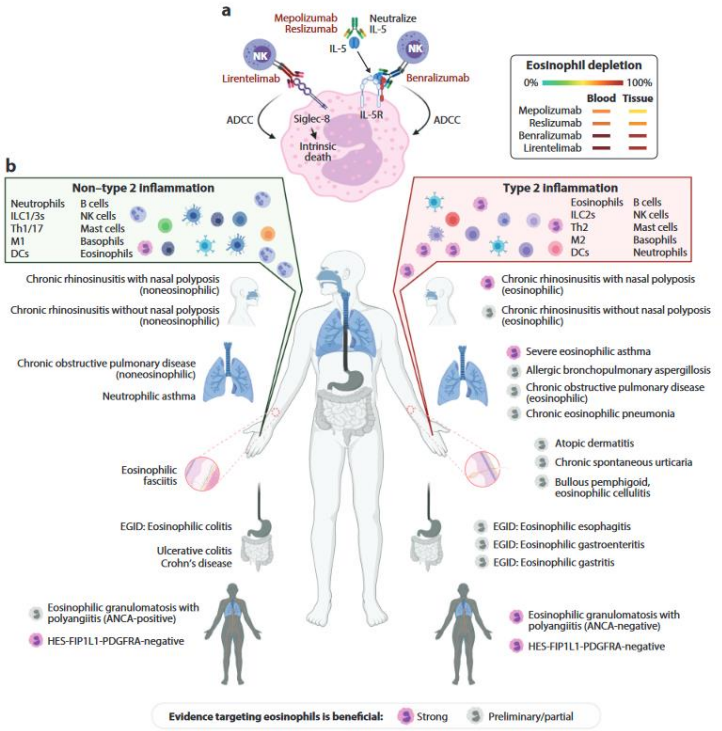


GONSALVES 2020

Neue Medikamente

Therapeutic parameters	Mepolizumab	Reslizumab	Benralizumab	Lirentelimab (AK002)
Target	IL-5	IL-5	IL-5Rα	Siglec-8
Antibody (parent)	Humanized IgG1κ (murine 2B6)	Humanized IgG4κ (rat 39D10)	Humanized nonfucosylated IgG1κ	Humanized nonfucosylated IgG1κ
Indicated for severe eosinophilic asthma	Yes (100 mg SC, four doses weekly)	Yes (3 mg/kg IV, four doses weekly)	Yes (30 mg SC, three doses weekly, then every eight weeks)	No
Indicated for EGPA/HES	Yes	No[a]	No[a]	No
Other indications being pursued	HES, EoE, CRSwNP	CRSwNP	HES, EGID, CRSwNP	EGID
Pediatric indication	6 years and above	No	12 years and above	No
Eosinophil reduction (blood/tissue)	Yes (↓)	Yes (↓↓)	Near complete (↓↓↓)	Near complete (↓↓↓)
Effect on other cells	No	No	Reduction of basophils	Inhibition of mast cells

JACOBSON, 2021 AHEAD OF PRINT



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VIELEN DANK FÜR IHRE AUFMERKSAMKEIT