Allergic Rhinitis : Current Hot topics

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Department of Otorhinolaryngology
Dankook University College of Medicine

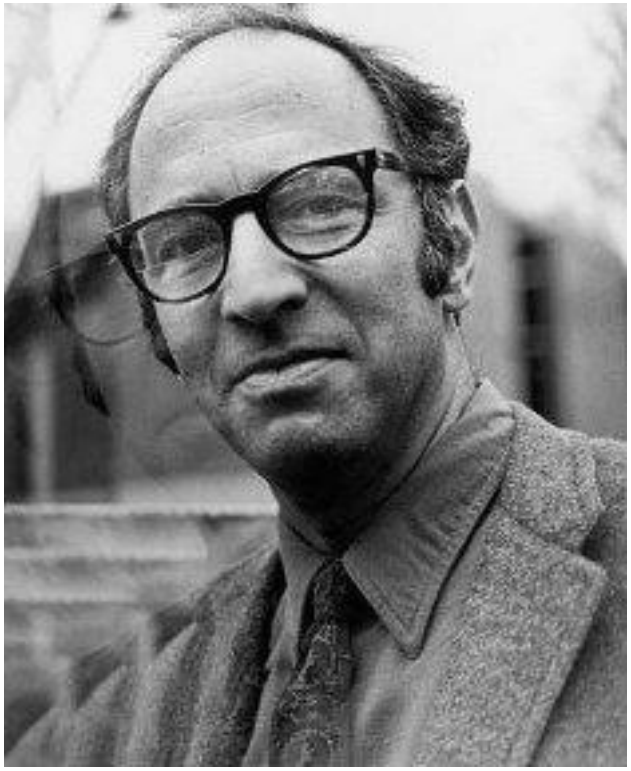
1. **New Innovative Treatment**

2. What internists should know

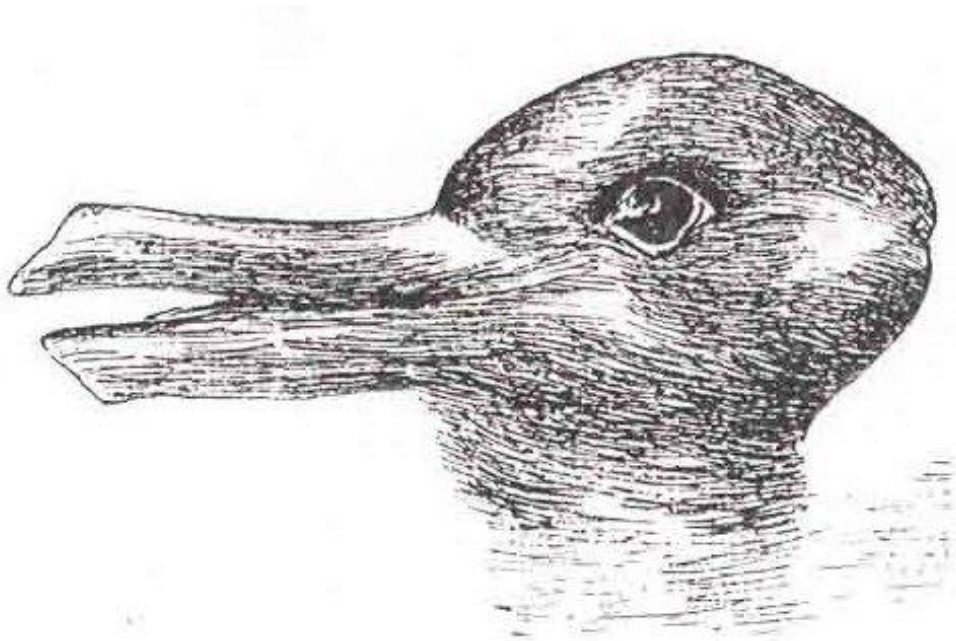
    Anatomy, physiology, and surgical Tx

- Innovative drug?

Paradigm Shift



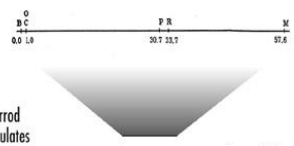
Thomas Kuhn



Thomas Kuhn, The Structure of Scientific Revolutions (3rd edn., p. 114)

10년내에 allergic rhinitis
치료가 주사 한번으로
해결될 것이다.

Human genome project



Mendel discovers laws of genetics
1865

Rediscovery of Mendel's work
1900

Garrod formulates the concept of human inborn errors of metabolism
1905

Sturtevant makes the first linear map of genes
1913

Avery, McLeod, and McCarty demonstrate DNA is the hereditary material
1944

Watson and Crick describe the double helical structure of DNA
1953

Nirenberg, Khorana and Holley determine the genetic code
1966

Cohen and Boyer develop recombinant DNA technology
1972

Issuing of Belmont Report on the use of human subjects in research
1974

Sanger and Maxan & Gilbert develop DNA sequencing methods
1977

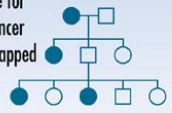
GenBank database established
1982

1990

Human Genome Project (HGP) launched in the U.S.

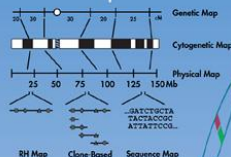
Ethical, Legal, and Social Implications (ELSI) programs founded at NIH and DOE

First gene for breast cancer (BRCA1) mapped



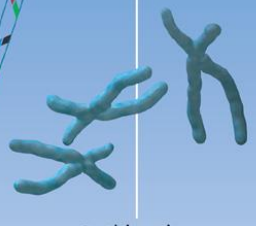
1991

First U.S. Genome Centers established



1992

Second-generation human genetic map developed



Rapid data release guidelines established by NIH and DOE

1993

New five-year plan for the HGP in the U.S. published

Sanger Centre founded (later renamed Wellcome Trust Sanger Institute)

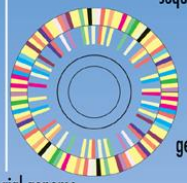
The Wellcome Trust

1994

HGP's human genetic mapping goal achieved

1995

HGP's human physical mapping goal achieved



First bacterial genome (*H. influenzae*) sequenced

U.S. Equal Employment Opportunity Commission issues policy on genetic discrimination in the workplace

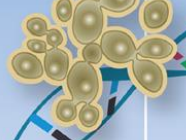
1996

First human gene map established

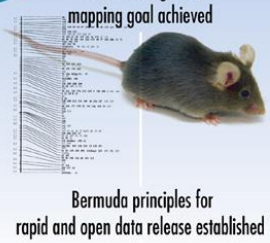
Pilot projects for human genome sequencing begin in U.S.

First archael genome sequenced

Yeast (*S. cerevisiae*) genome sequenced



HGP's mouse genetic mapping goal achieved



Bermuda principles for rapid and open data release established

1997

DOE forms Joint Genome Institute

JGI
DOE JOINT GENOME INSTITUTE
US DEPARTMENT OF ENERGY
OFFICE OF SCIENCE

NCHGR becomes NHGRI

National Human Genome Research Institute

E. coli genome sequenced

Genoscope (French National Genome Sequencing Center) founded

1

Incorpo genes into h

New fiv the HGP in

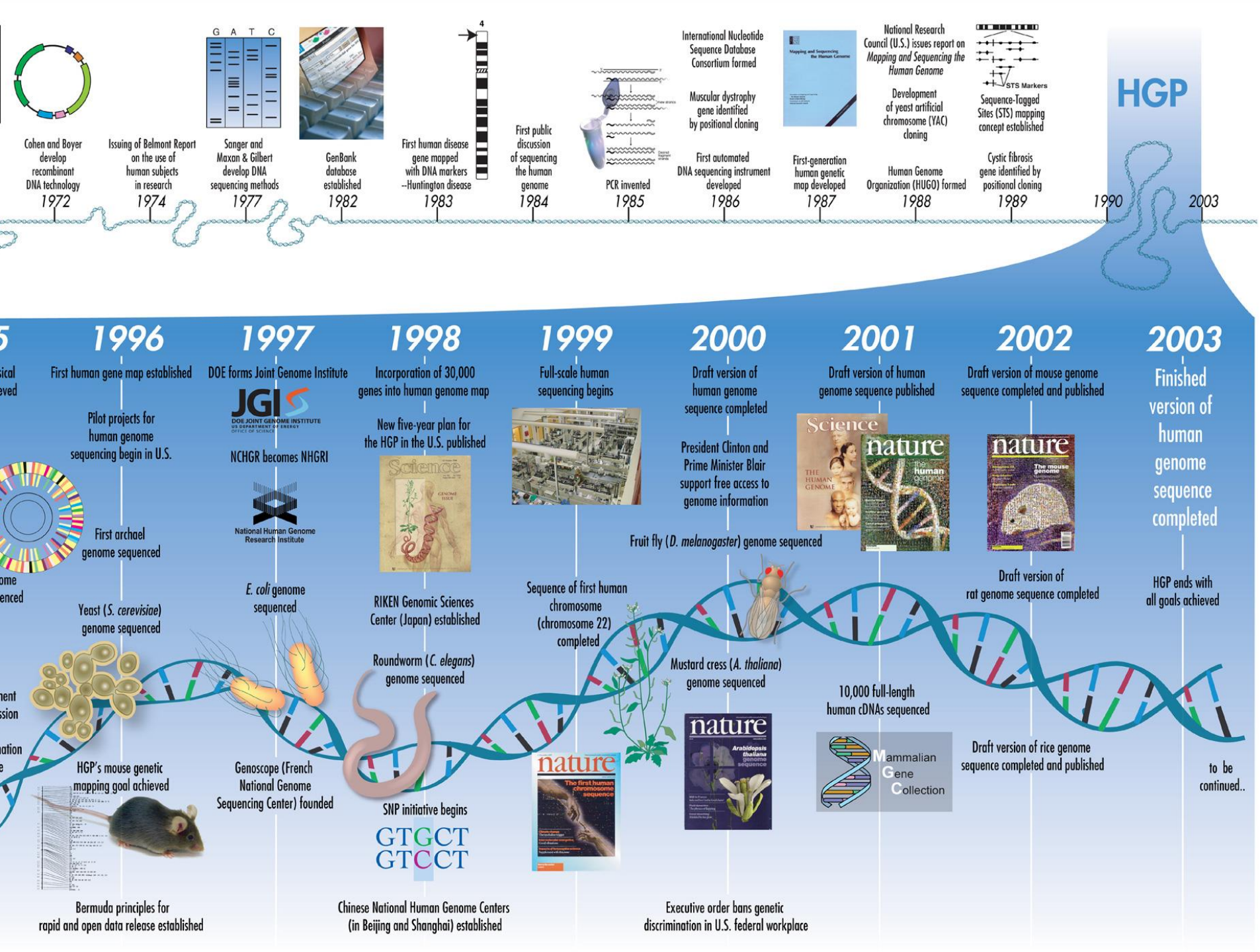
RIKEN G Center (J

Roundwo genor

SNP in

GT GT

Chinese National (in Beijing and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1972
Issuing of Belmont Report on the use of human subjects in research
1974
G A T C
Sanger and Maxan & Gilbert develop DNA sequencing methods
1977
GenBank database established
1982
First human disease gene mapped with DNA markers --Huntington disease
1983
First public discussion of sequencing the human genome
1984
PCR invented
1985
International Nucleotide Sequence Database Consortium formed
Muscular dystrophy gene identified by positional cloning
First automated DNA sequencing instrument developed
1986
Mapping and Sequencing the Human Genome
First-generation human genetic map developed
1987
National Research Council (U.S.) issues report on Mapping and Sequencing the Human Genome
Development of yeast artificial chromosome (YAC) cloning
Human Genome Organization (HUGO) formed
1988
STS Markers
Sequence-Tagged Sites (STS) mapping concept established
Cystic fibrosis gene identified by positional cloning
1989
1990
2003
HGP
1996
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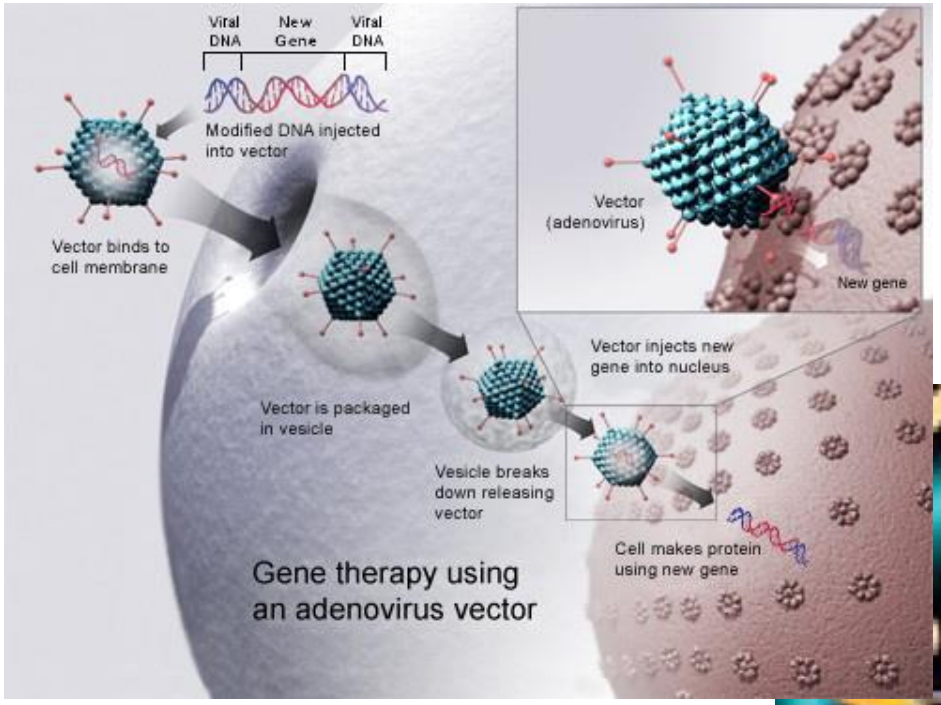
1998
Incorporation of 30,000 genes into human genome map
New five-year plan for the HGP in the U.S. published
Science
GENOME ISSUE
RIKEN Genomic Sciences Center (Japan) established
Roundworm (C. elegans) genome sequenced
SNP initiative begins
GTGCT
GTCCT
Chinese National Human Genome Centers (in Beijing and Shanghai) established
1999
Full-scale human sequencing begins
Sequence of first human chromosome (chromosome 22) completed
nature
The first human chromosome sequence
2000
Draft version of human genome sequence completed
President Clinton and Prime Minister Blair support free access to genome information
Fruit fly (D. melanogaster) genome sequenced
Mustard cress (A. thaliana) genome sequenced
nature
Arabidopsis thaliana genome sequence
Executive order bans genetic discrimination in U.S. federal workplace
2001
Draft version of human genome sequence published
Science
THE HUMAN GENOME
nature
the human genome
10,000 full-length human cDNAs sequenced
Mammalian Gene Collection
2002
Draft version of mouse genome sequence completed and published
nature
The mouse genome
Draft version of rat genome sequence completed
Draft version of rice genome sequence completed and published
2003
Finished version of human genome sequence completed
HGP ends with all goals achieved
to be continued..

Gene therapy



Personalized medicine

Endotype

Industrial Revolution

From Industry 1.0 to Industry 4.0

1.0 | **1784** | based on mechanical production equipment driven by water and steam power

2.0 | **1870** | based on mass production enabled by the division of labor and the use of electrical energy

3.0 | **1969** | based on the use of electronics and IT to further automate production

4.0 | **tomorrow** | based on the use of cyber-physical systems

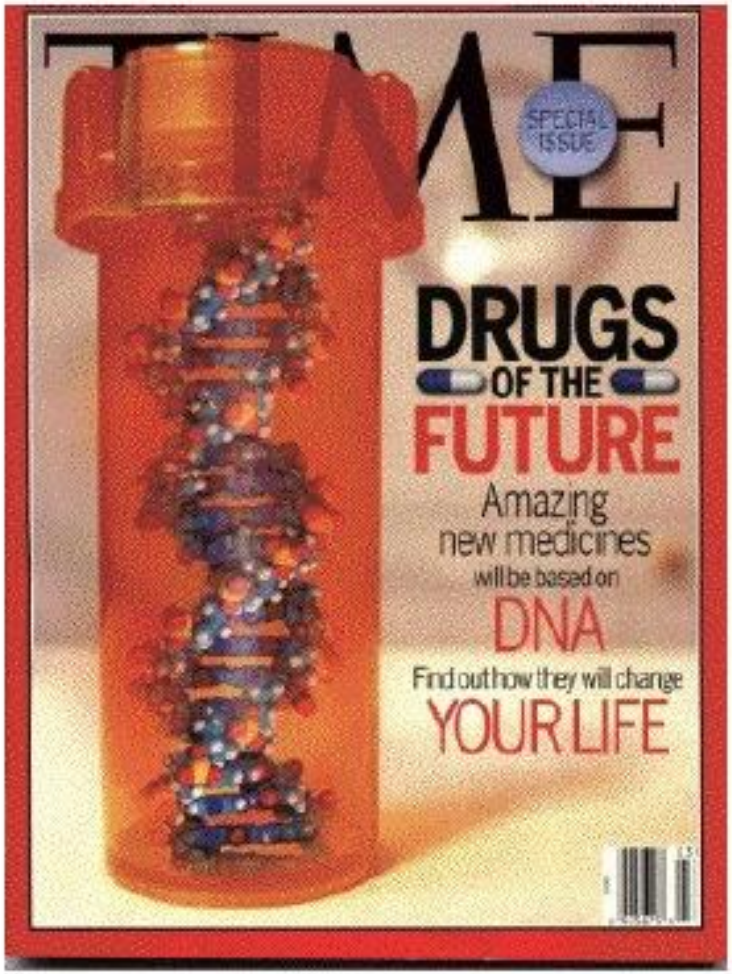
Expert Systems – Today: Medicine

One example domain, medicine, has expert systems whose tasks include:

- arrhythmia recognition from electrocardiograms
- coronary heart disease risk group detection
- monitoring the prescription of restricted use antibiotics
- early melanoma diagnosis
- gene expression data analysis of human lymphoma
- breast cancer diagnosis

Big data | Artificial Intelligence | Cloud | Informatics | Robotics

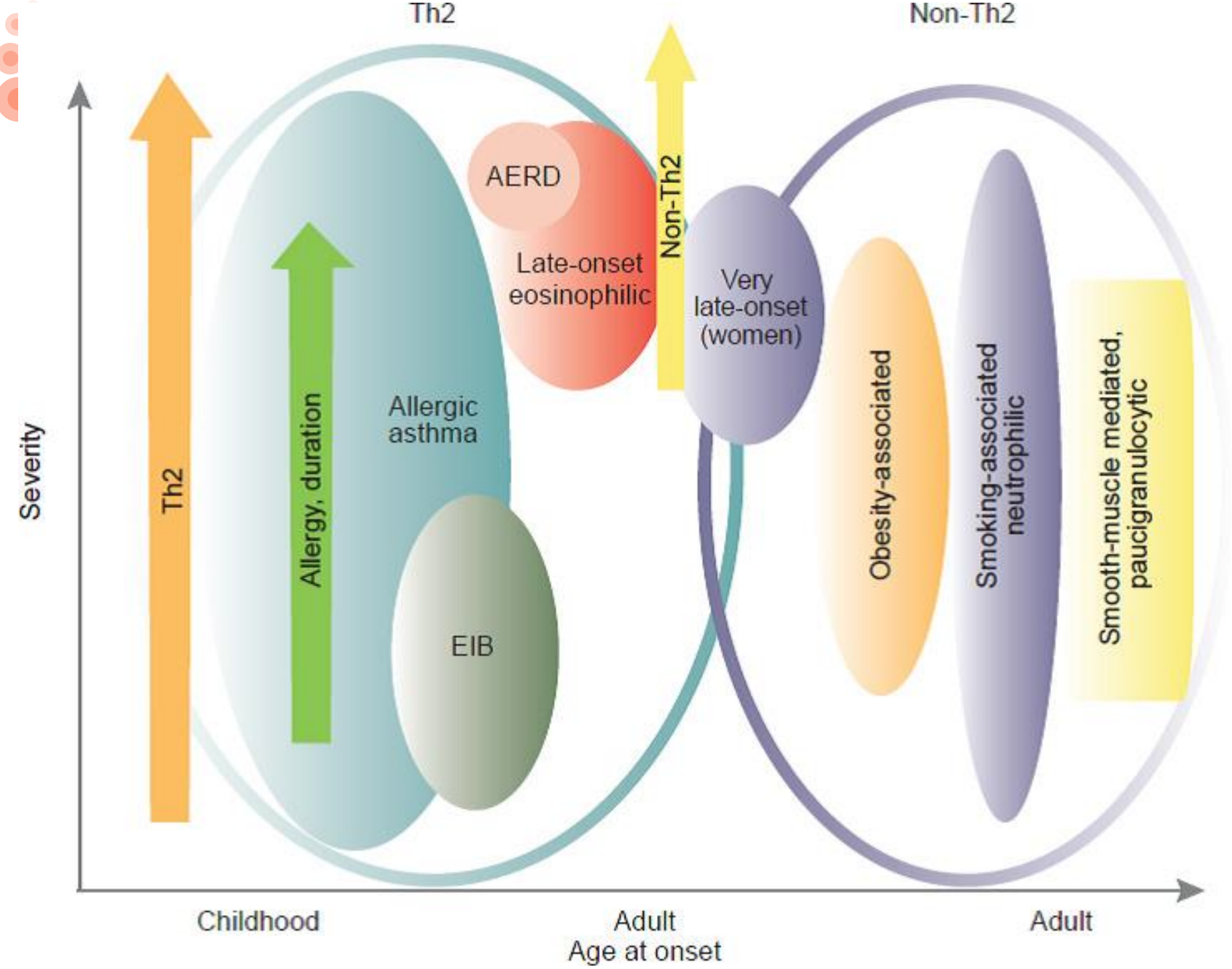
Personalized Medicine



The ability to offer

- **The Right Drug**
- **To The Right Patient**
- **For The Right Disease**
- **At The Right Time**
- **With The Right Dosage**

Genetic and metabolic data will allow drugs to be tailored to patient subgroups


Th2
Non-Th2
Severity
Th2
Allergy, duration
Allergic asthma
EIB
AERD
Late-onset eosinophilic
Non-Th2
Very late-onset (women)
Obesity-associated
Smoking-associated neutrophilic
Smooth-muscle mediated, paucigranulocytic
Childhood
Adult
Adult
Age at onset

Concept of Endotype

- Phenotype (표현형)
- Endotype (내재형)

Observable characteristic or trait of a disease

Subtype of a condition, which is defined by a distinct functional or pathobiological mechanism

Tx of AR 20YA?

Rynacrom 10개
처방해
Packing 10장 했어?

알레르기비염에서 수술을 뭐하러 해? 약물치료만으로 충분한데.....

뭣이 중헌디 워시 중허냐고?

면역치료가 좋아!!!

AR Tx : 20 years ago

Antihistamine	Ebastel
Nasal spray	Beclomethasone
	Rynacrom
Turbinoplasty	Laser vaporization
ImmunoTx	Not popular, SCIT

1997년

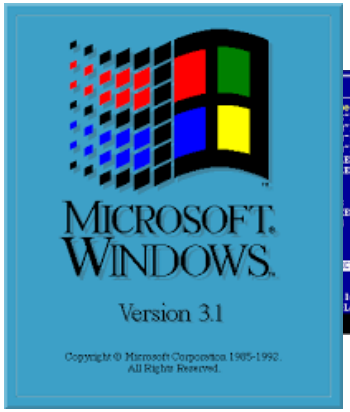
- 10년이면 강산이 변한다.

- 桑田碧海

1990

1997

2016

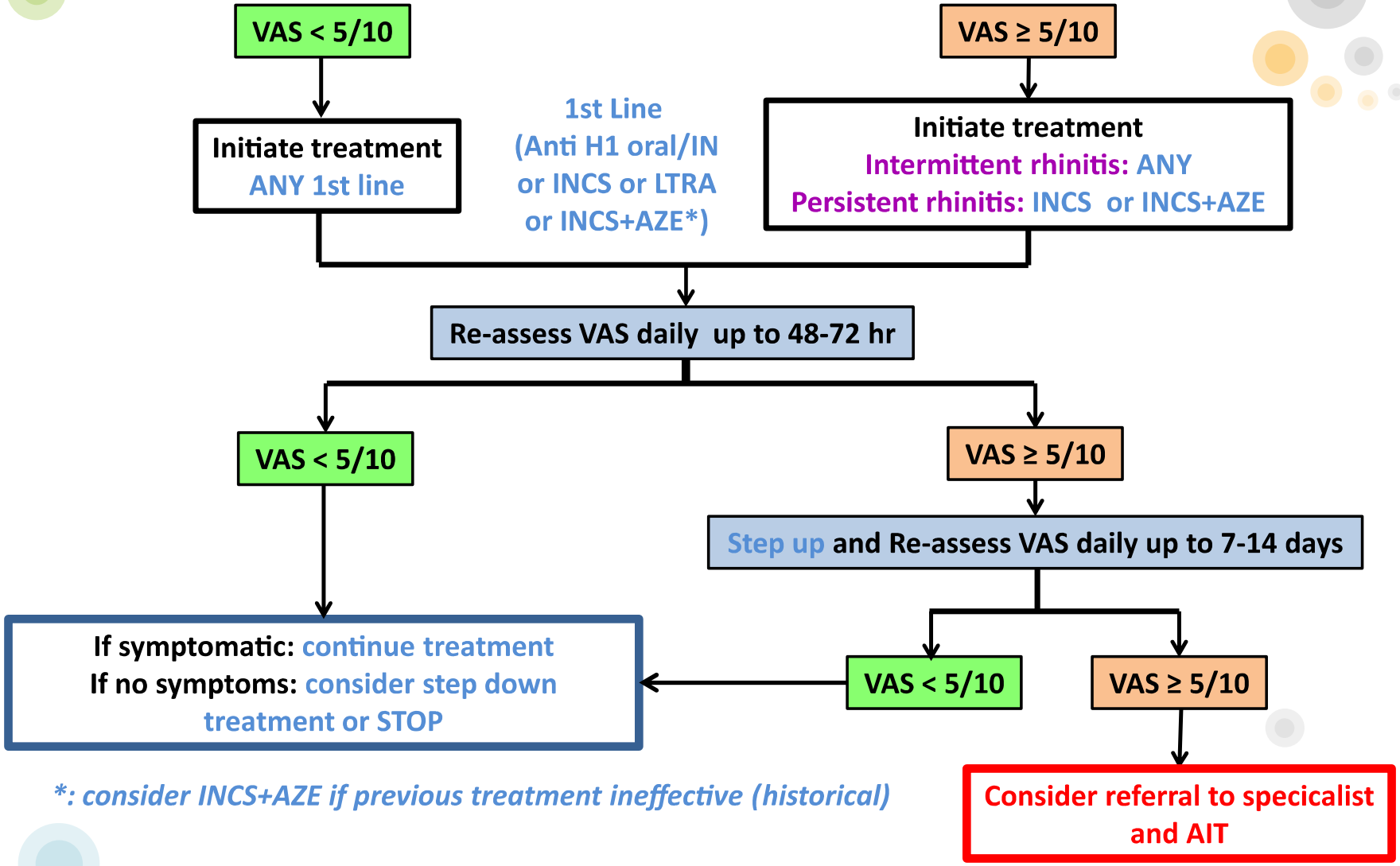


AR Tx: Now

Antihistamines	Fexofenadine
	Bepostatine
LTRA	Montelukast
Nasal spray	Ciclesonide
	Fluticasone
	Mometasone
Turbinoplasty:	Microdebrider
	RF ablation
ImmunoTx:	SLIT

2016년

Assessment of control in untreated symptomatic patient



**: consider INCS+AZE if previous treatment ineffective (historical)*

FIG 1. Step-up algorithm in untreated patients using the VAS (adolescents and adults). The proposed algorithm considers the treatment steps and patient preference and VAS levels in ratio. If ocular symptoms remain, add intraocular treatment.

1. Combination of Drugs

2. Biologics

3. Modification of Immunotherapy

4. Modification of gut microbiome

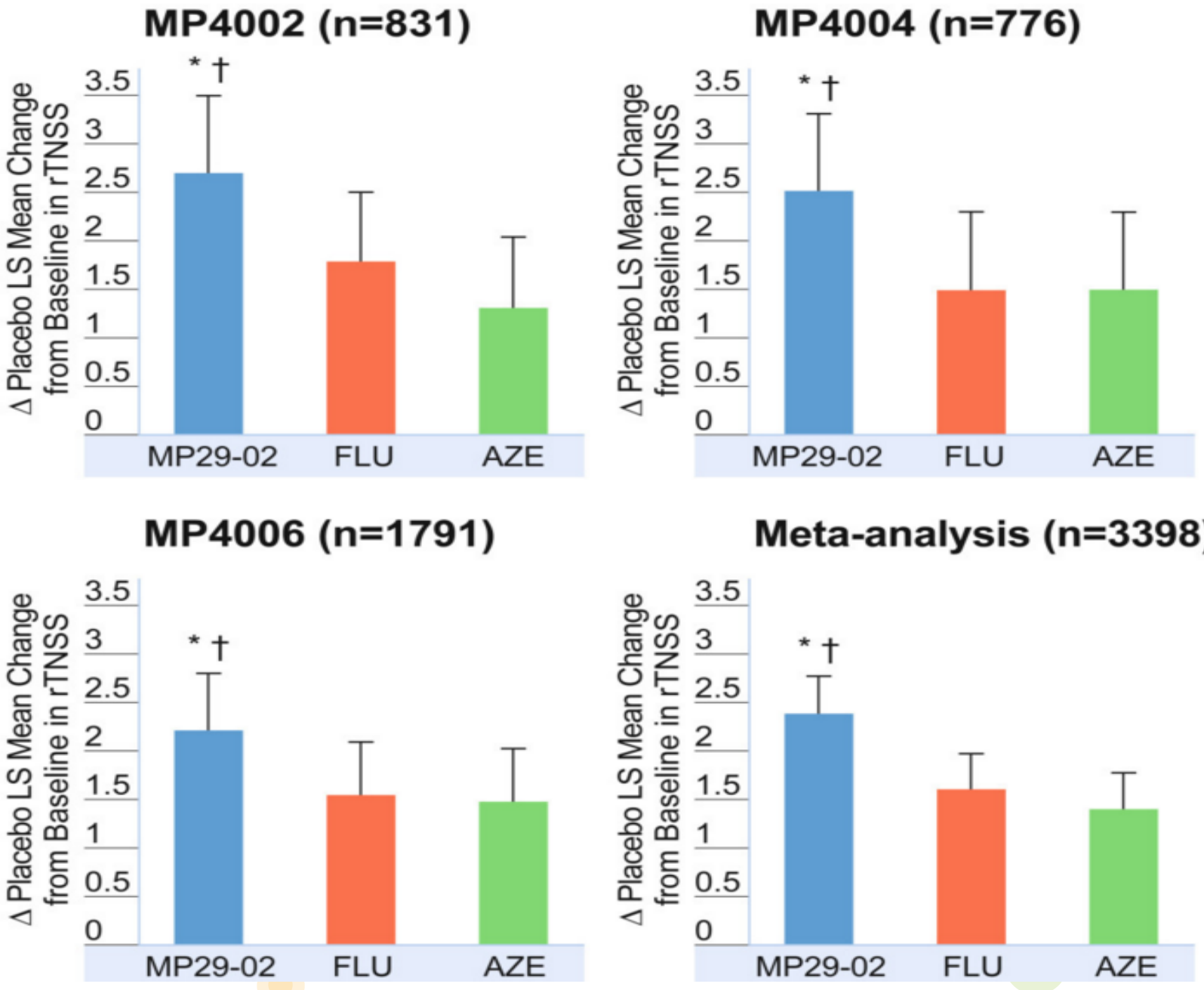
1. Combination of Drugs

Intranasal Spray

- MP29-02
  - A new intranasal formulation
  - Azelastine hydrochloride (AZE) + fluticasone propionate (FP)
  - Approved by the FDA in 2012 and European Medicines Agency in 2013

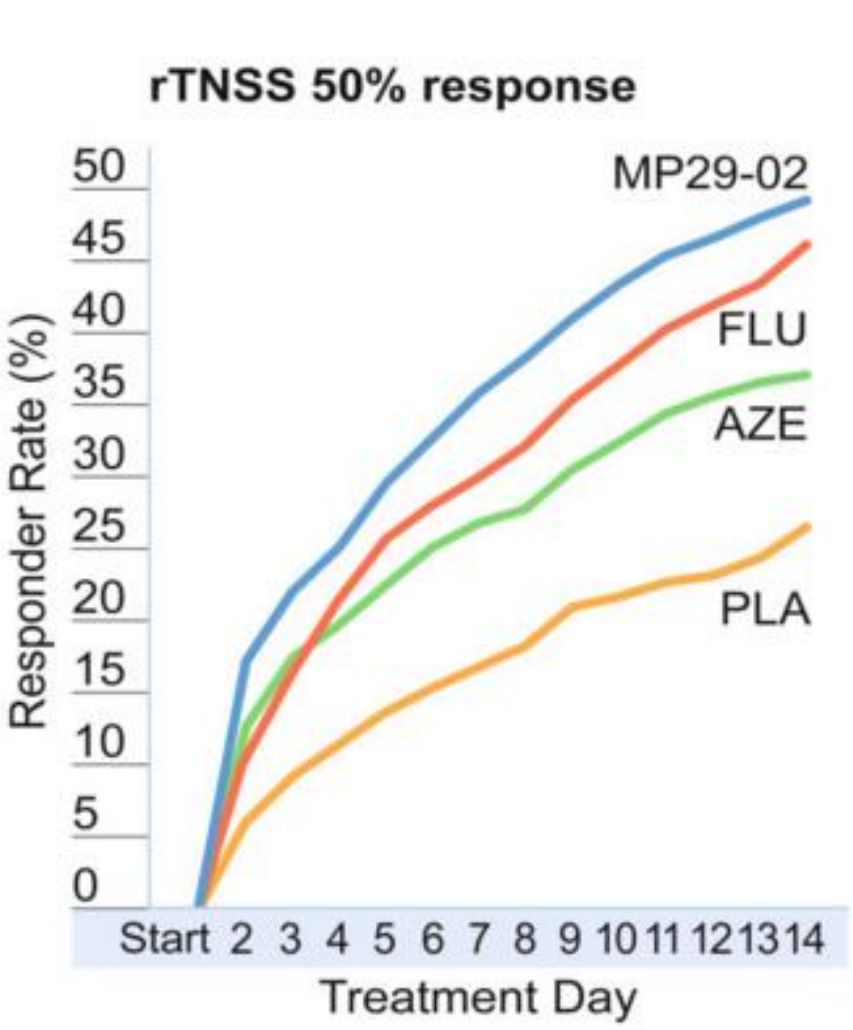
    Price et al., 2013
  - Acts on both the early and late allergic responses
    - Including also an inhibitory effect on mast-cell degranulation and owns the potential of covering all the symptoms of AR

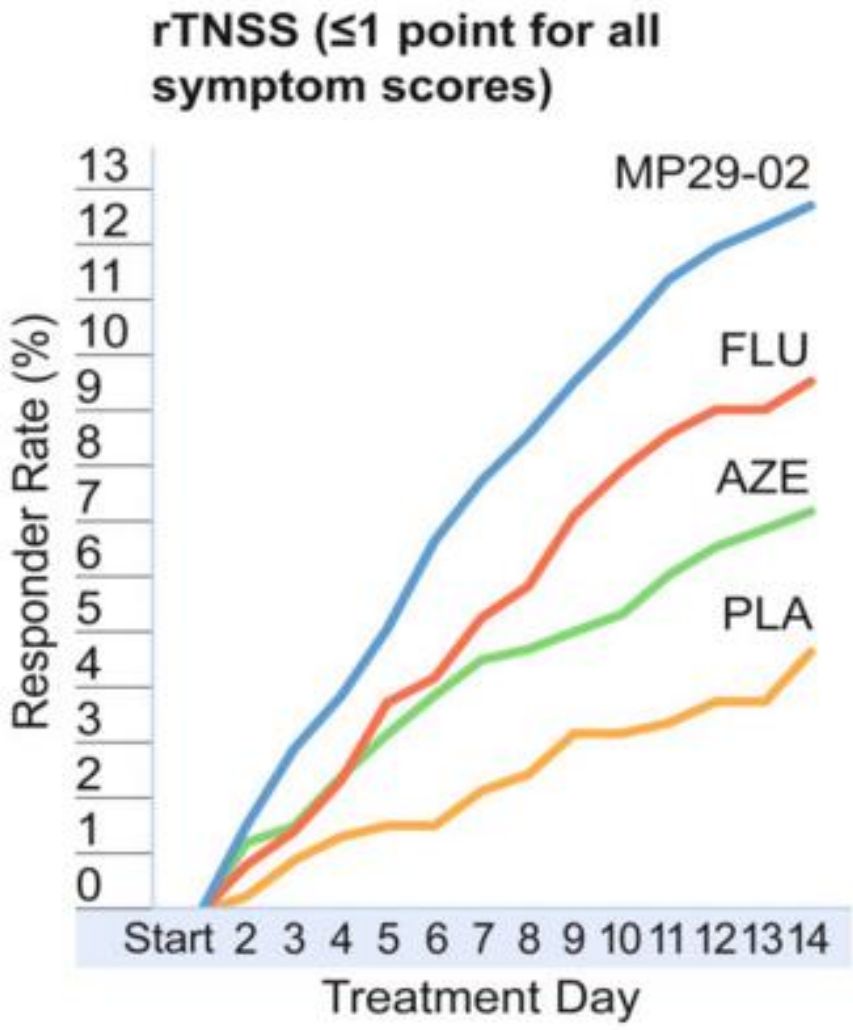
Bousquet et al., 2015



Carr et al., 2012

MP29-02





Carr et al., 2012

Intranasal formulation

- CKD-342
  - mometasone furoate + levocabastine hydrochloride
  - phase III clinical trial (NCT02498509) for the treatment of PAR
  - 종근당 임상시험

Leukotriene modifier

- Montelukast
  - Effects were inferior to H1-antihistamines and INCS

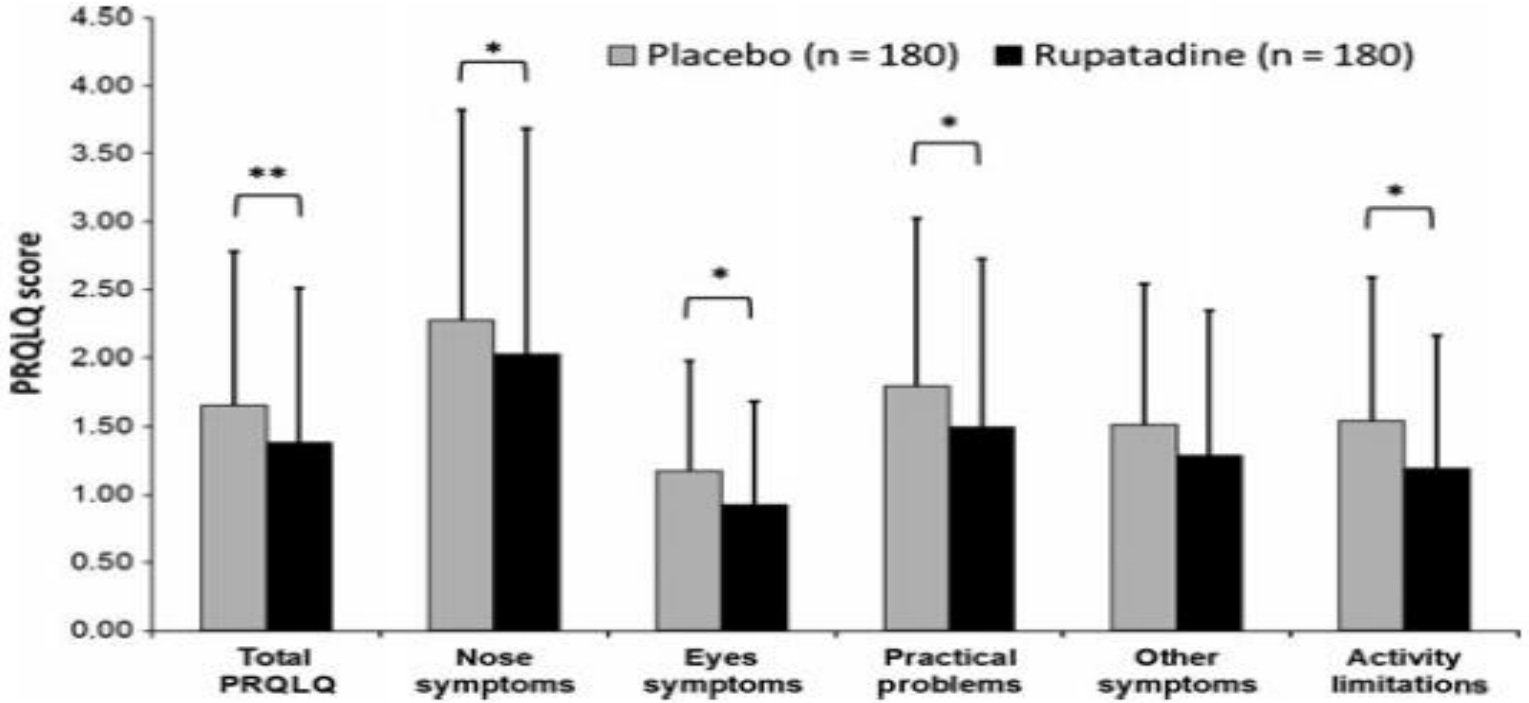
    Patel et al., 2005
  - A combination with a non-sedating second generation H1-antihistamine
    - limited results

    Ciebiada et al., 2005
  - **HCP-1102**
    - montelukast + levocetirizine
    - phase III clinical trial (NCT02552667)
    - 한미약품

Antihistamines

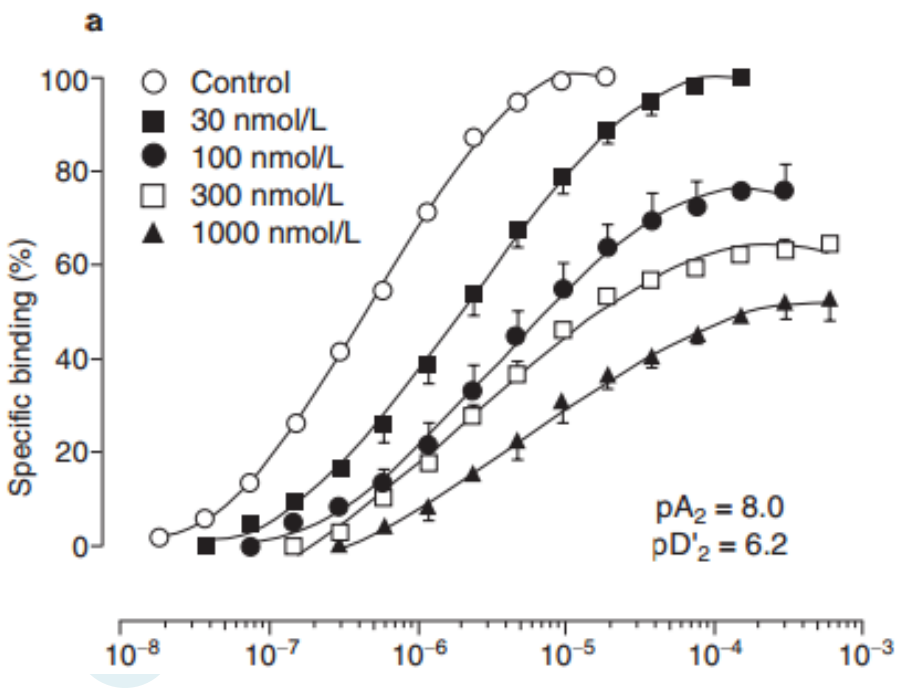
- Rupatadine
  - 2nd generation
  - efficacy and safety of rupatadine oral solution in children 6–11 years old with PAR

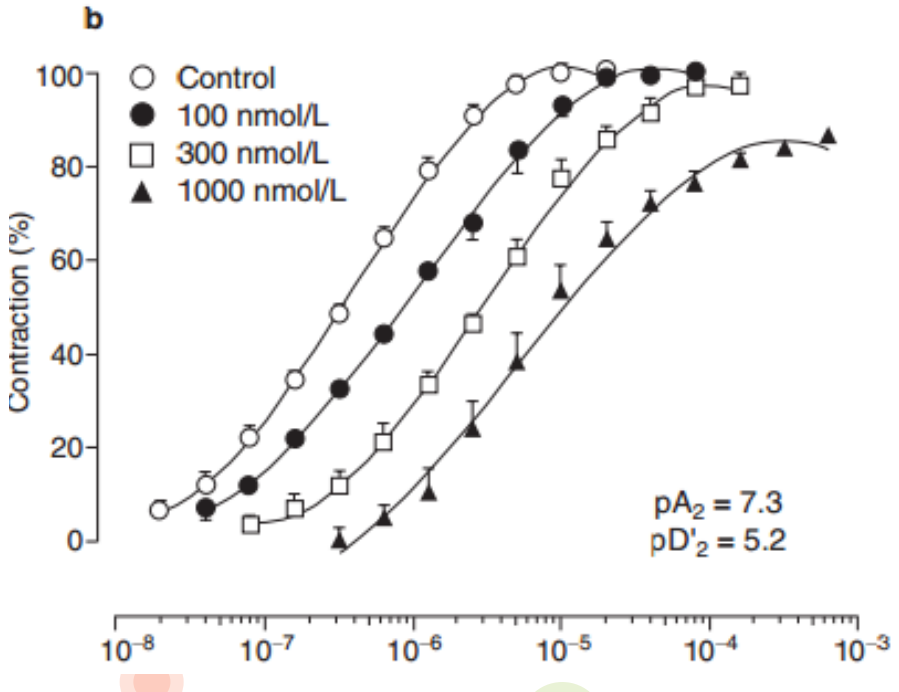
Potter et al., 2013



Antihistamines

- Bilastine
  - new nonsedating H1 receptor inverse agonist, belongs to the piperidine class





Corcóstegui et al., 2005

H_3 receptor antagonists

- Histamine receptors H_3
  - Recently demonstrated in human nasal tissue in close proximity of H_1 receptors
  - Modulating vascular contractile responses
  - Lead to an increase in norepinephrine
  - Might have an advantageous decongestant effect in patients with AR
  - Potential superior safety and efficacy profile to the currently available oral decongestants

Simons et al., 2004

H_3 receptor antagonists

- PF-03654746
  - A highly selectively potent H3 receptor antagonist
  - Shown to reduce allergeninduced nasal symptoms

Stokes et al., 2012

  - **PF-03654764 + fexofenadine** failed to provide superior relief of AR-associated nasal symptoms compared to pseudoephedrine + pseudoephedrine

North et al., 2014

- JNJ-39220675
  - Another new selective H3 receptor antagonist
  - Showed a limited potential anti-inflammatory effect

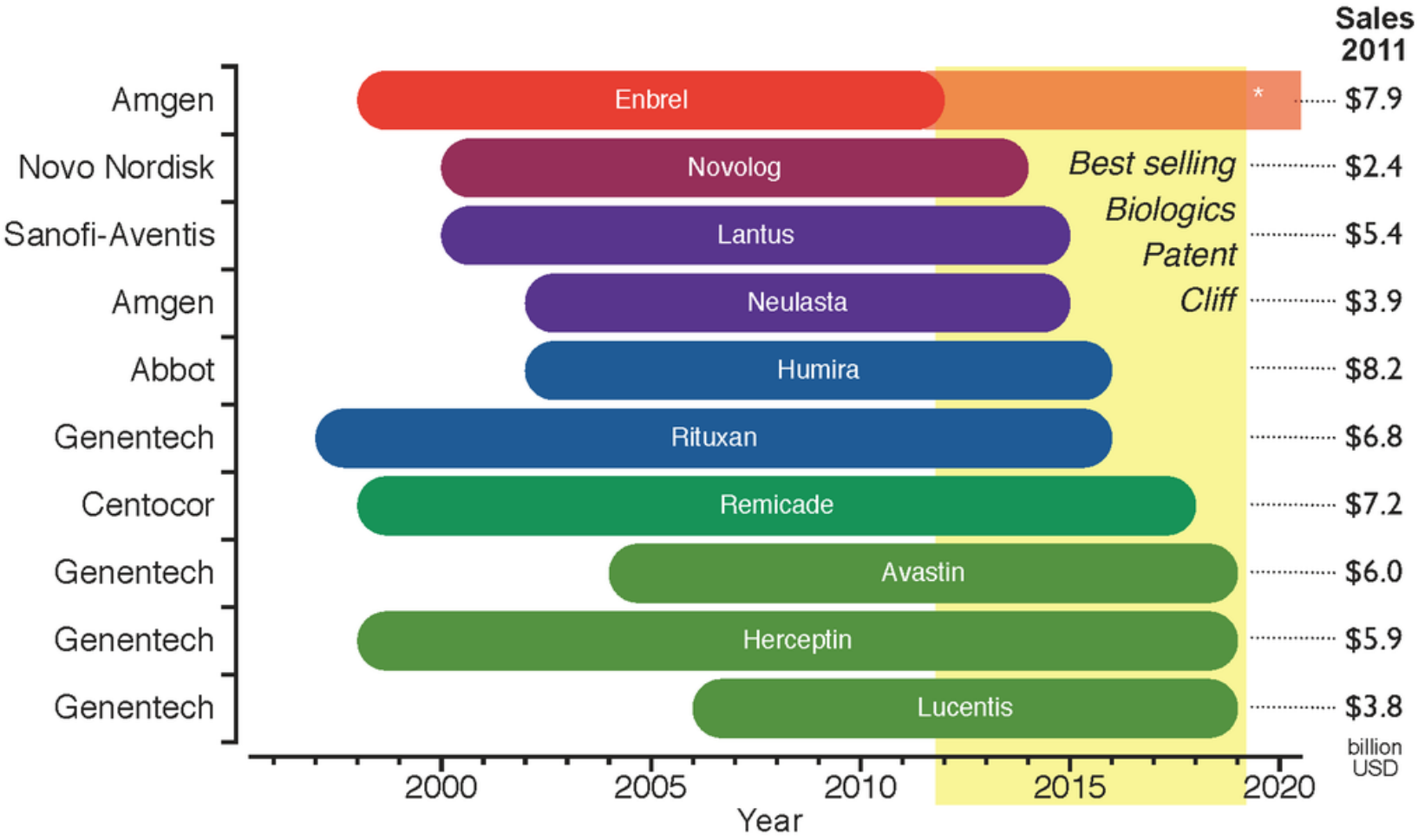
Barchuk et al., 2013

H_3 receptor antagonists

- Intranasal GSK1004723 and oral GSK835726
  - H1/H3 receptor antagonists
  - Phase II safety and efficacy studies
  - Did not show superiority from H1 antagonism in reducing AR symptom score or nasal blockage

2. Biologics

The era of biologics & biosimilar

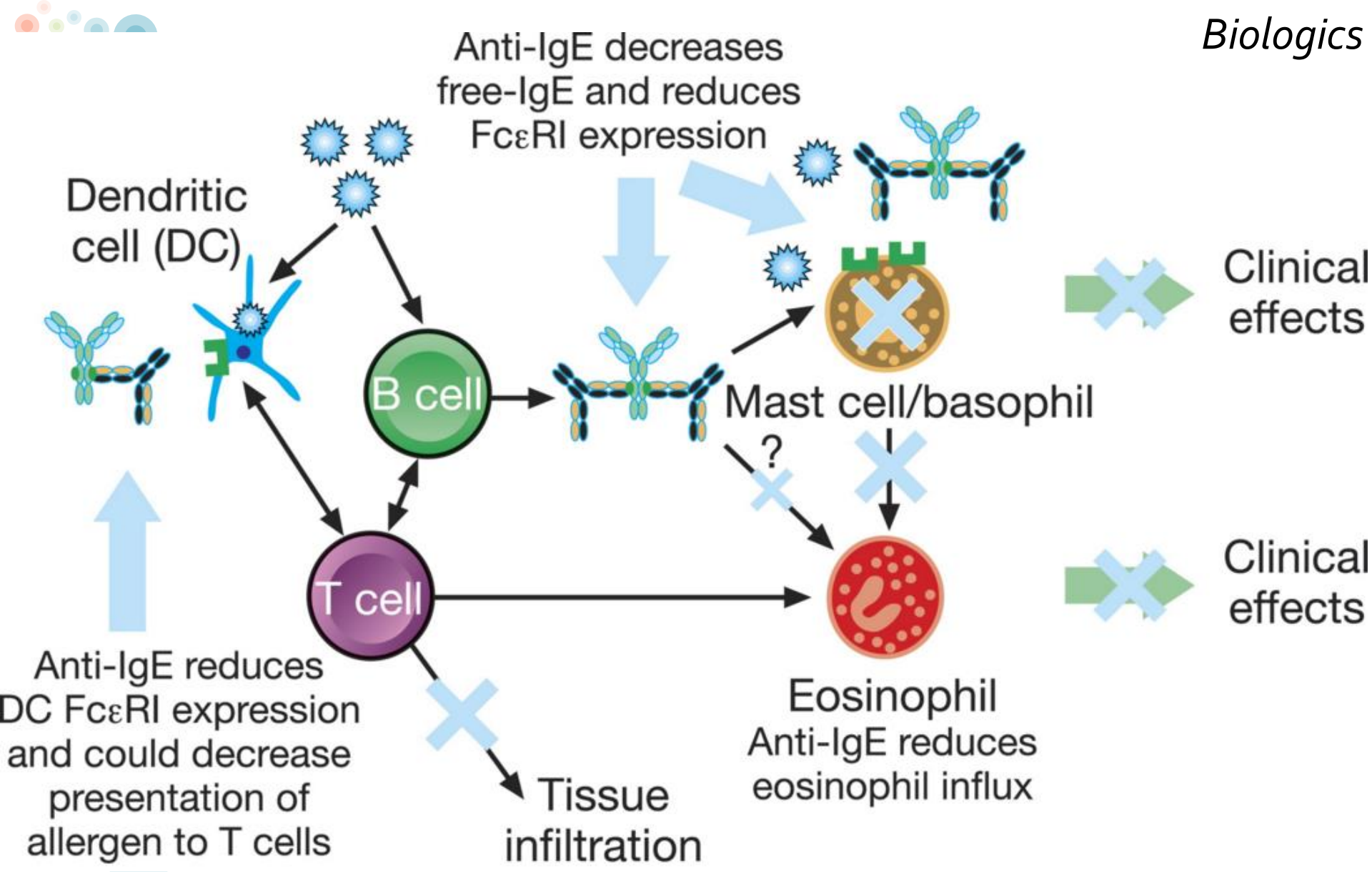


Biologics

- New therapeutic agents directed against a specific target, cytokine or receptor

- Omalizumab
  - the first humanized **anti-IgE mAb**
  - acts specifically binding serum free IgE
  - interrupting the allergic cascade
  - preventing binding of IgE with its high-affinity FceRI receptors on mast cells, basophils, antigen presenting cells and other inflammatory cells.

Stephen et al., 2005



Stephen et al., 2005

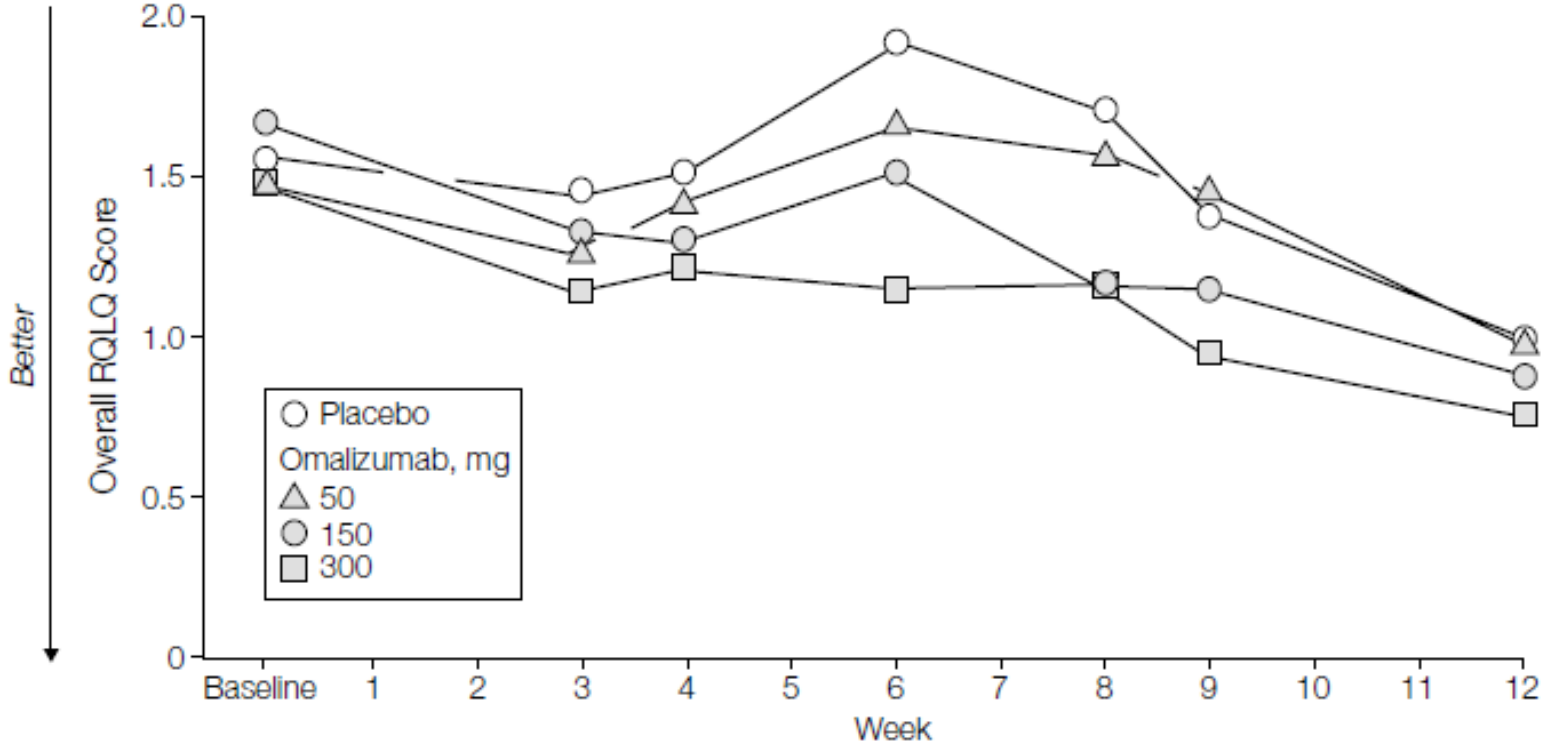
Omalizumab

- Several randomized controlled trials evaluated the effectiveness of omalizumab alone in both seasonal AR and PAR.

- However, the use of omalizumab for the treatment of AR has not been approved
  - its high cost limits this application.

Omalizumab

- SAR



Casale et al., 2001

Omalizumab

- Meta-analysis
  - Significant reduction in the daily nasal symptom severity score
    - (standardized mean difference −0.67 [95% CI, −1.3 to −0.31]; $P < .0001$; I^2, 92%)
  - Significant reduction in daily nasal rescue medication score
    - (−0.22 [95% CI, −0.39 to −0.05; $P = .01$; I^2, 58%)
  - Not a statistically significant difference in the occurrence of any adverse event
    - (relative risk 1.06 [95% CI, 0.94-1.19; I^2, 55%)

Tsabouri et al., 2014

Other biologics

- VAK694 and QAX576
  - Targeting IL-4 and IL-13
  - Completed phase II studies

- No other studies are actually ongoing on PAR

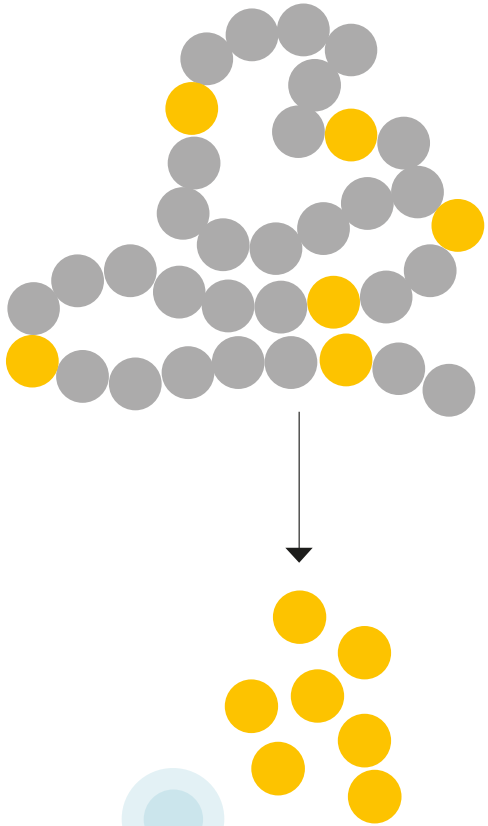
Biologicals

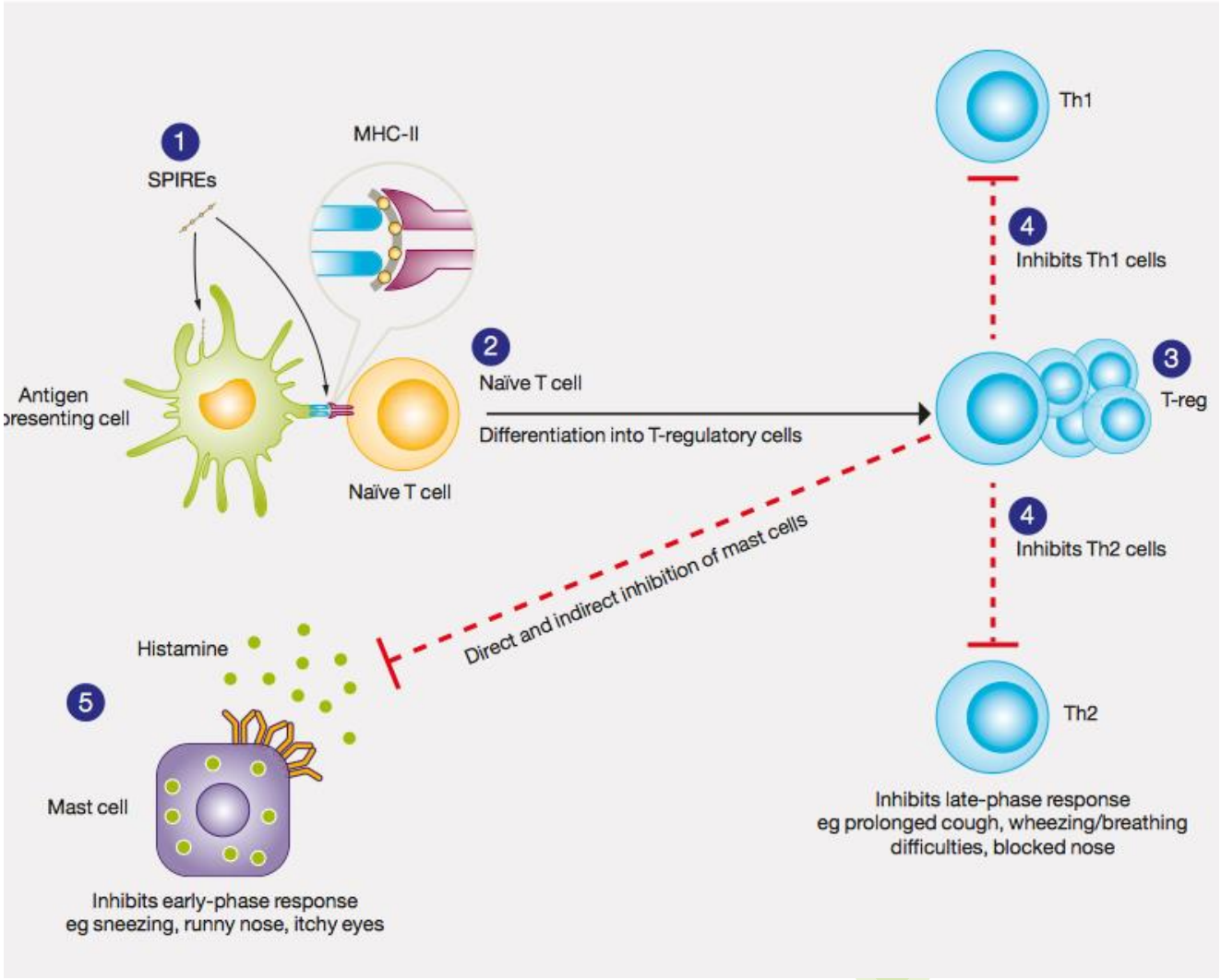
TABLE I. Reported studies with hmAbs in nasal polyposis

Antagonist	Target	Year	Therapeutic effects	Limitations	Status of development
Omalizumab[39]	IgE	2013	Significant reduction of polyp and CT scores, improvement of symptoms of upper and lower airways and quality of life	No reduction of serum or nasal secretion mediators, frequent rhinopharyngitis	PoC
Mepolizumab[40]	IL-5	2011	Significant reduction of polyp score, reduction of blood eosinophil count, as well as ECP and IL-5Rα levels, in serum	No significant improvement of symptoms, frequent rhinopharyngitis	Clinical trial, phase 3
Reslizumab[41]	IL-5	2006	Significant reduction of polyp score, reduction of blood eosinophil counts, as well as ECP levels, in serum	No significant improvement of symptoms	PoC
Dupilumab[42]	IL-4Rα	2015	Significant reduction of polyp and CT scores, improvement of smelling, symptoms, and quality of life (SNOT-22); improvement of pulmonary function (FEV_1) and asthma control test score (ACQ5)	Side effects include headache, rhinopharyngitis, and reaction at injection site	PoC

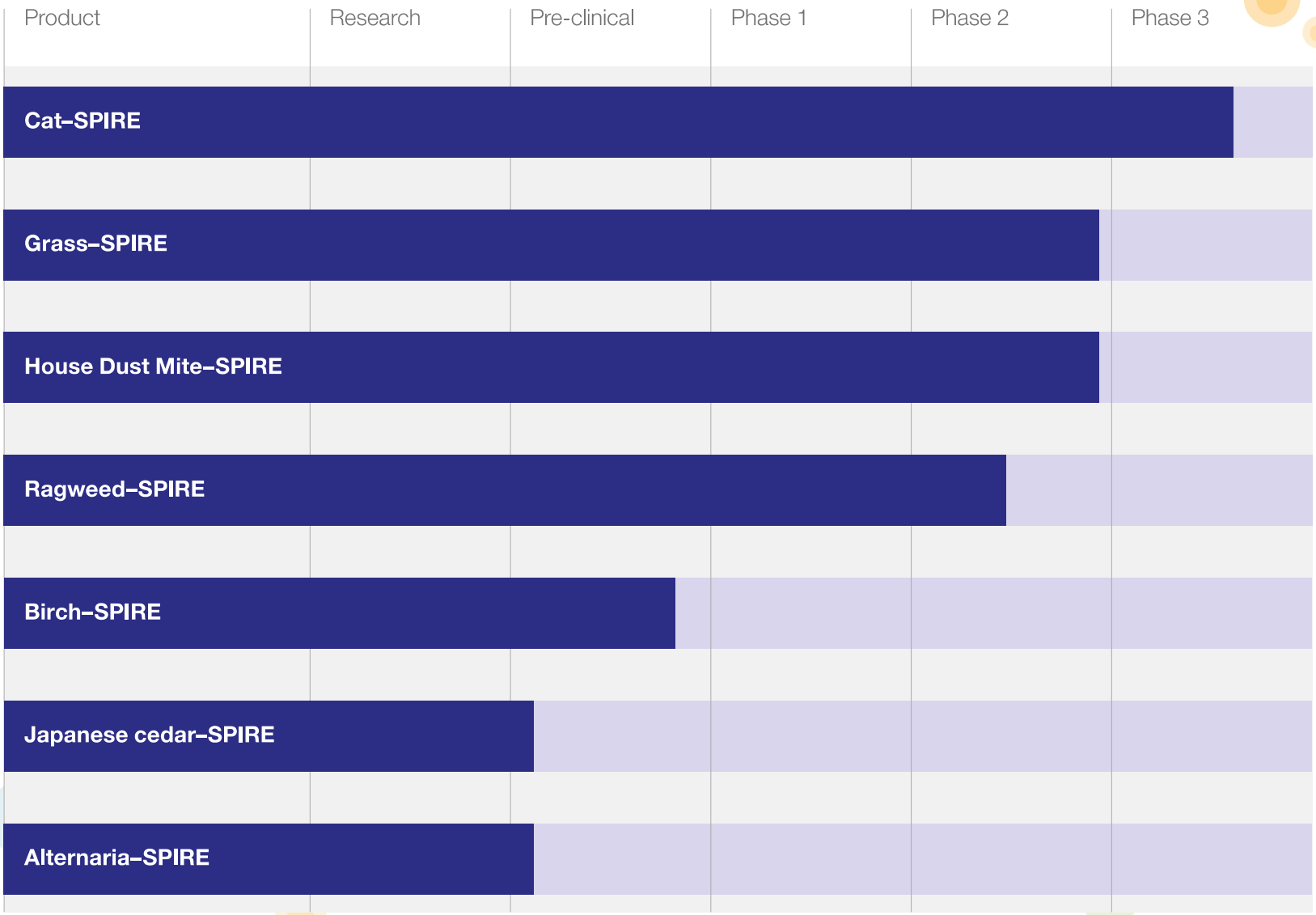
3. Modification of Immunotherapy

Synthetic Peptide ImmunoRegulatory Epitopes (SPRIE)





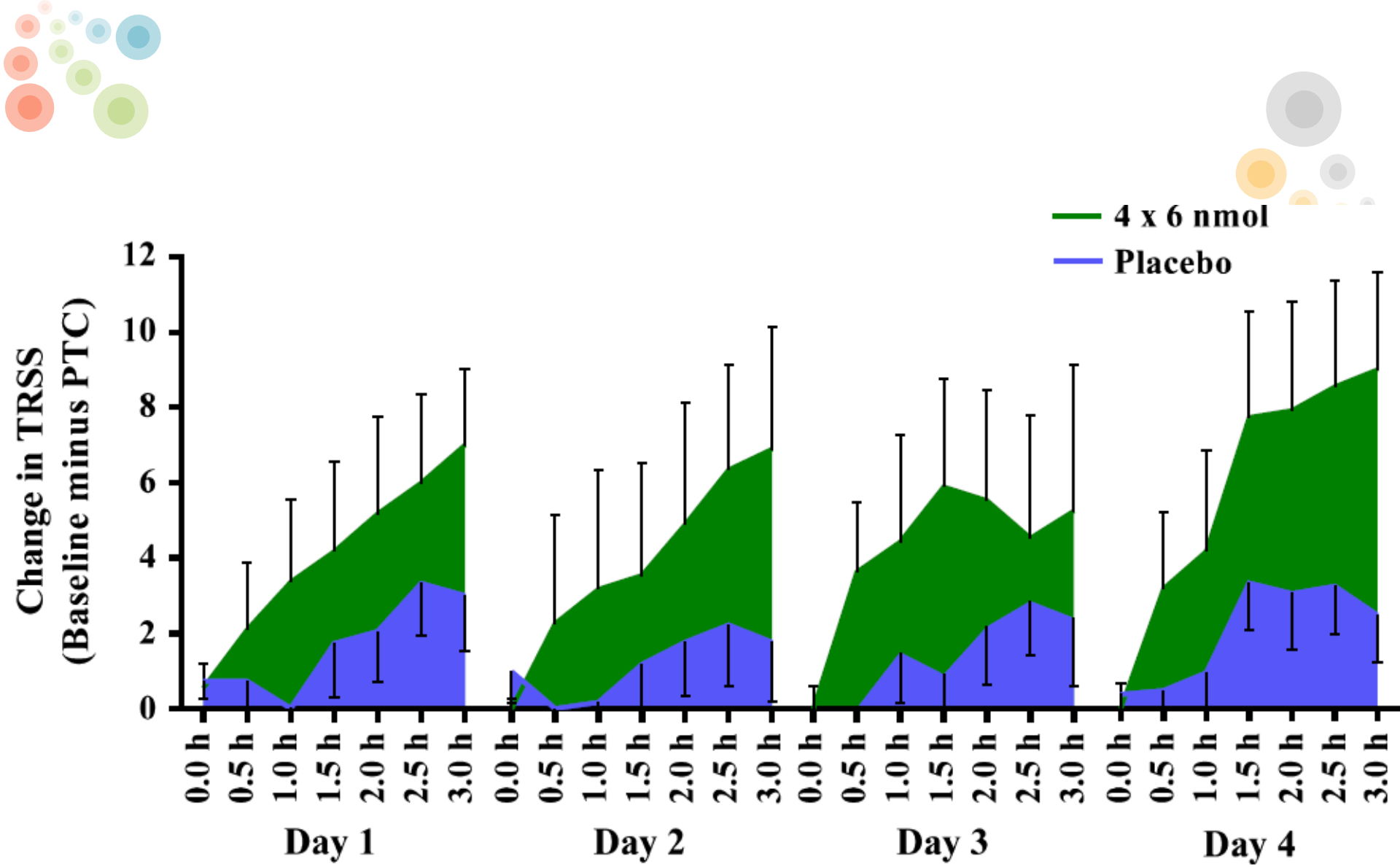
SPRIE


Product
Research
Pre-clinical
Phase 1
Phase 2
Phase 3
Cat–SPIRE
Grass–SPIRE
House Dust Mite–SPIRE
Ragweed–SPIRE
Birch–SPIRE
Japanese cedar–SPIRE
Alternaria–SPIRE

SPRIE

- Cat SPIREs
  - A set of 7 synthetic peptide T-cell epitopes
  - derived from Fel d 1
  - showed for the first time the persistence of a clinically relevant effect
  - rhinoconjunctivitis symptoms following standardized allergen challenge 2 years after treatment

Couroux et al., 2015



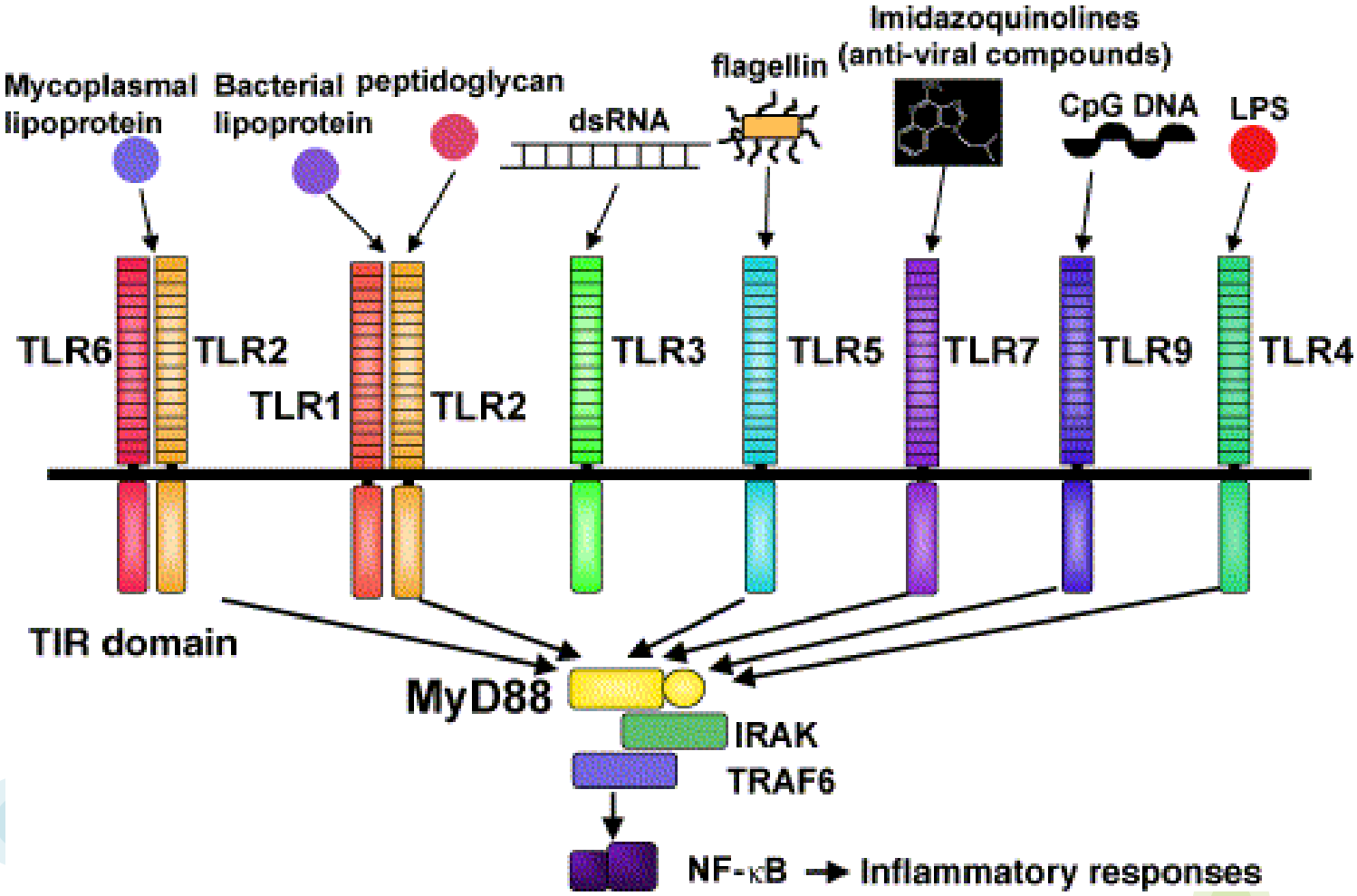
Couroux et al., 2015

Toll-like receptors (TLRs)

- Pattern recognition receptors
- TLRs are located at the first line of defense against invading pathogens as well as aeroallergens
  - interesting targets to modulate the natural history of respiratory allergy
  - widely employed as adjuvants in some SCIT formulations, showing strong immunomodulatory effects

Aryan et al., 2014

TLRs Recognize Signature Molecules of Microorganisms



TLR-4 agonist (MPL)

Pfaar et al 2011

Combined Nasal and chest symptoms — NS — Improved

Lymphocyte activation — NS — Increased

Mothes et al 2003

Nasal symptoms — NS — Improved

Chest symptoms — NS — Improved

Boost of Ig-E — NS — Decreased

Ig-M Ig-G — NS — Increased

Week Drachenberg et al 2001

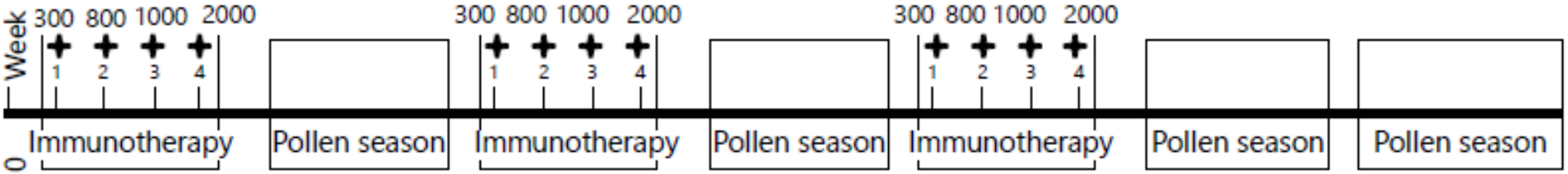
Nasal symptoms — NS — Improved

Skin prick test Mean wheal diameter — NS — Decreased

Boost of Ig-E — NS — Decreased

Ig-G — NS — Increased

Injection immunotherapy with Pollinex Quattro



First year of immunotherapy — Second year of immunotherapy — Third year of immunotherapy — Five years after discontinuation

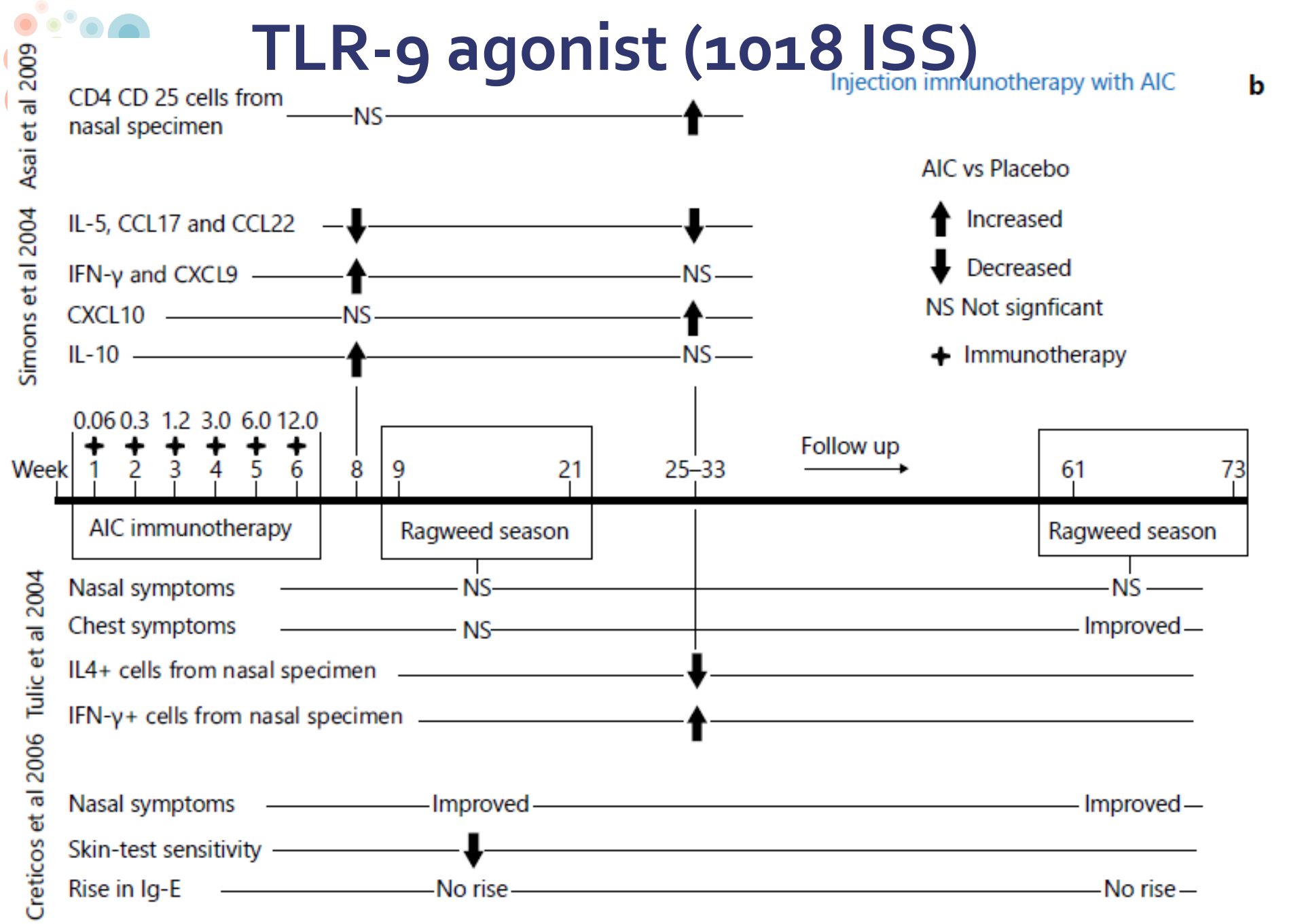
Musarra et al 2010

FEV1 — NS — NS — Improved

Skin prick test Mean wheal diameter — NS — Decreased — NS

Nasal symptoms — NS — Improved — Improved

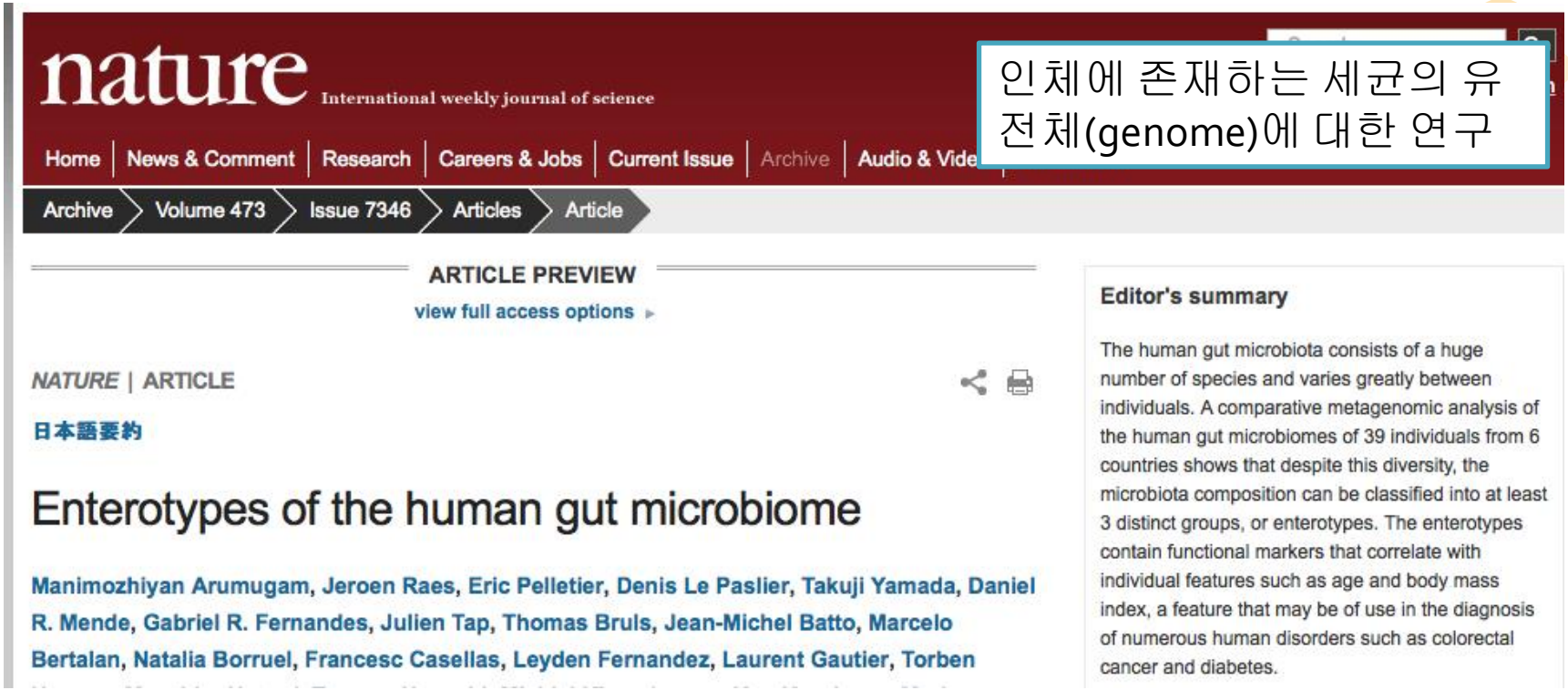
TLR-9 agonist (1018 ISS)



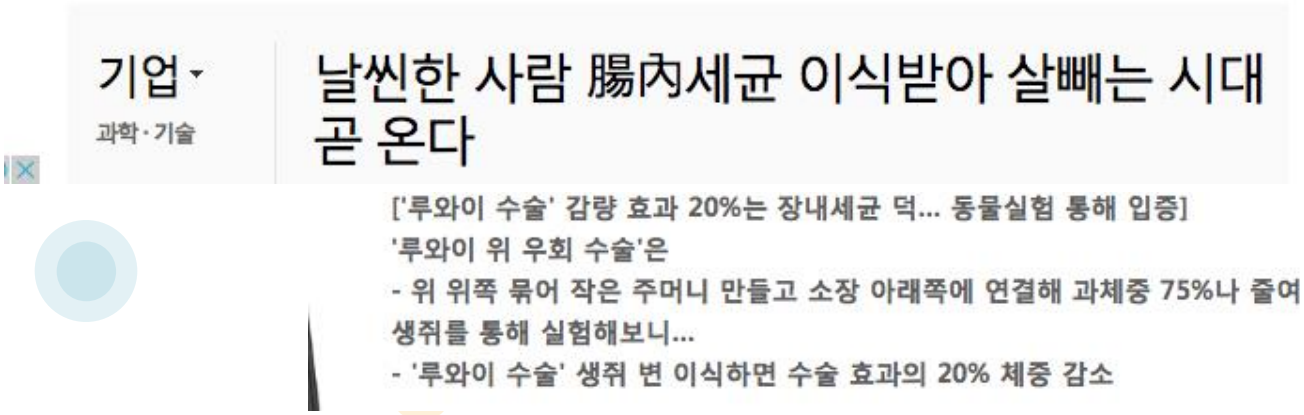
Aryan et al., 2014

4. Modification of gut microbiome

Probiotics and microbiome



인체에 존재하는 세균의 유전체(genome)에 대한 연구



Microbiota & Human Health

SCIENCE WORLD REPORT

HOME SPACE NATURE & ENVIRONMENT HEALTH & MEDICINE TECH PHYSICS HUMAN VIDEO

Baby's Gut Bacteria Determined by Breastfeeding and C-Section

A baby's gut microbiota may be influenced greatly by their moms, according to new research. Cesarean delivery and bottle feeding both affect exactly how much bacteria is in a baby's gut.

- Obesity
- Allergy/Asthma
- Irritable Bowel Syndrome
- Celiac disease
- Diabetes

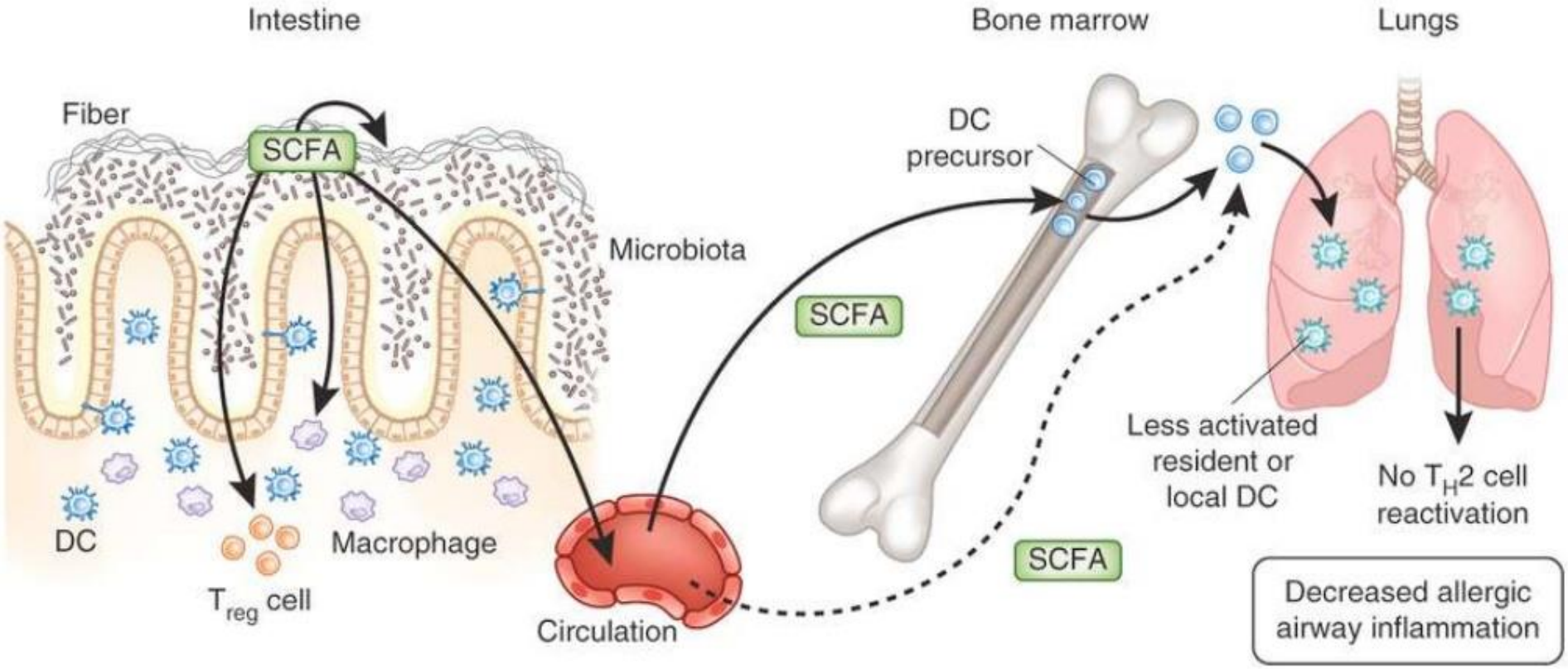
TIME

HEALTH

You Are Your Bacteria: How the Gut Microbiome Influences Health

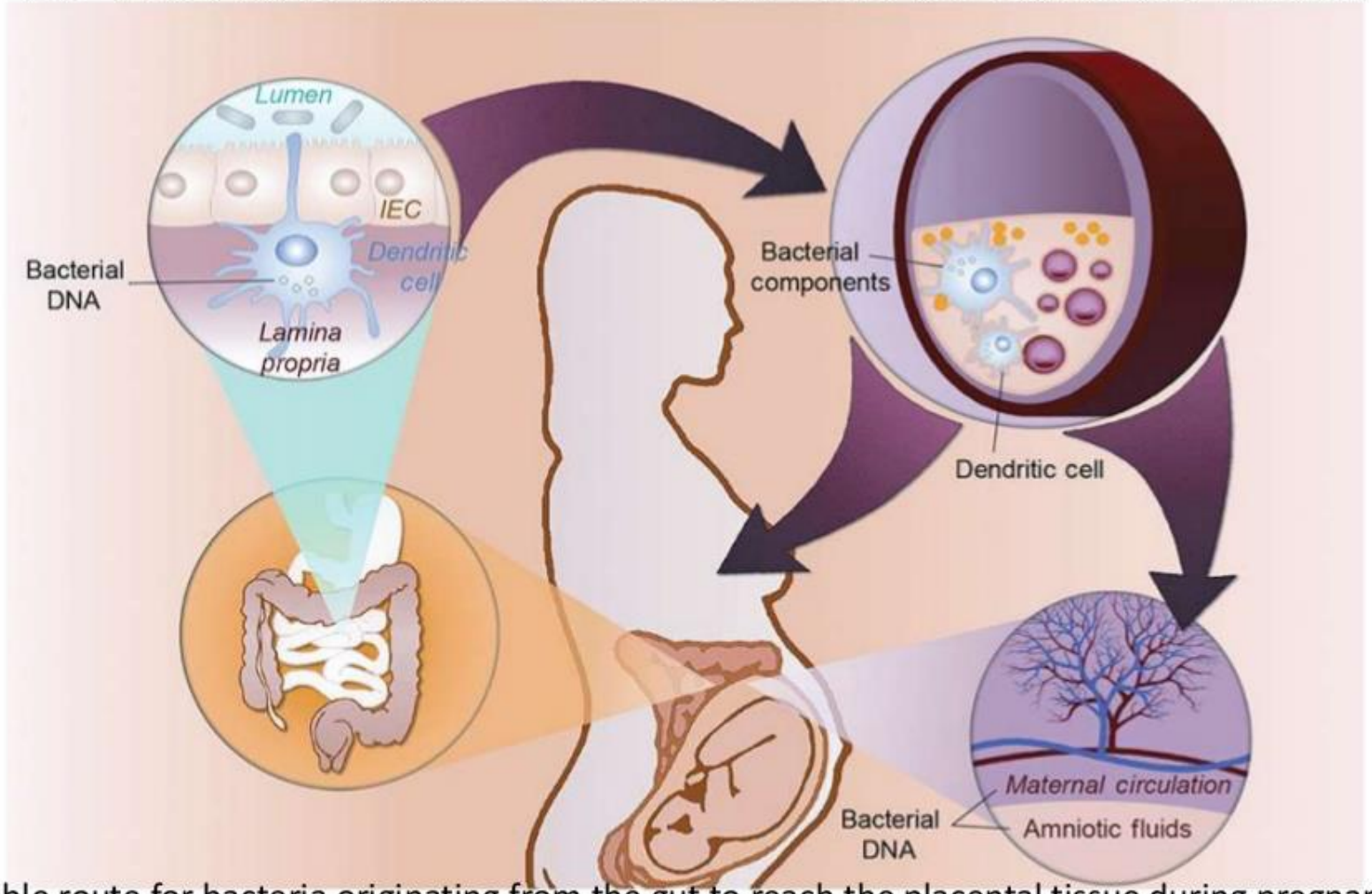
The bacteria in our gut already plays an important role in digestion. But new studies indicate that our bacteria could play a major role in whether or not we become obese

Studies on prevention :
3. The gut microbiota and fiber diet



Increase in dietary fiber dampens allergic responses in the lung. Gary B Huffnagle. Nature Medicine 20, 120–121 (2014

Studies on prevention :
5. The gut microbiota of the pregnant woman



A possible route for bacteria originating from the gut to reach the placental tissue during pregnancy. Dendritic cells (DCs) actively penetrate the epithelium, sample the microbes within the gut lumen, and transport them to the placenta…

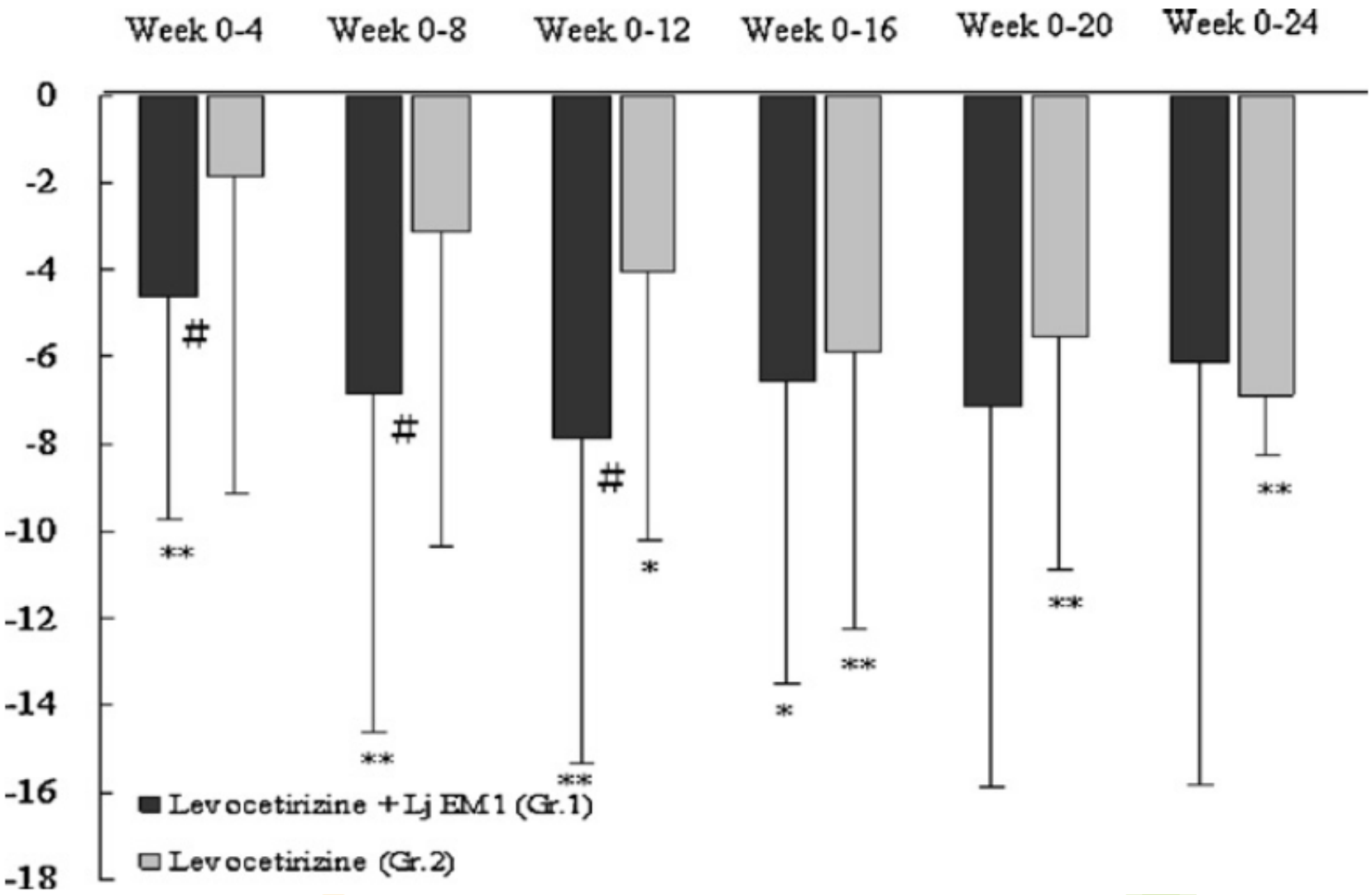
Gut microbiota and allergy: the importance of the pregnancy period
Thomas R. Abrahamsson, Richard You Wu, Maria C. Jenmalm
Pediatric Research (2015) 77, 214–219 doi:10.1038/pr.2014.165

Probiotics

- Probiotics may modulate immune responses beneficial for the prevention and treatment
- consumption of probiotics has been shown to reduce the level of eosinophils in allergic patients

Wheeler et al., 1997

Probiotics



Lue et al., 2012

Take Home Messages (I)

- New drugs and therapies are always under investigation
- Everything is changing gradually and paradigm shift can happen abruptly even in medical field.
- We need to keep up with new changes not to be fallen behind times.

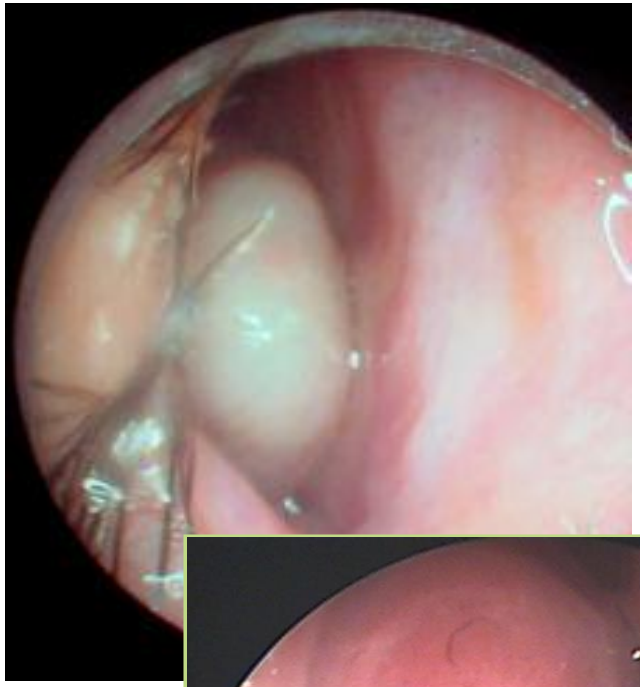
1. New Innovative Treatment

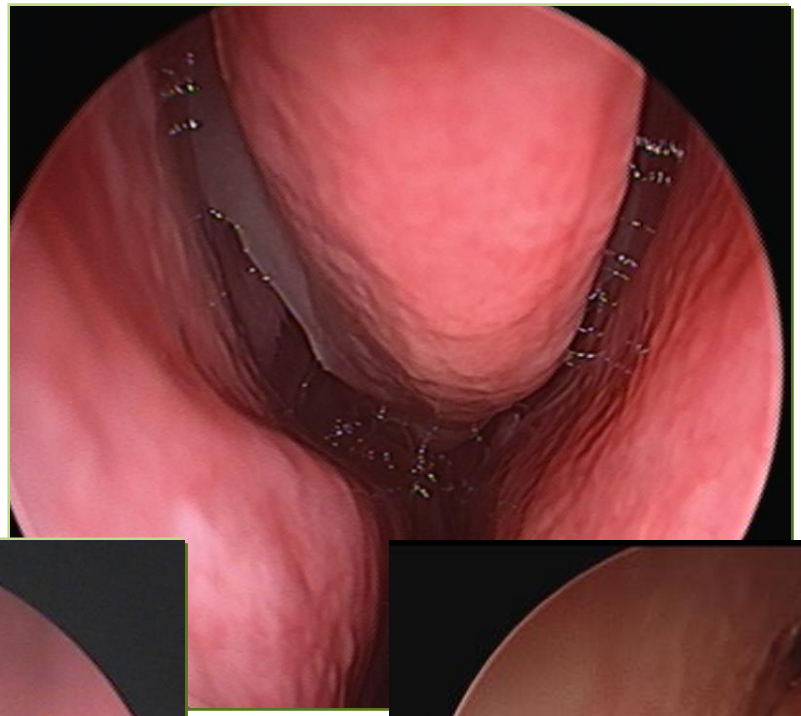
2. What internists should know

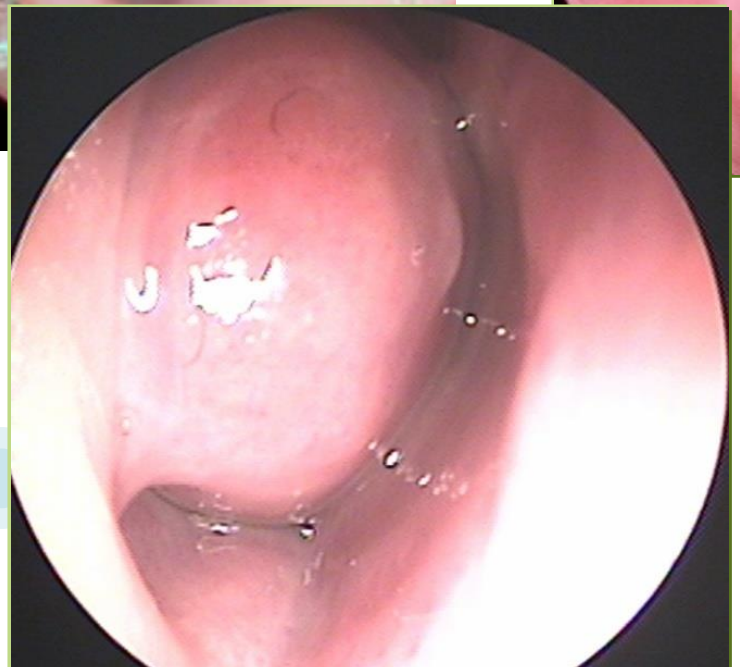
Anatomy, physiology, and surgical Tx

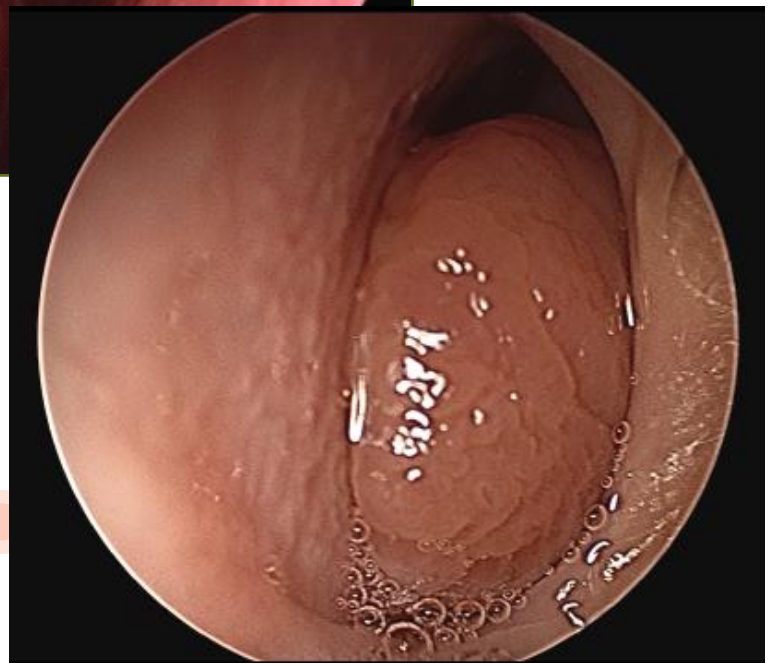
Nasal cavity evaluation

Diversity of allergic mucosa









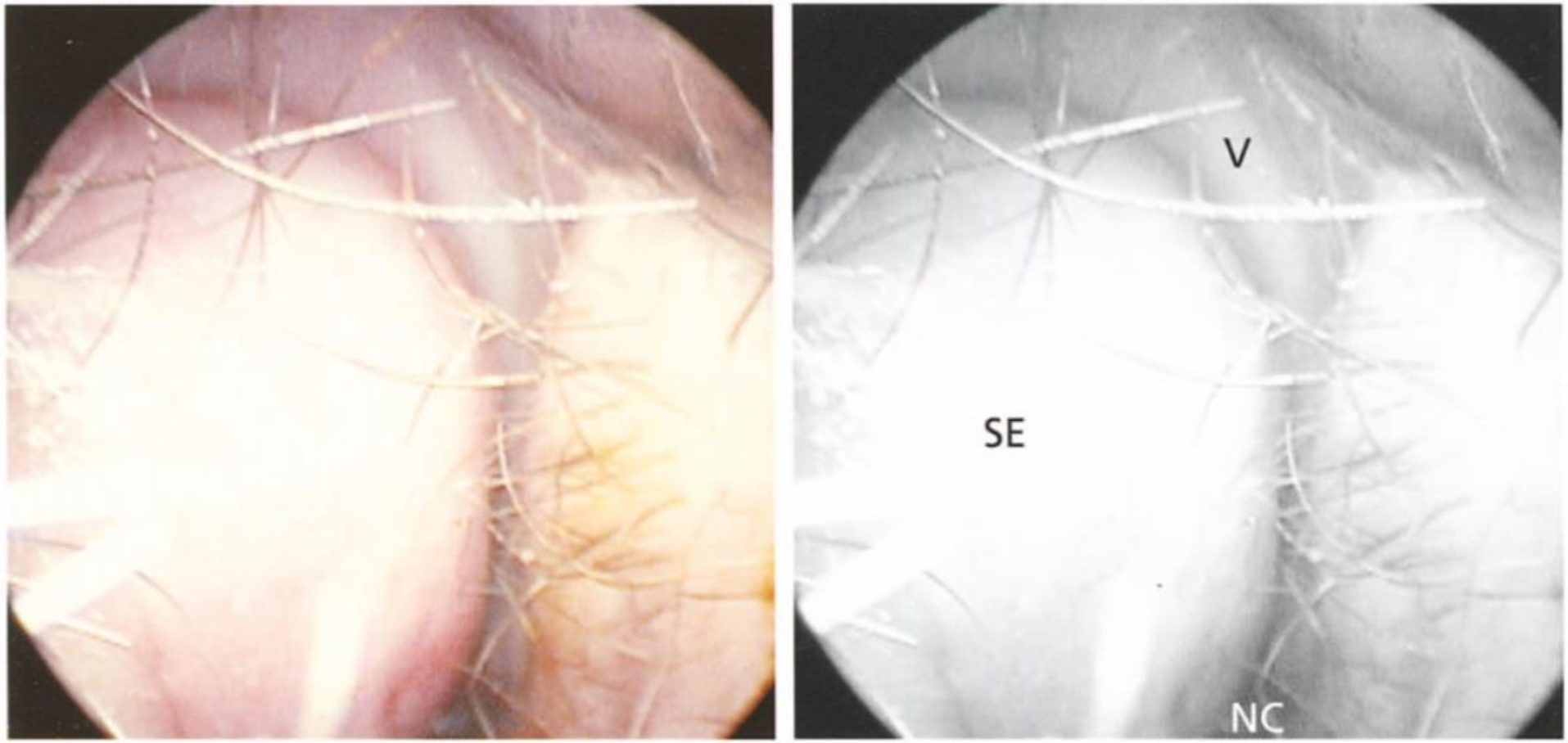
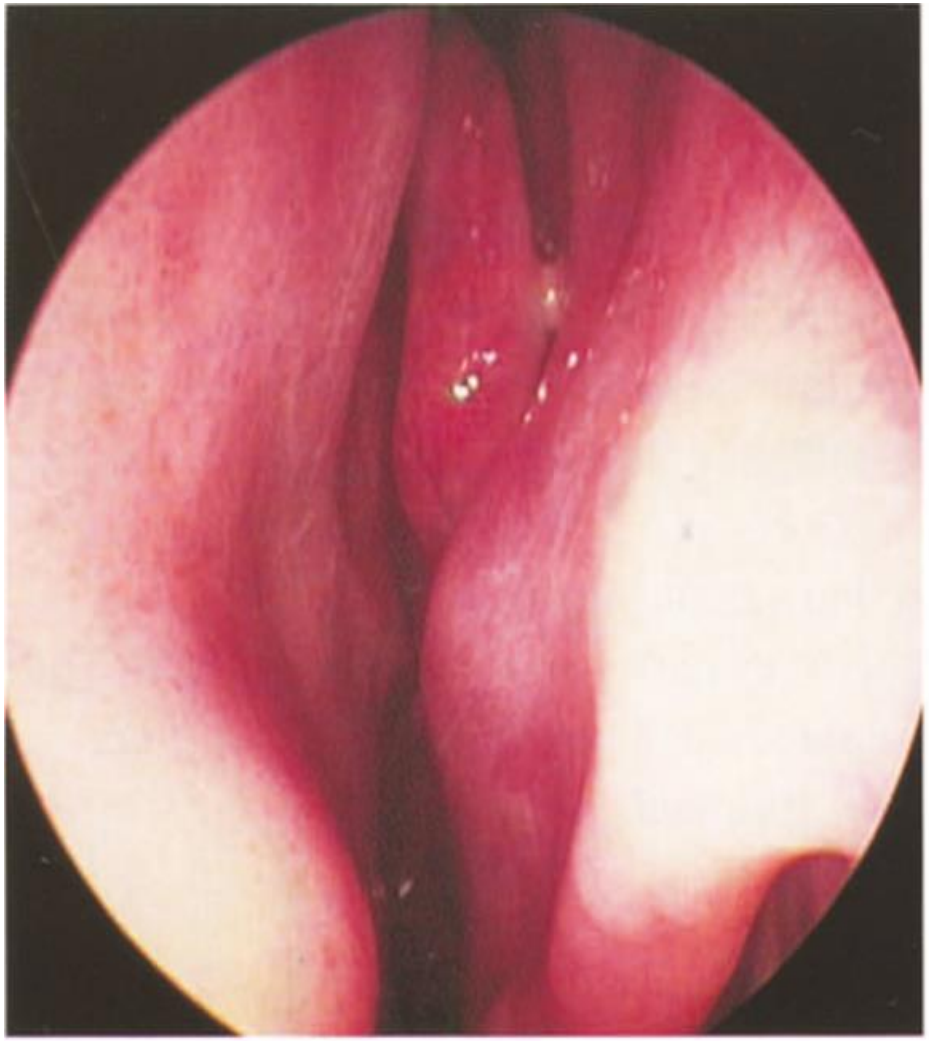
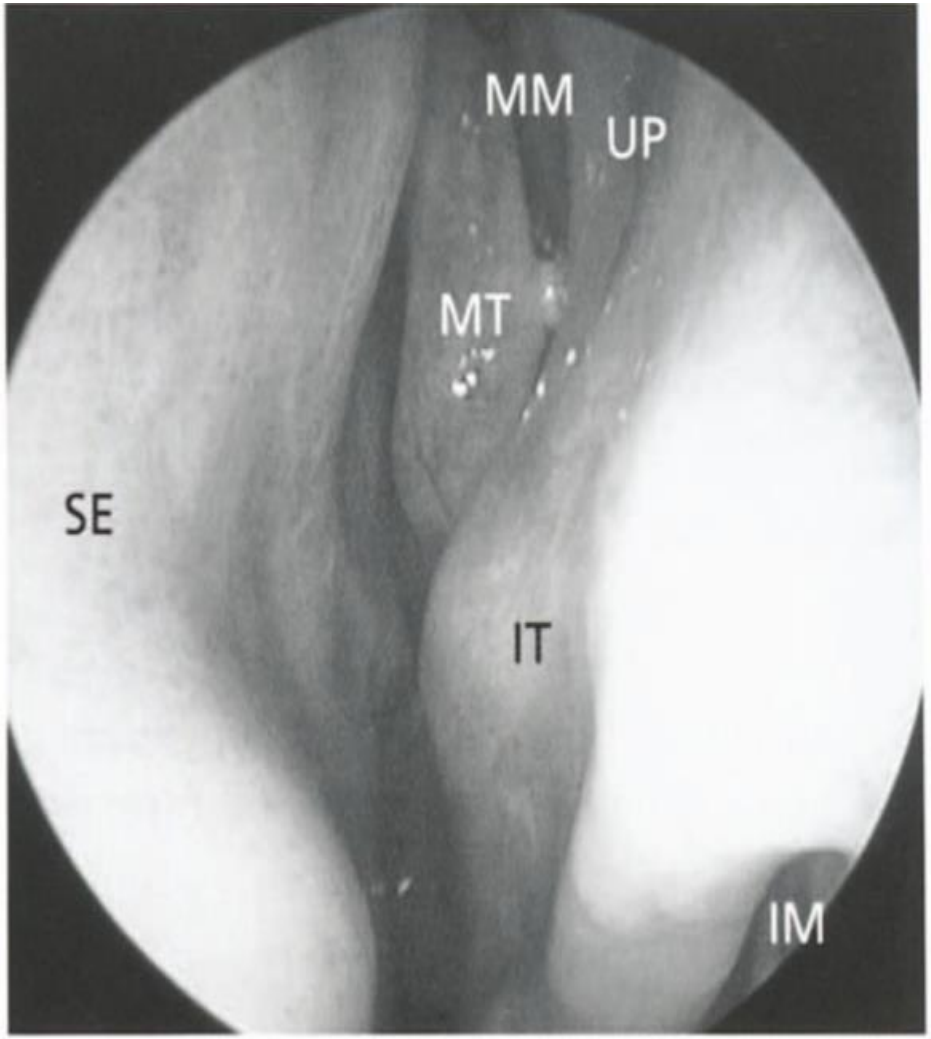


Fig. 1.1. Left side, zero degree lens, septal obstruction at nasal vestibule.

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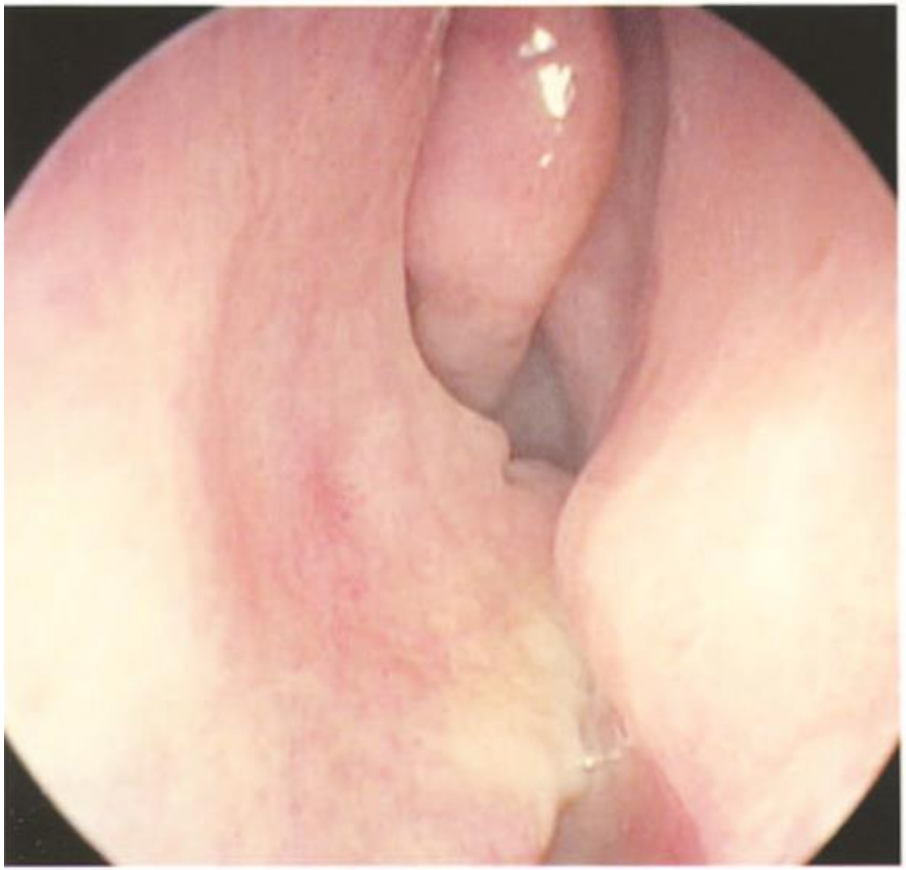

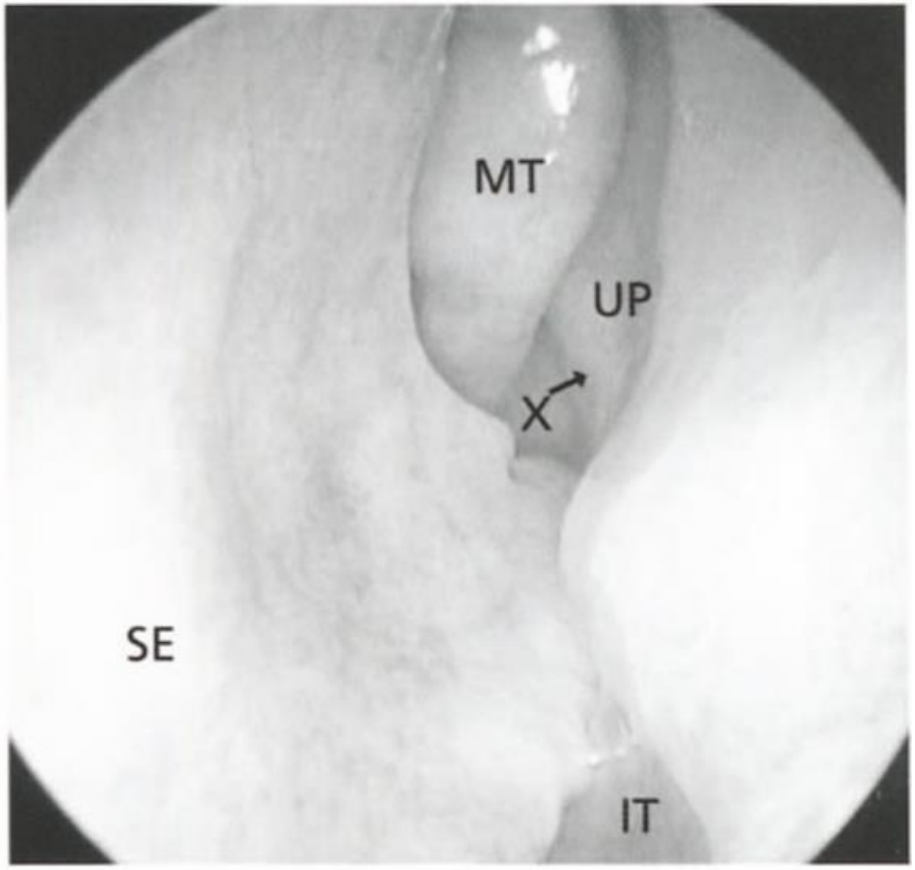
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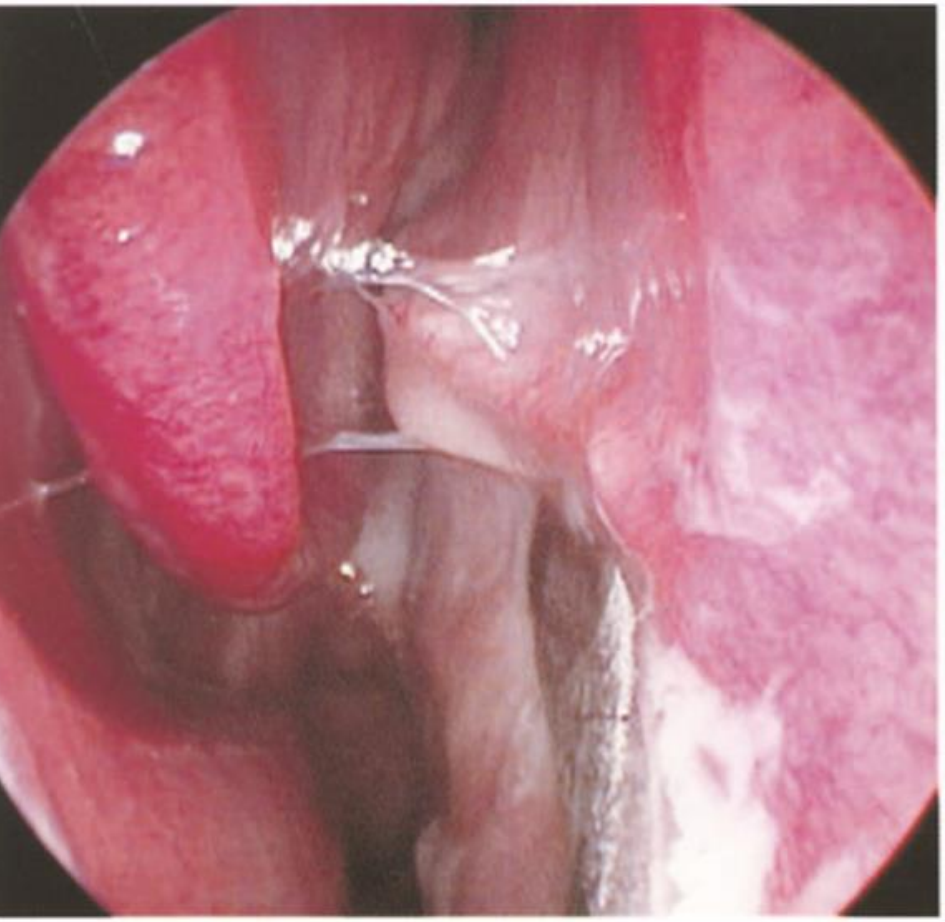

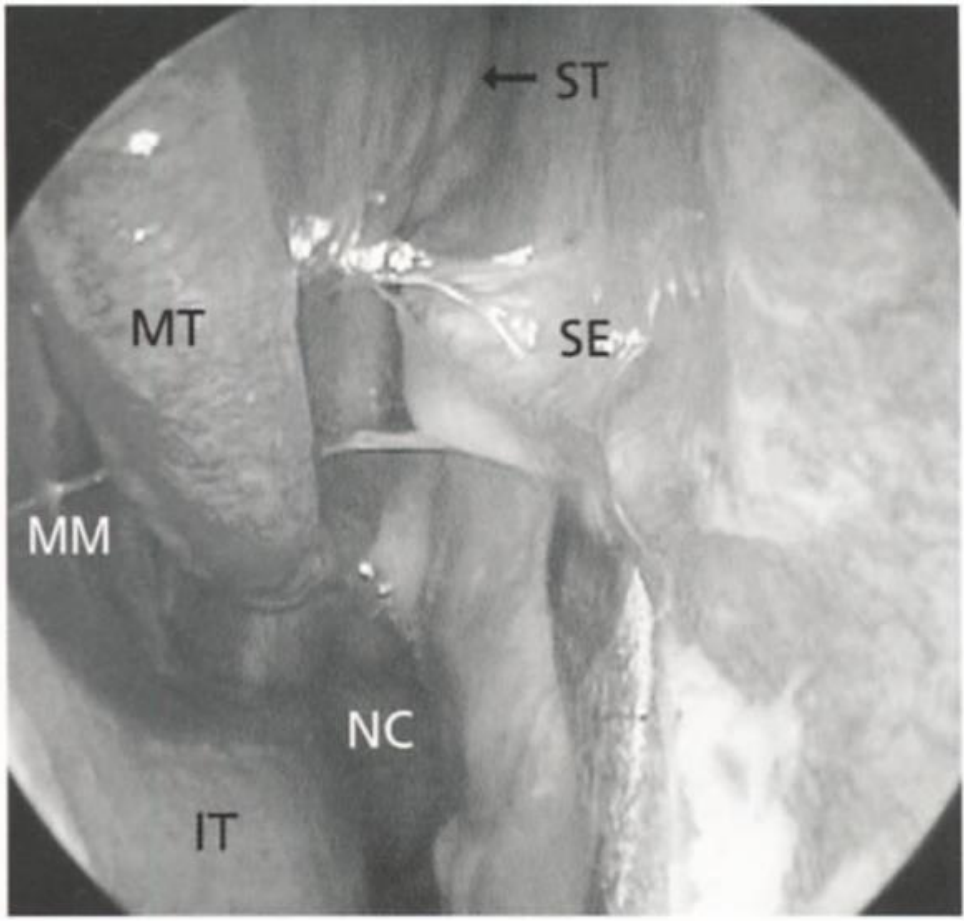
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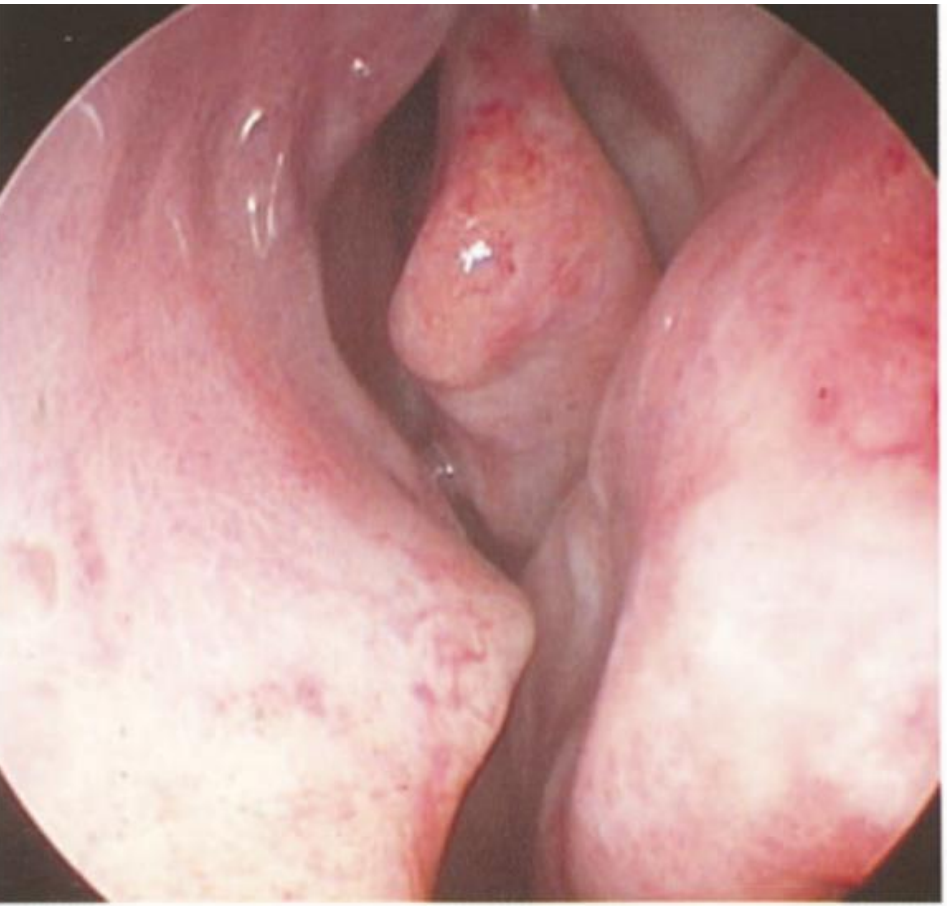

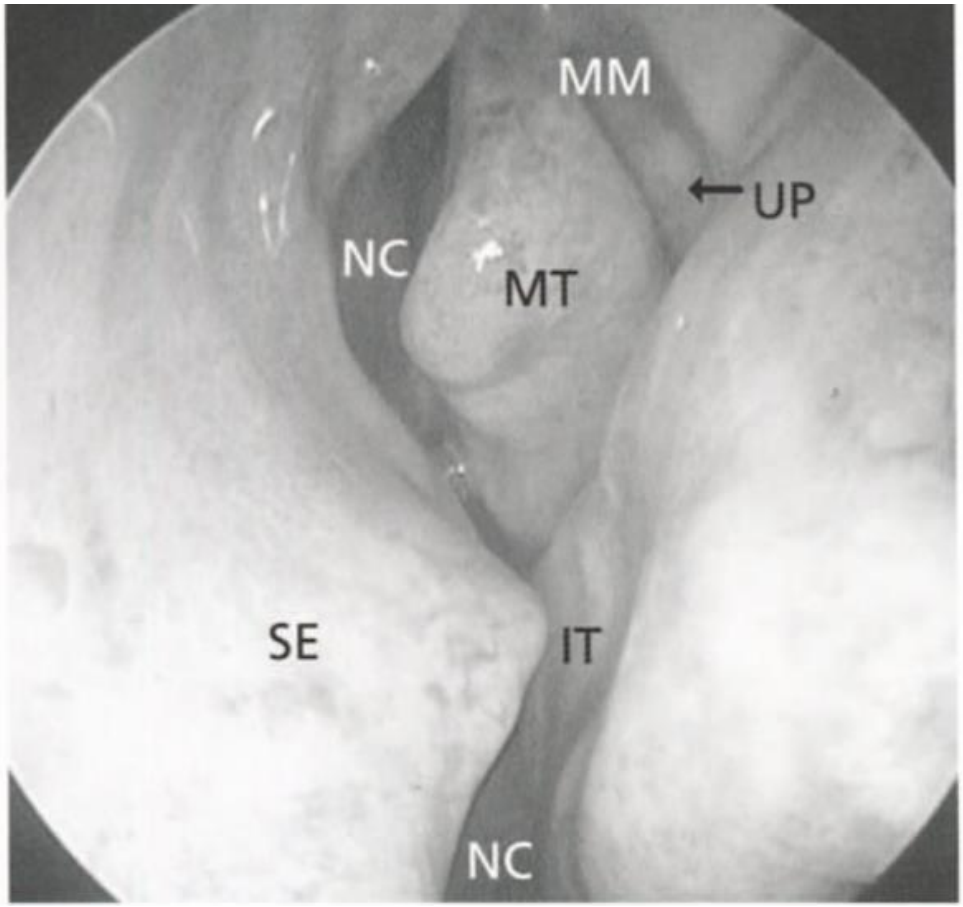
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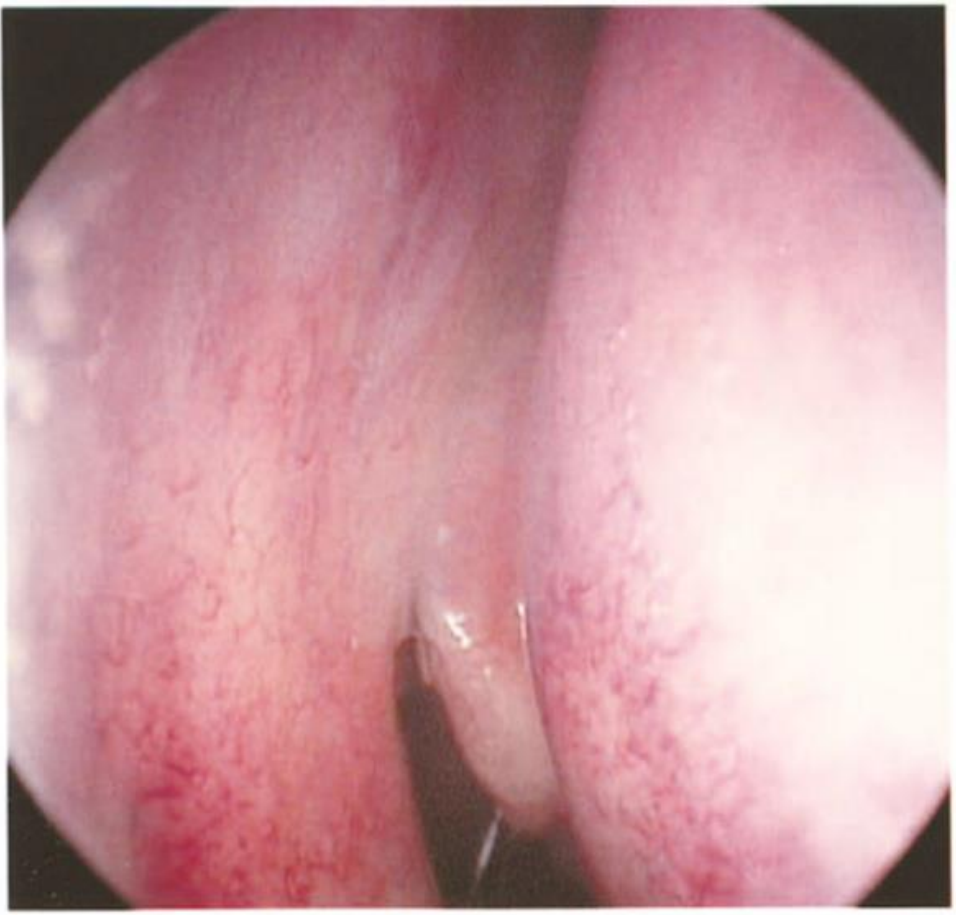


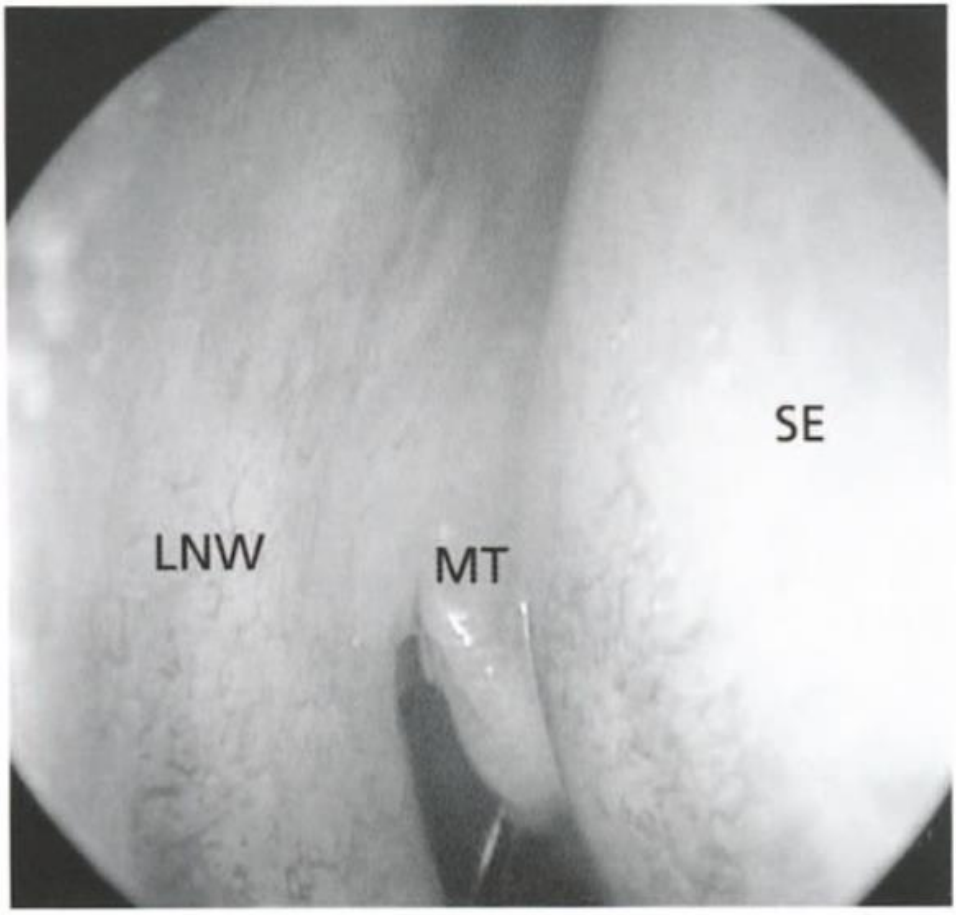


Fig. 1.7. Right side, zero degree lens, middle turbinate squeezed between nasal septum and lateral nasal wall, partial closure of middle meatus.

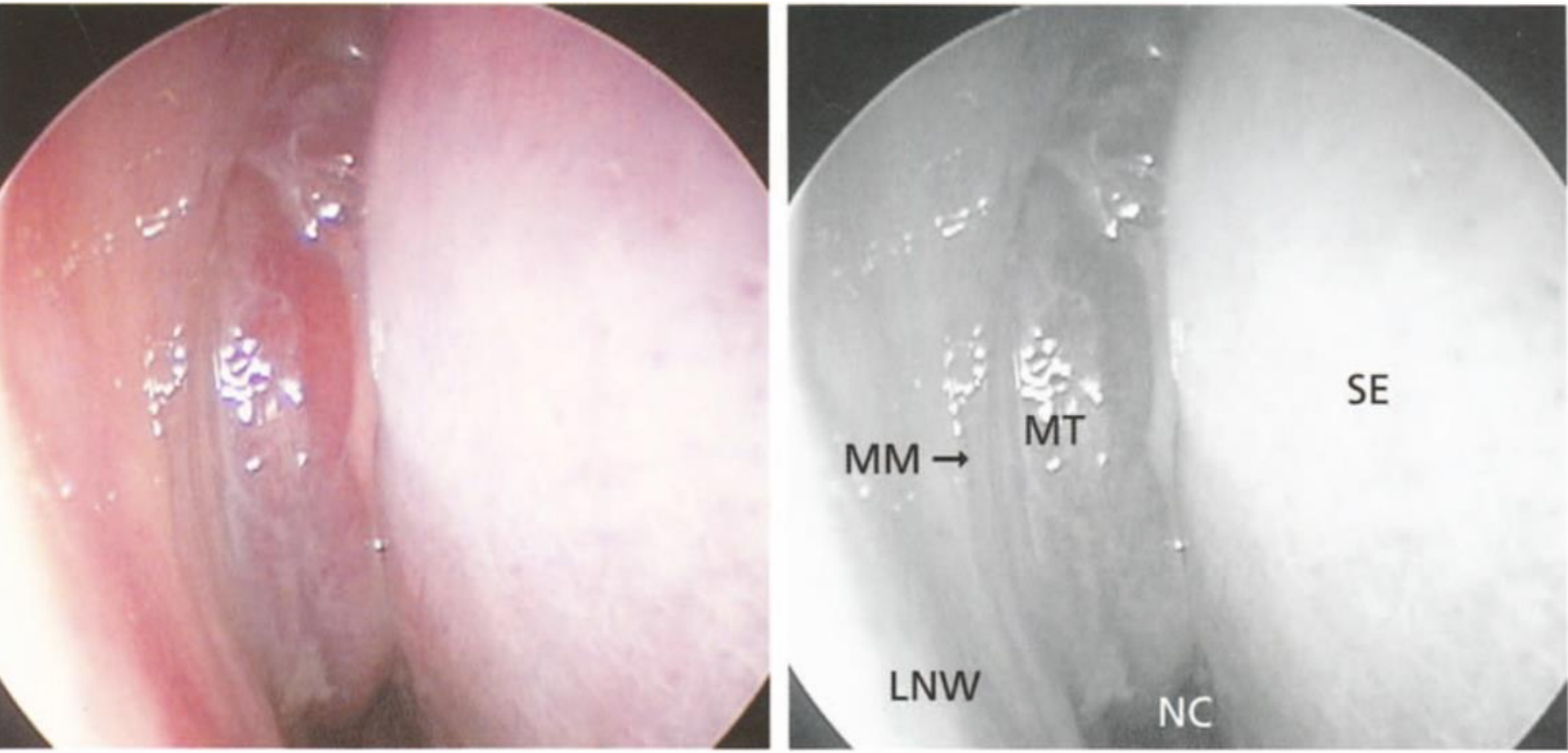
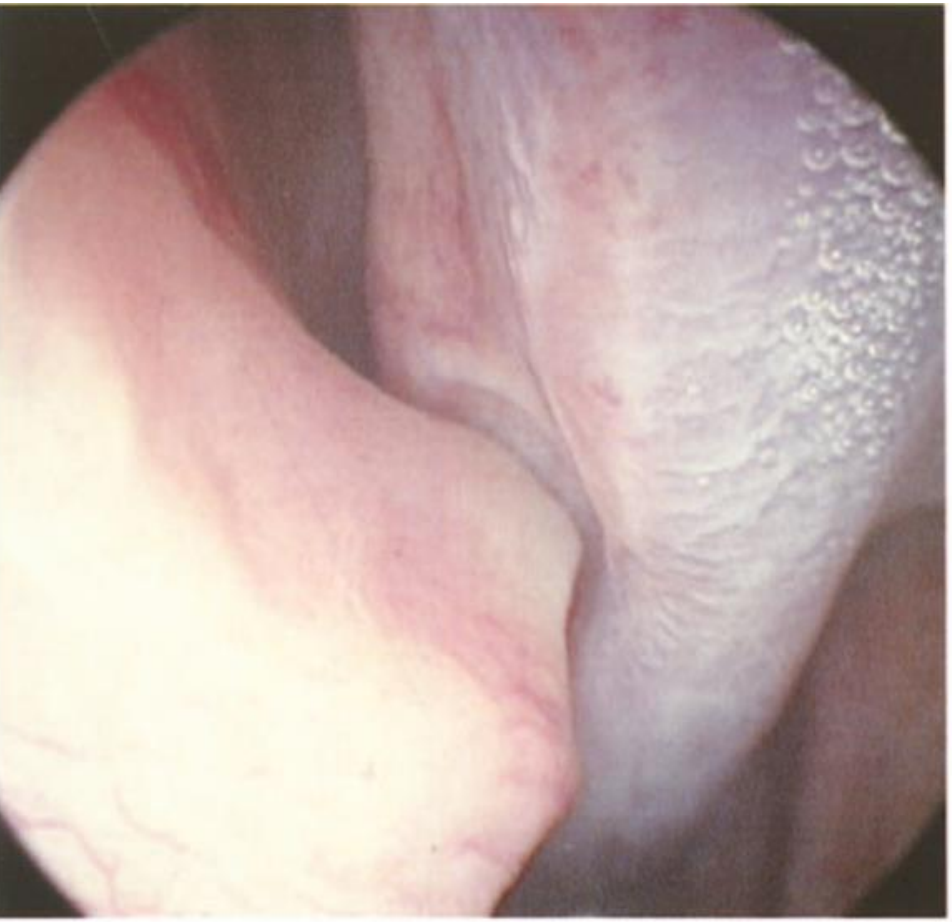


Fig. 1.8. Right side, zero degree lens, marked deviation with middle turbinate contact and polyp with middle meatus closed.



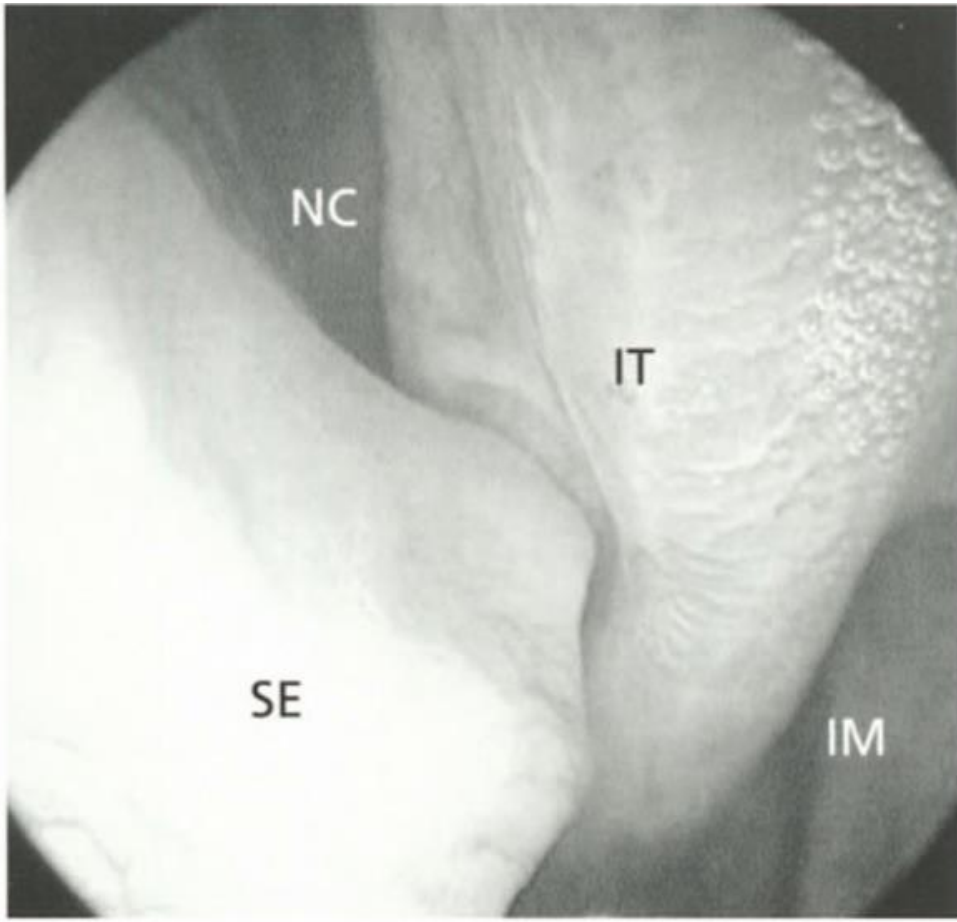


Fig. 1.12. Left side, zero degree lens, septal spur indenting inferior turbinate.

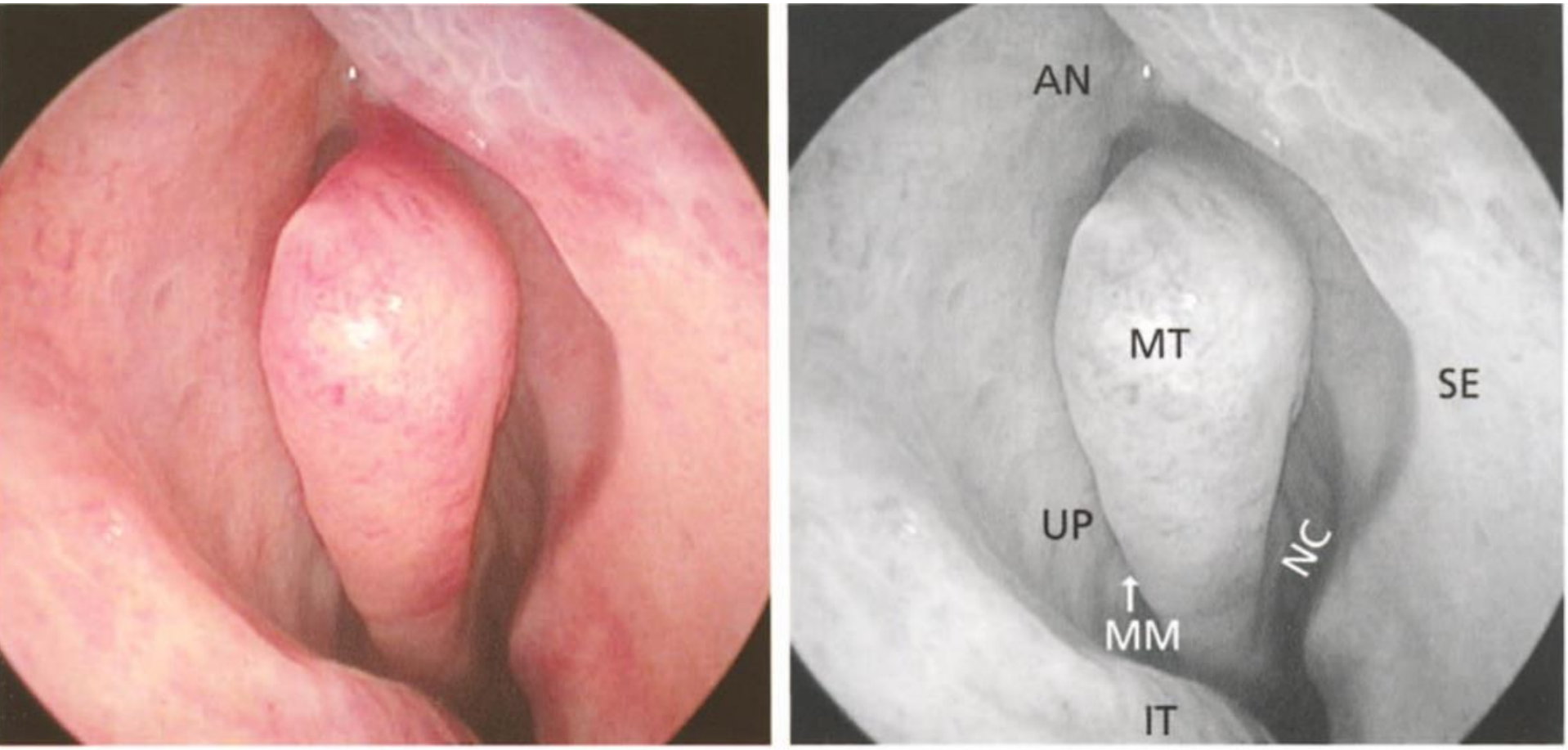


Fig. 2.2. Right side, zero degree lens, slightly bulbous middle turbinate with convex side of deviated septum.

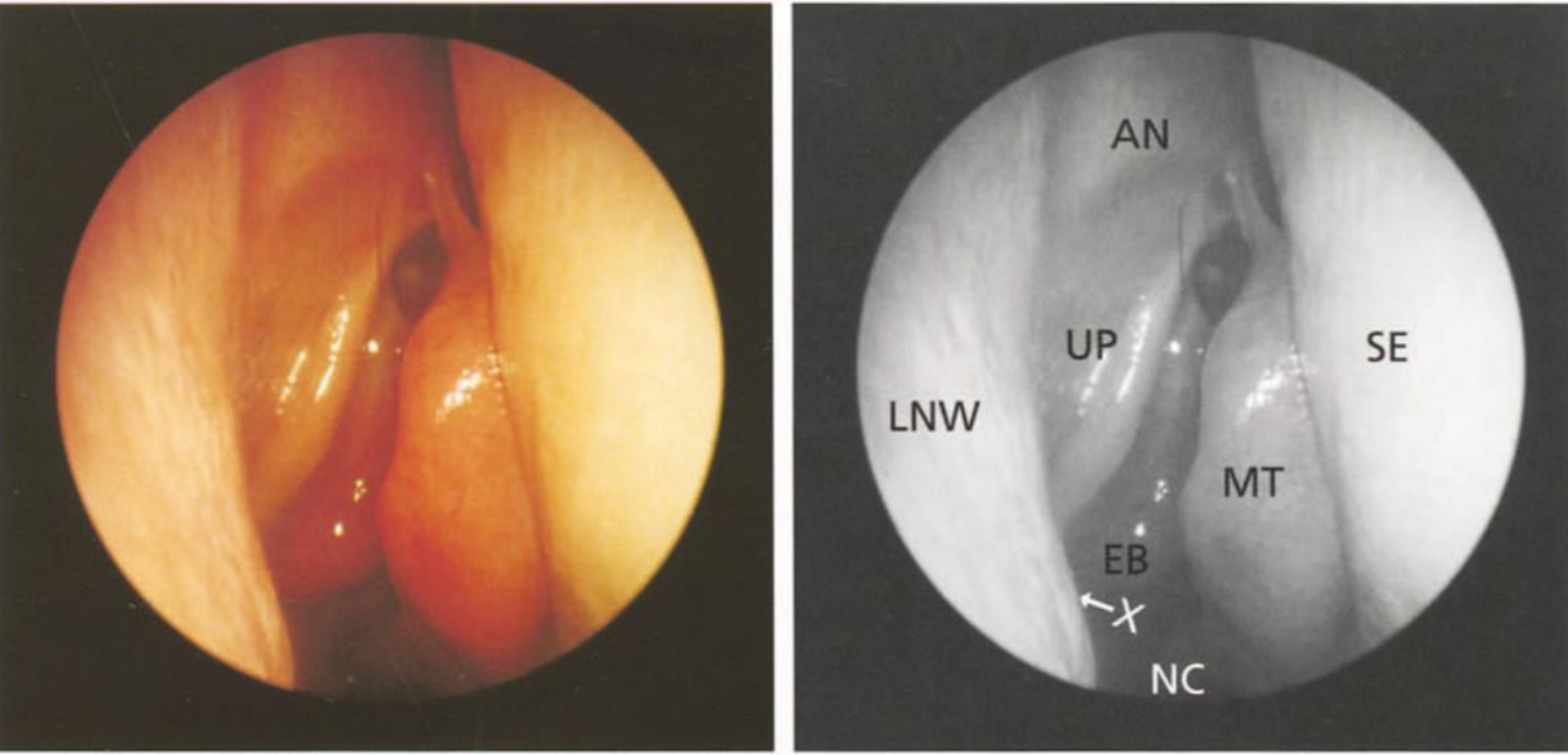


Fig. 2.3. Right side, zero degree lens, unobstructing middle turbinate, structures of middle meatus readily visible.

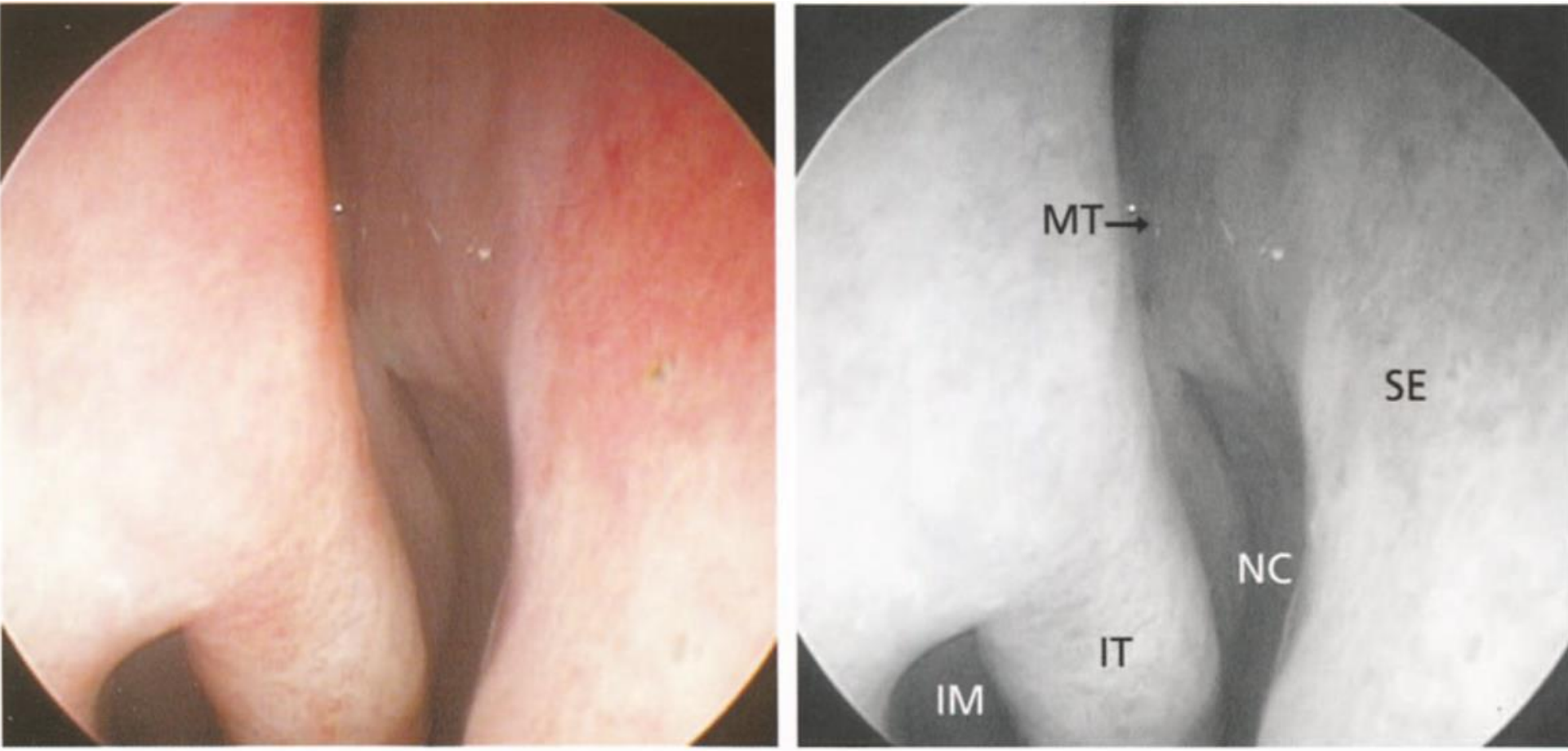


Fig. 2.4. Right side, zero degree lens, middle turbinate barely visible.

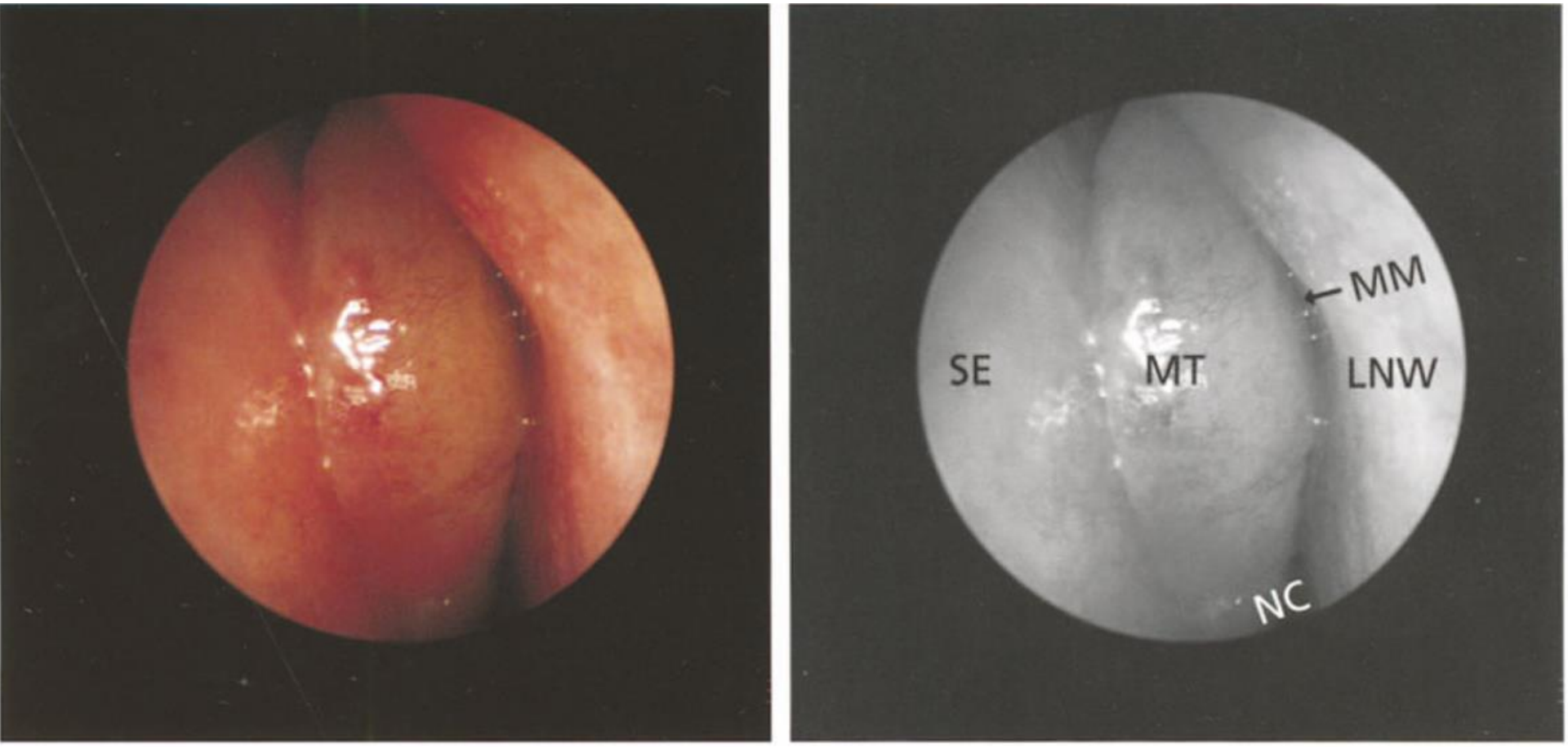
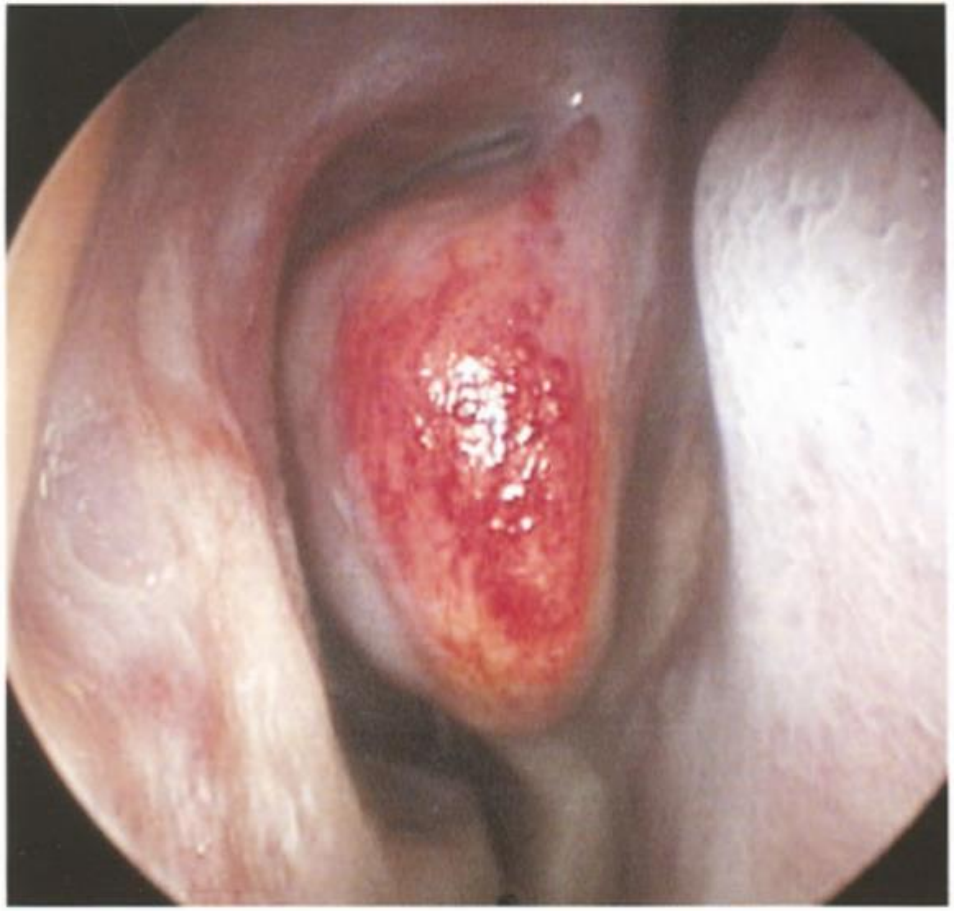


Fig. 2.5. Left side, zero degree lens, polypoid middle turbinate.



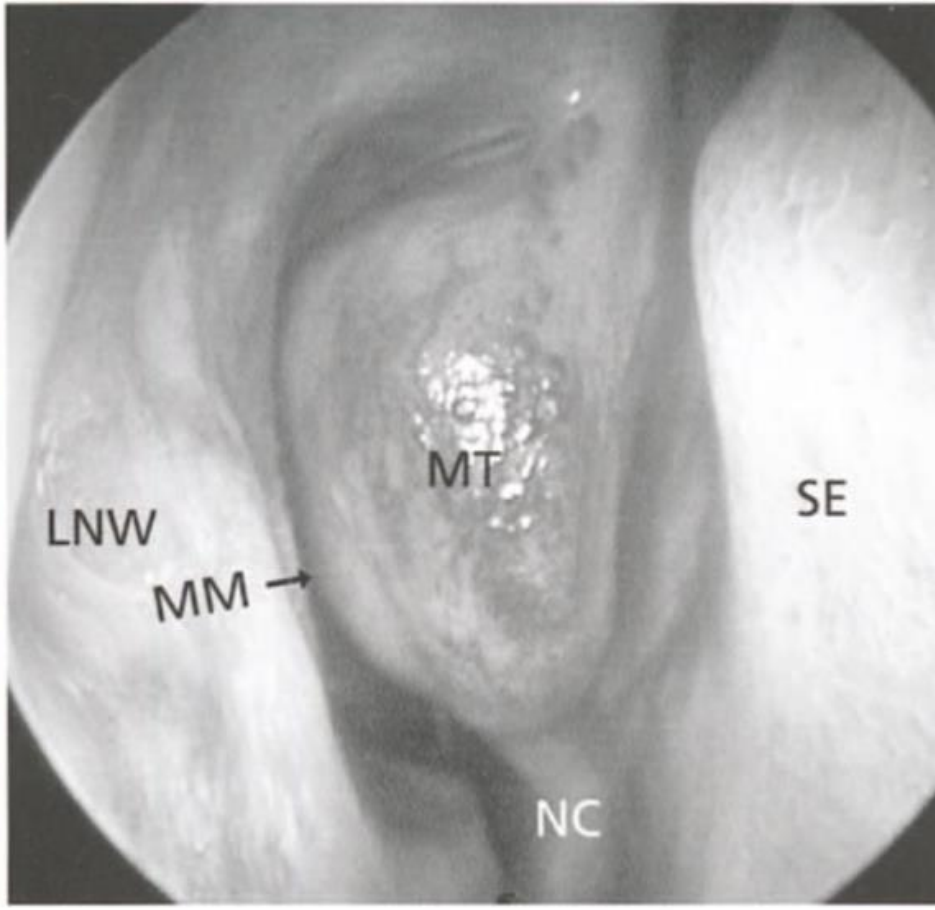
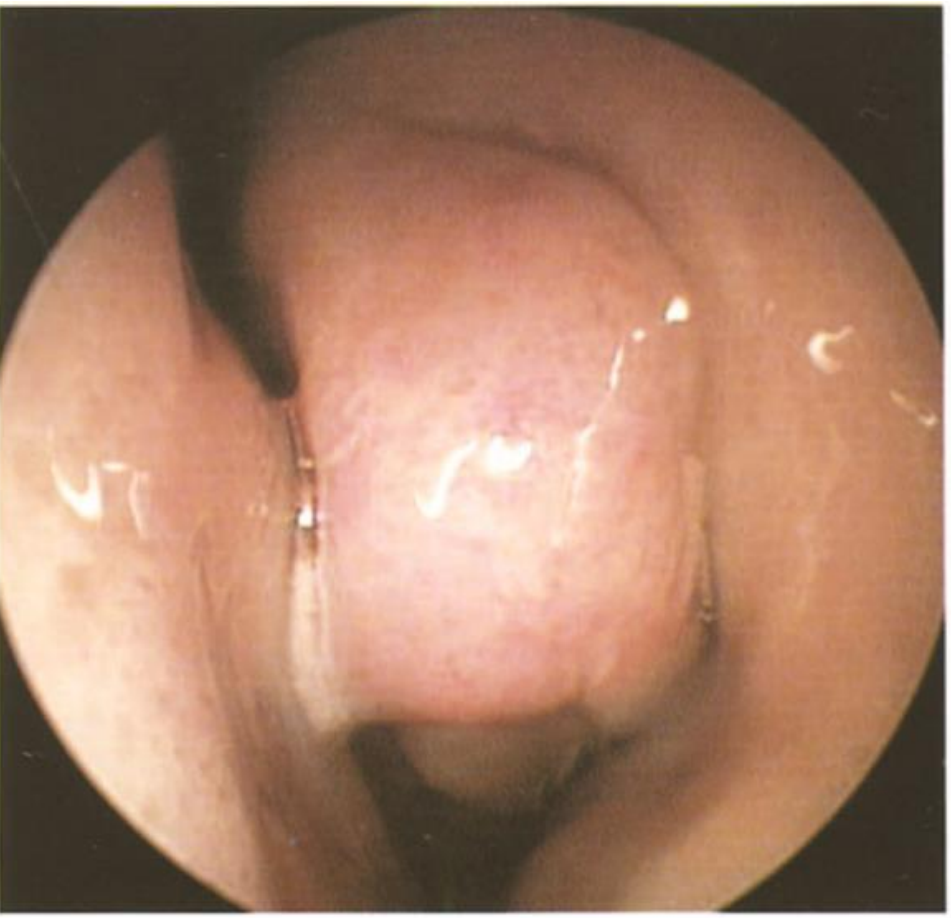


Fig. 2.7. Right side, zero degree lens, large concha bulla, middle meatus closed.



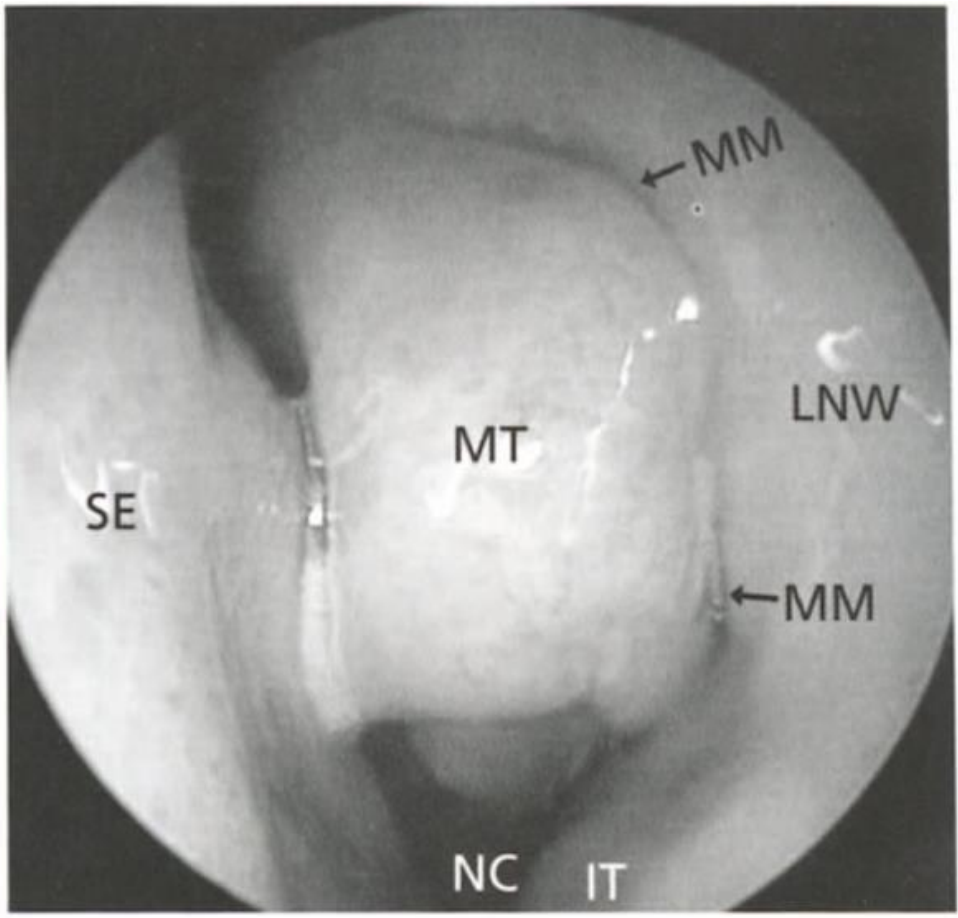
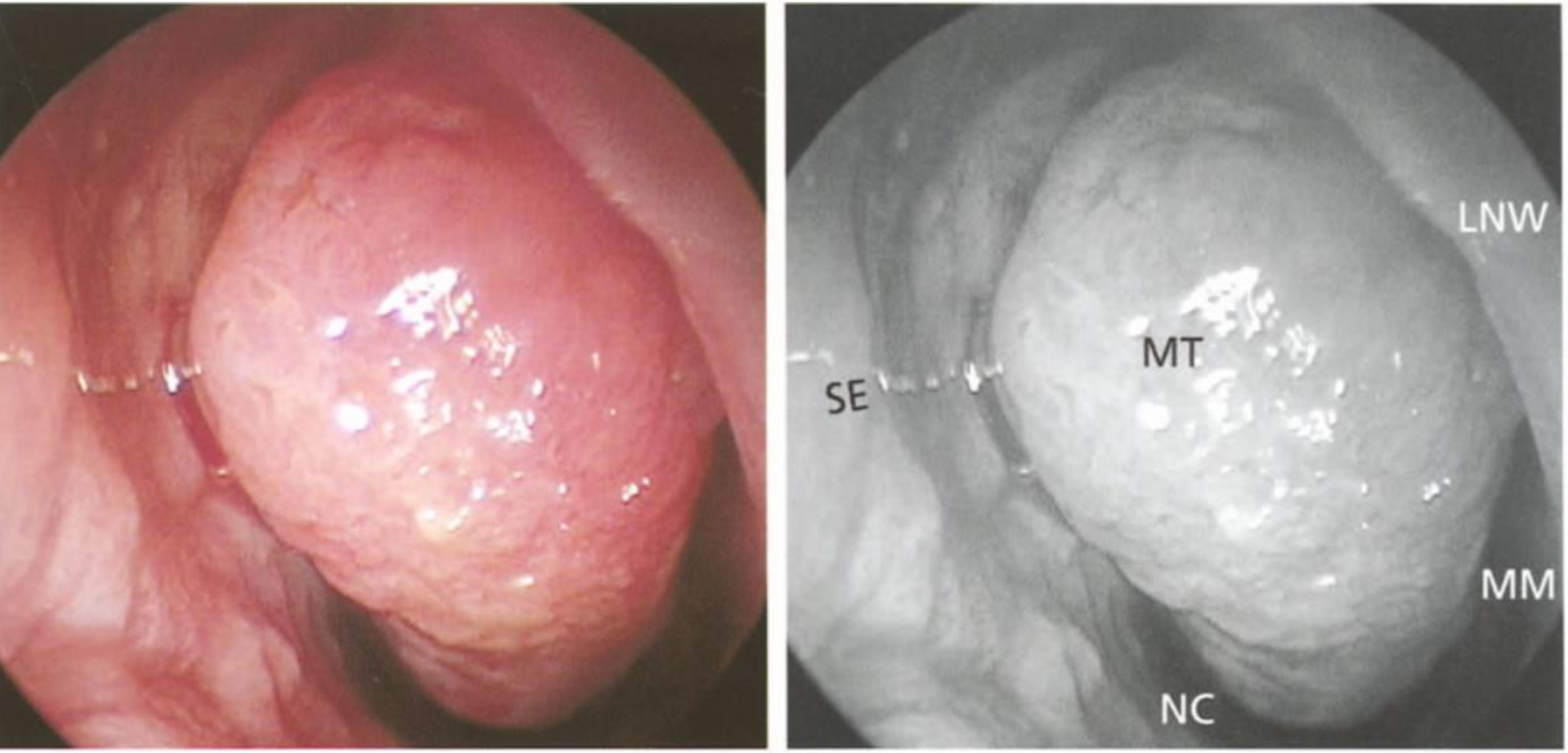


Fig. 2.9. Left side, zero degree lens, large concha bulla with polypoid change.



ig. 2.11. Left side, zero degree lens, mulberry-type polypoid change with partially closed
niddle meatus.

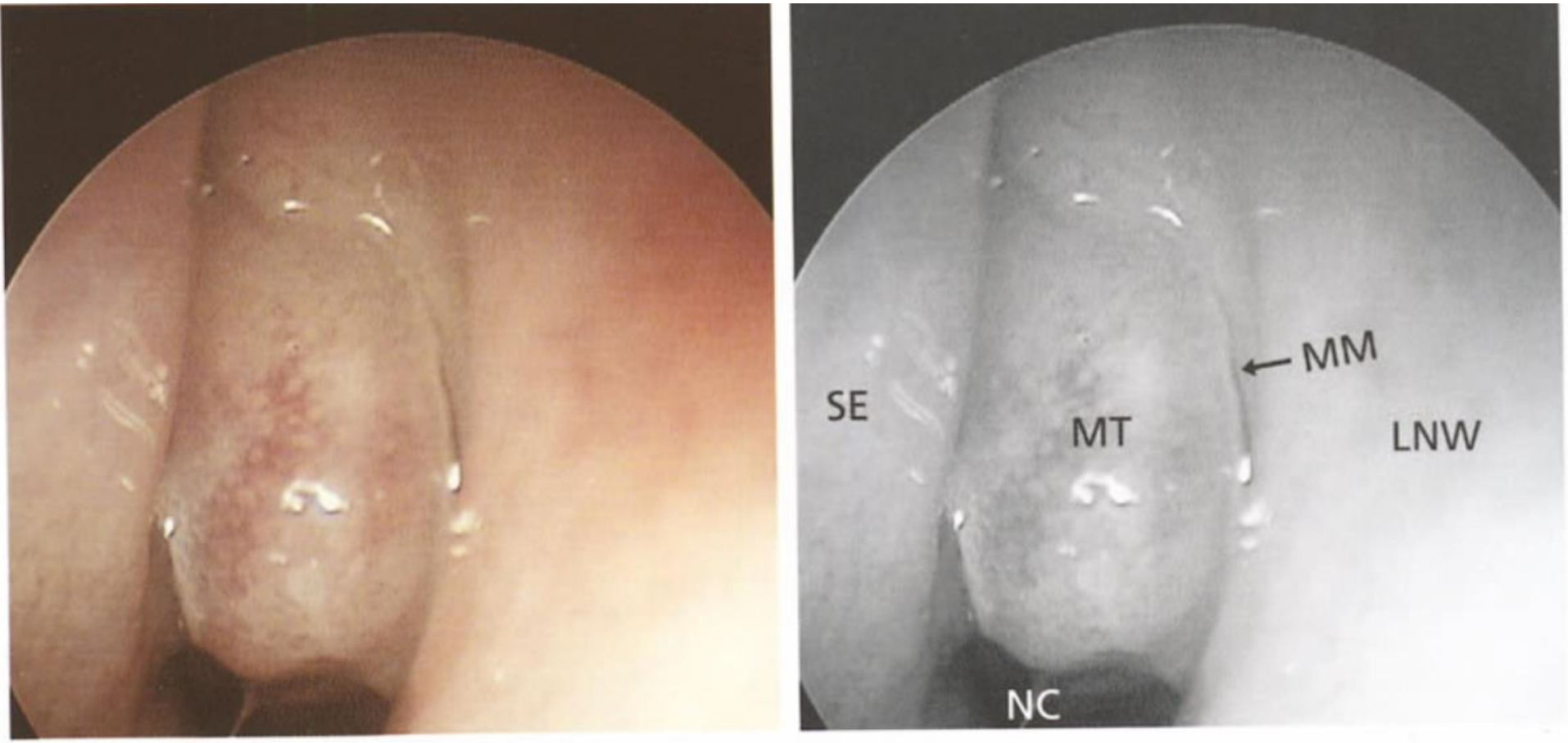


Fig. 2.18. Left side, zero degree lens, inflammation of middle turbinate with polypoid upper middle meatus.

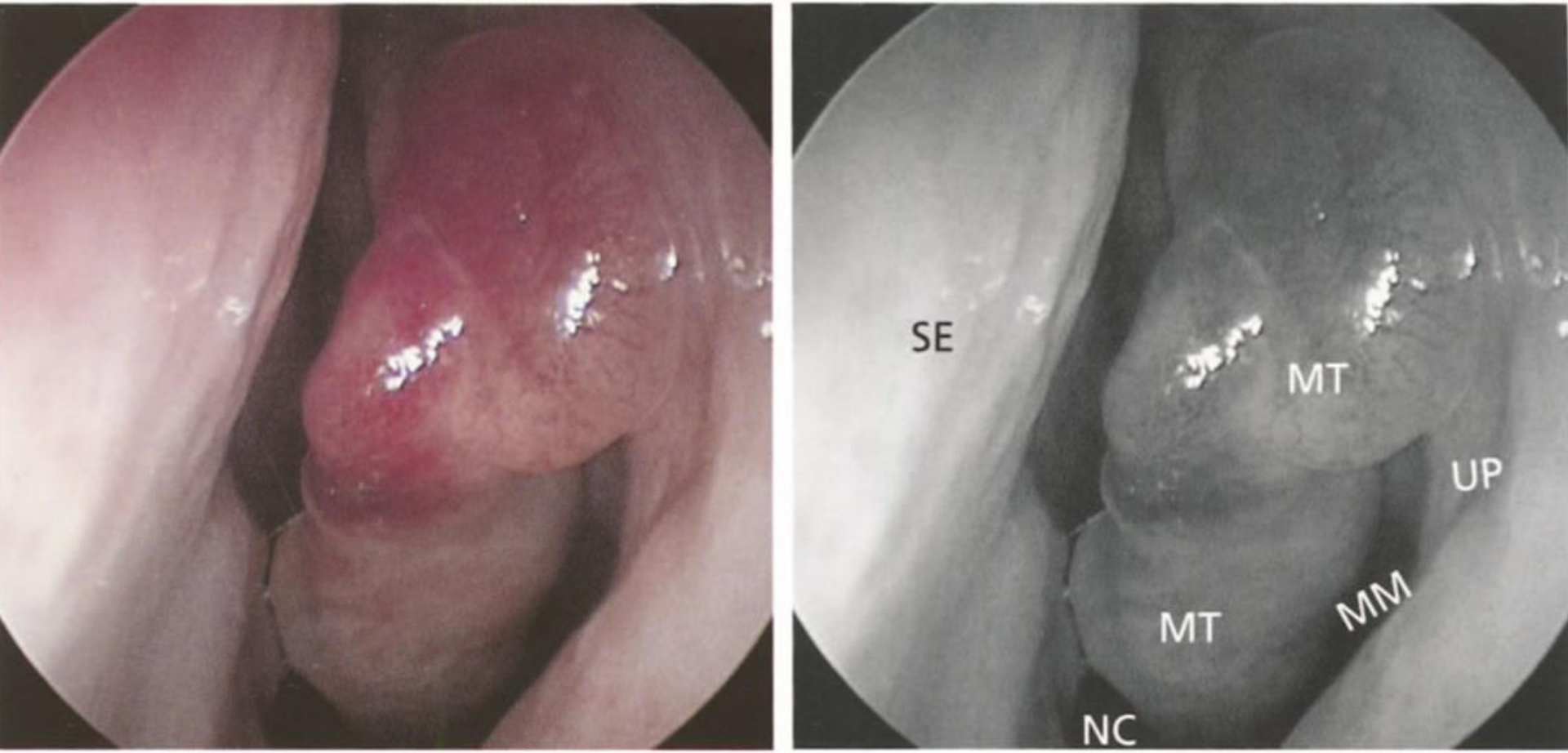


Fig. 2.19. Left side, zero degree lens, vascular polyp middle turbinate.

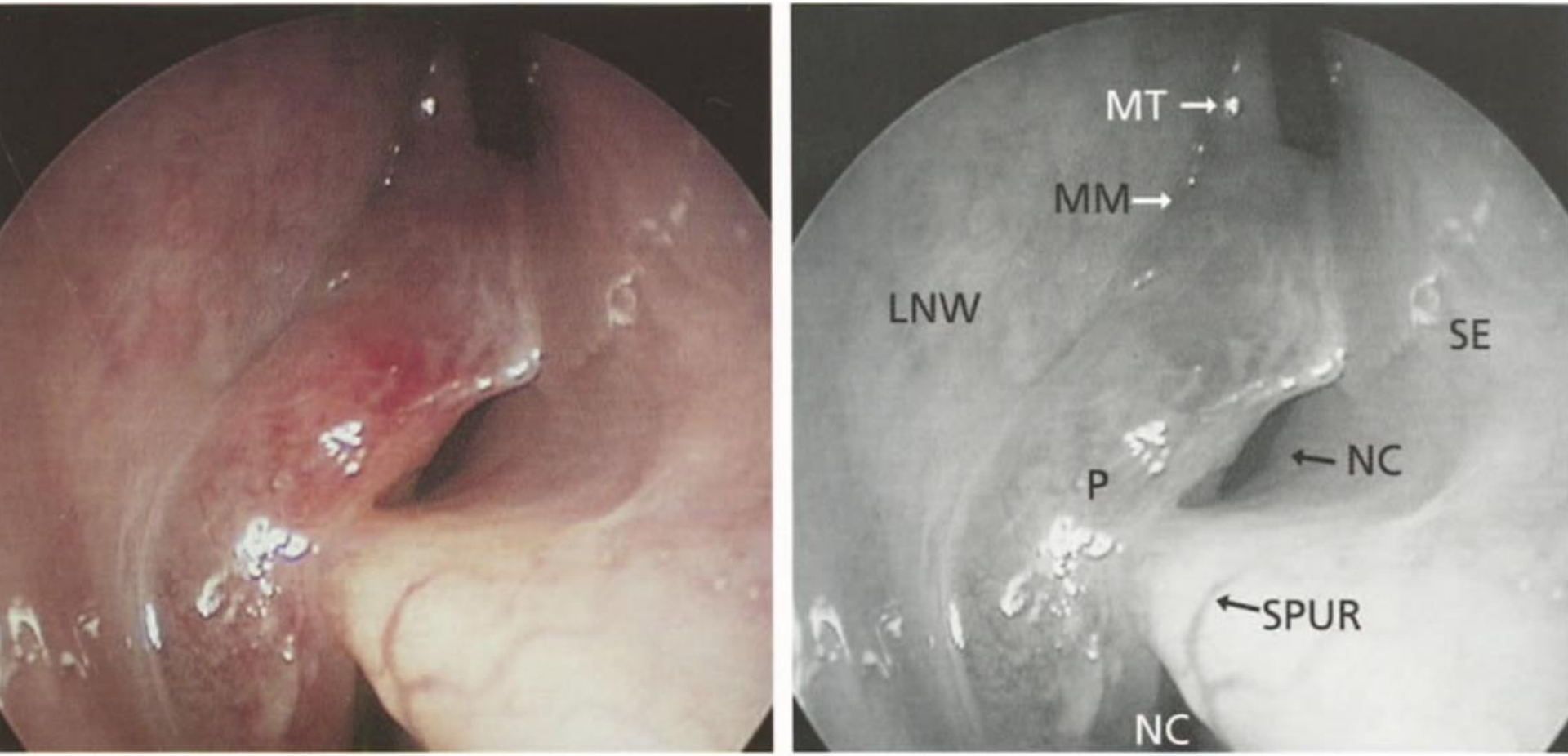


Fig. 2.21. Right side, zero degree lens, superior attachment of the middle turbinate visible
t 12 o'clock, septal spur and polyp anteriorly.

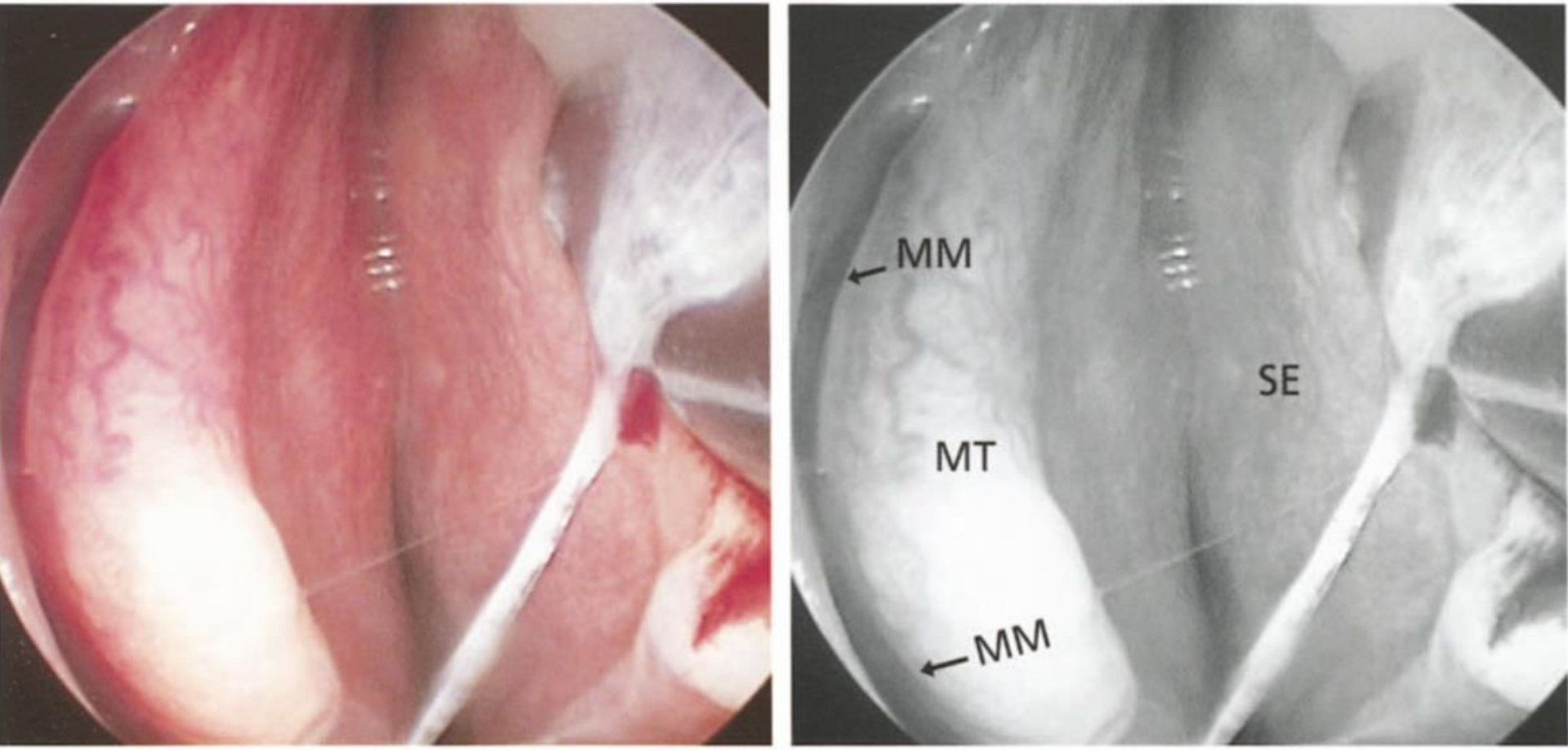
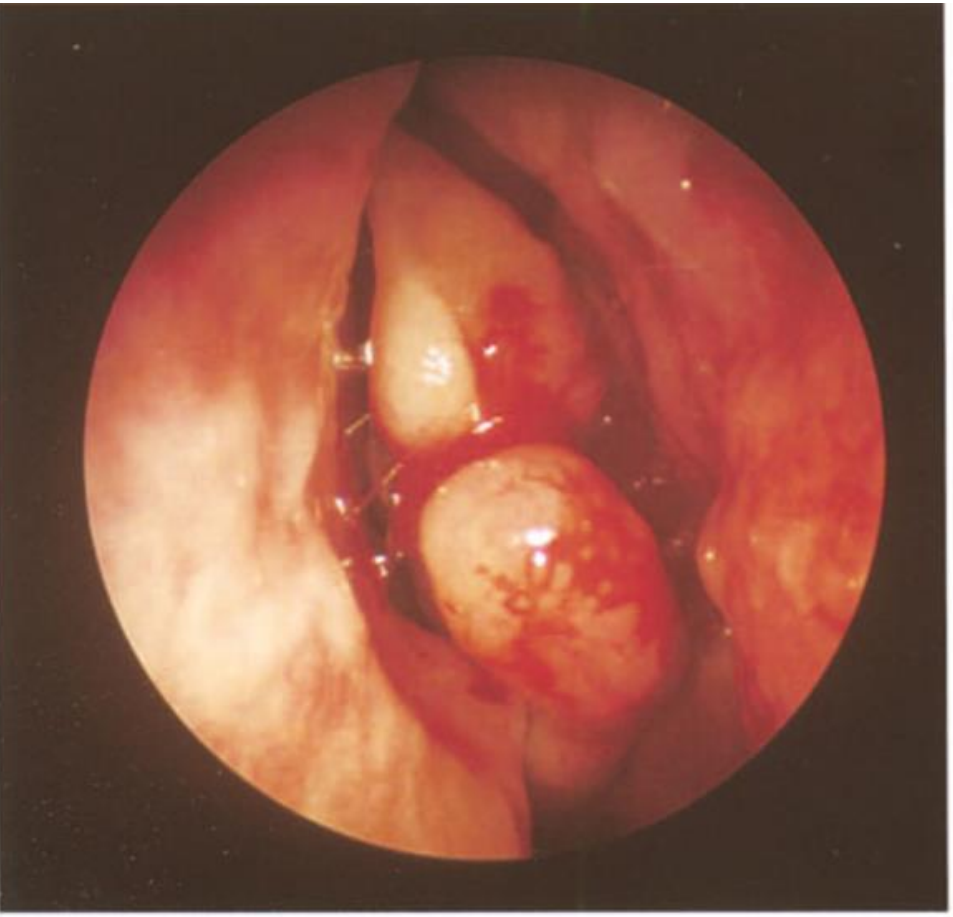


Fig. 2.24. Right side, zero degree lens, inflammatory mucosa in association with septal pressure relieved by Adson elevator. Remaining contact between middle turbinate and septum in center of picture. Septum pushed away from turbinate by Adson elevator.



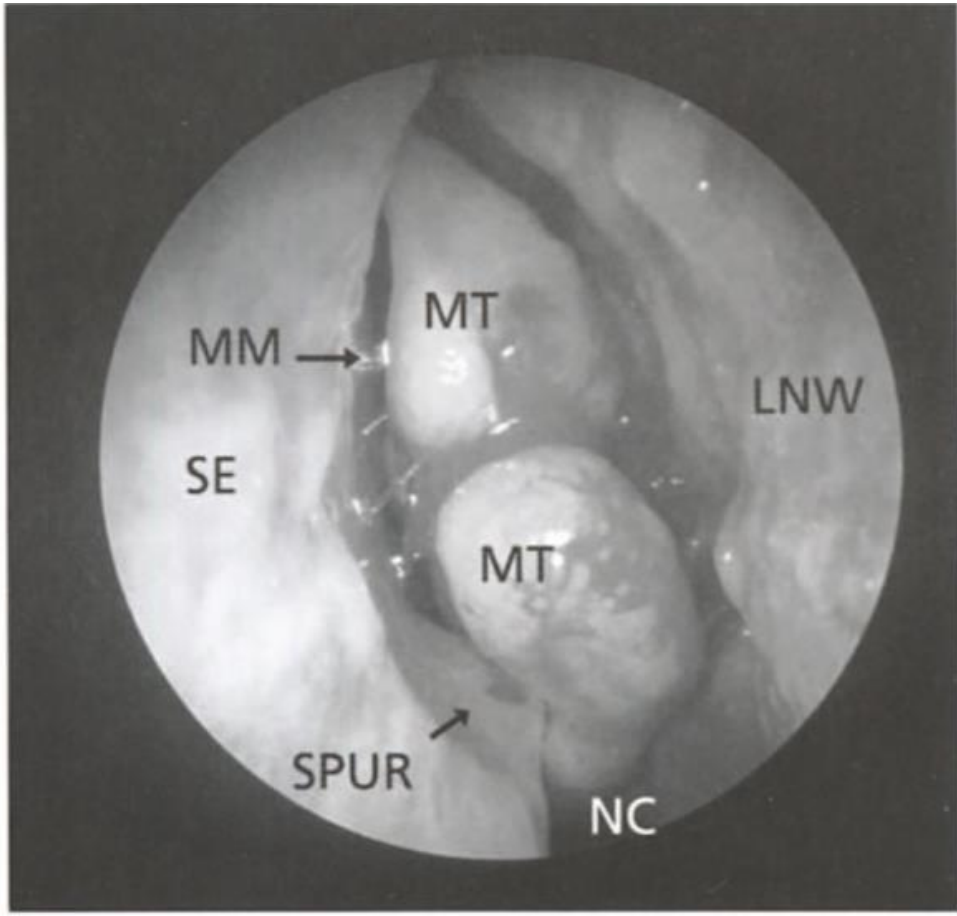
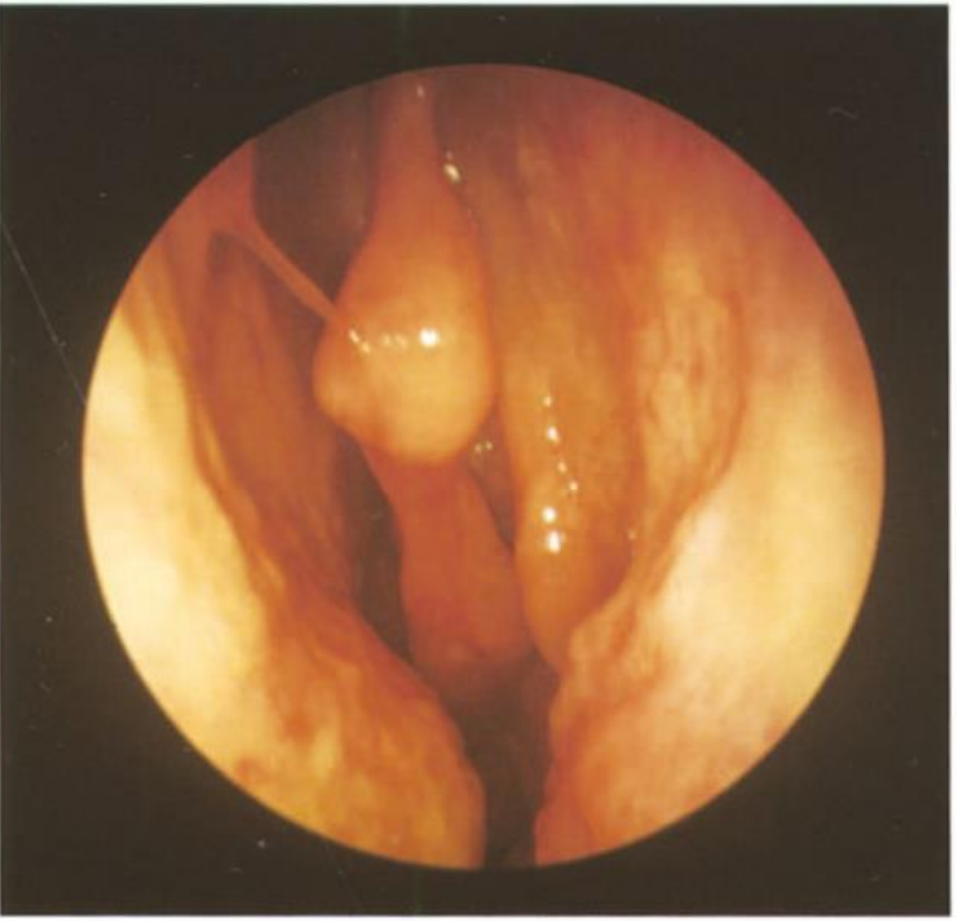


Fig. 2.28. Left side, zero degree lens, "double" middle turbinate-horizontal plane and septal spur.



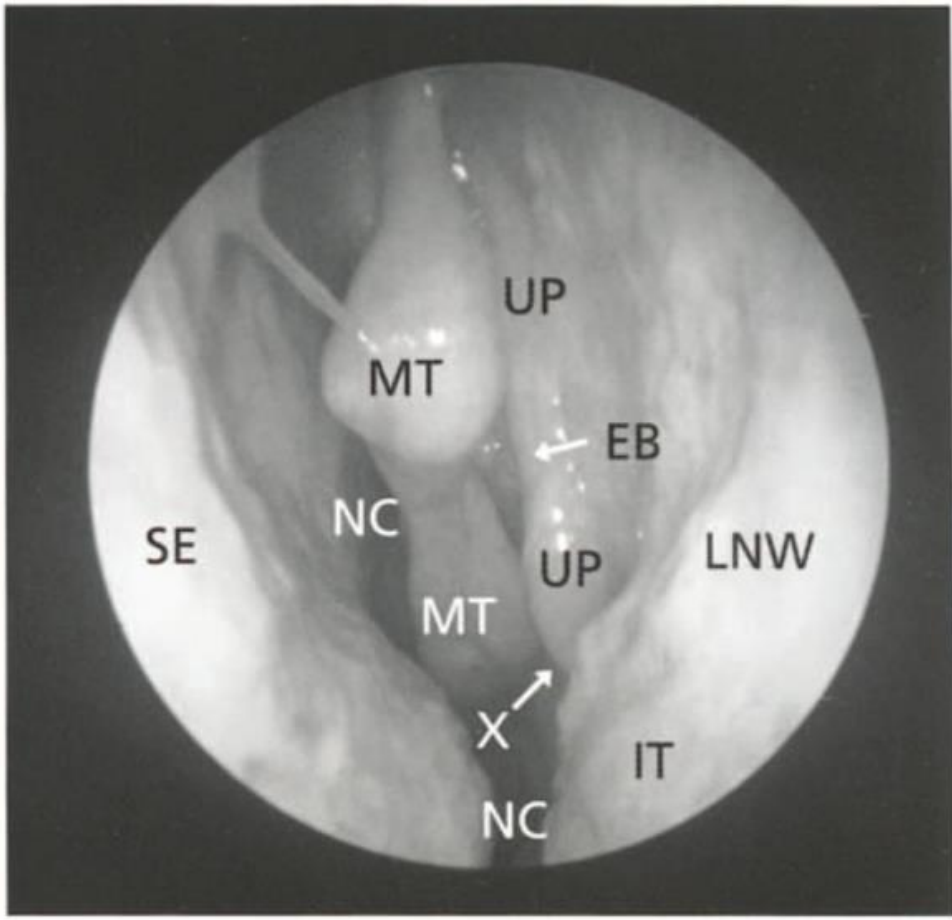
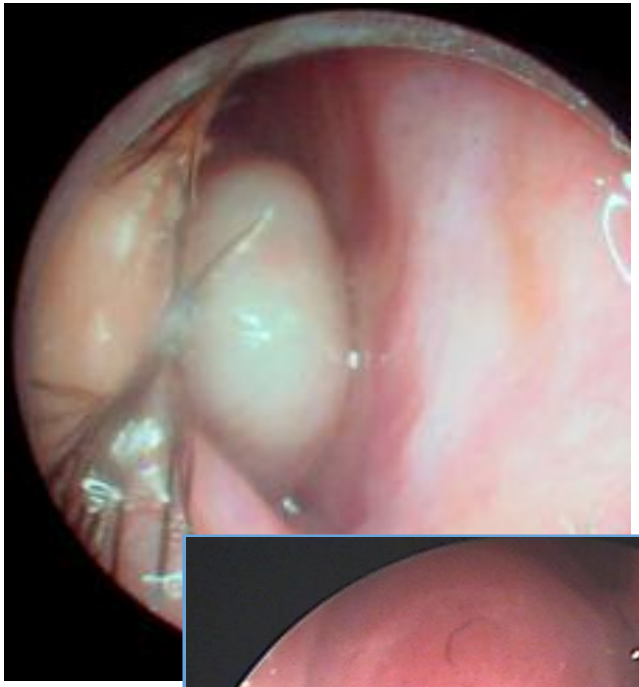
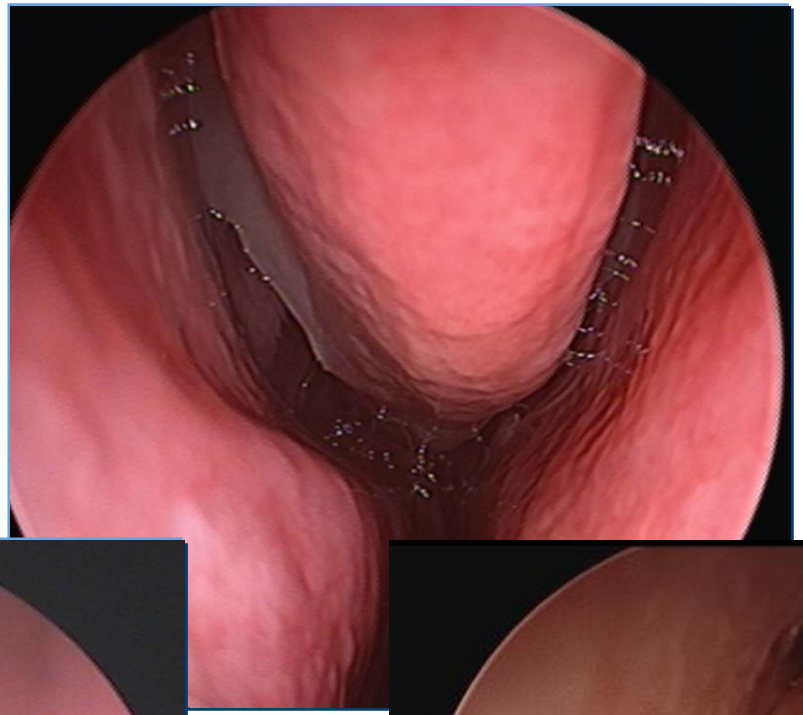
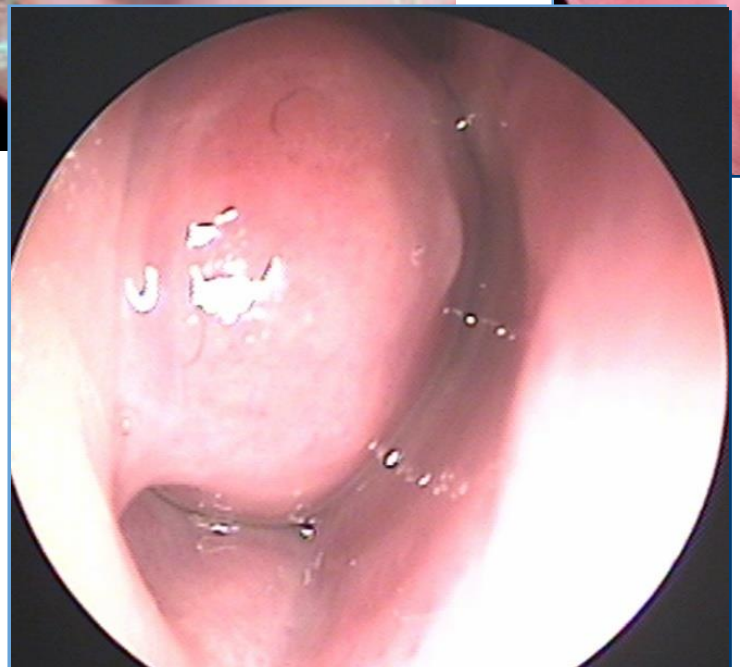


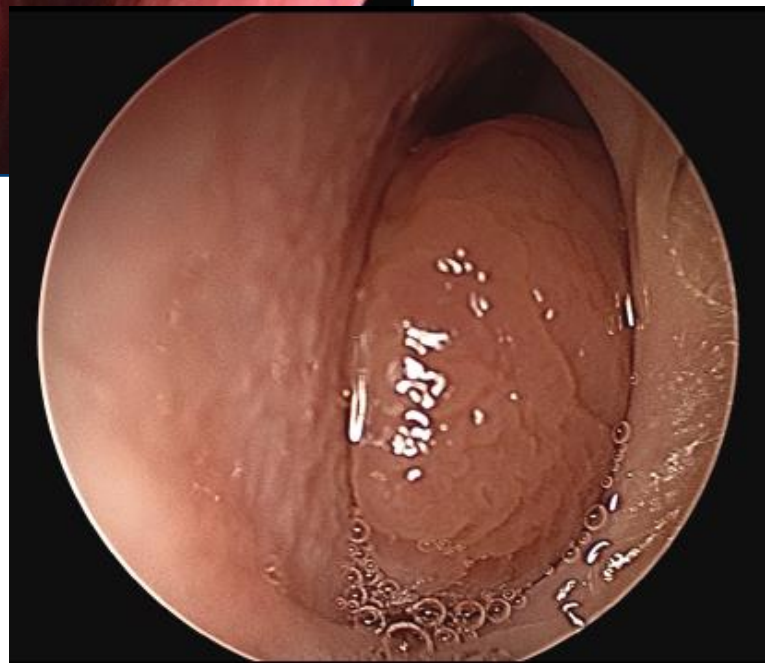
Fig. 2.33. Left side, zero degree lens, healed partial resection of middle turbinate.

Diversity of allergic mucosa









Aim of Surgical Treatment in AR

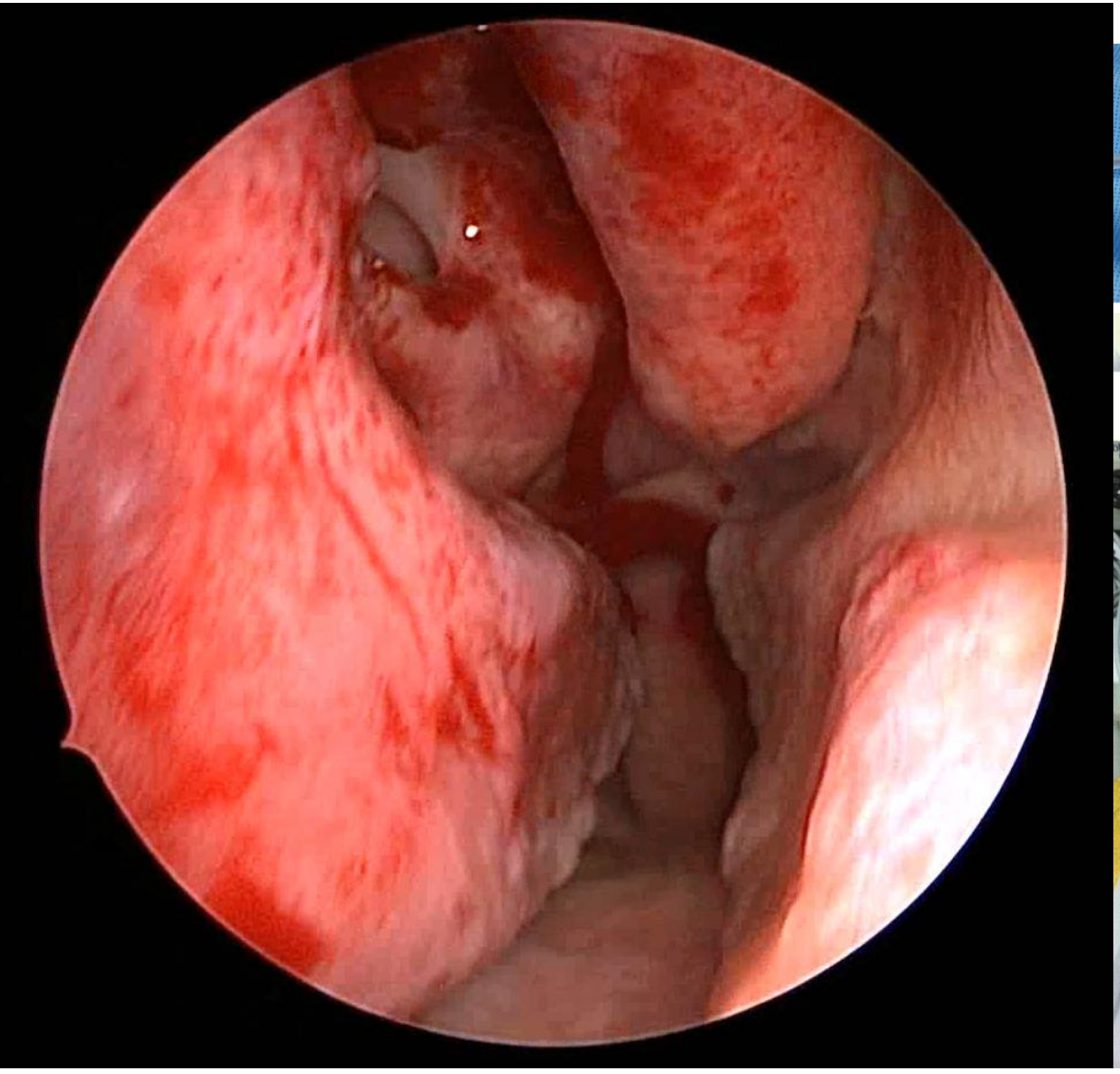
- Alleviating nasal obstruction
  to better reduce static obstruction
  while improving compliance of the nasal passages

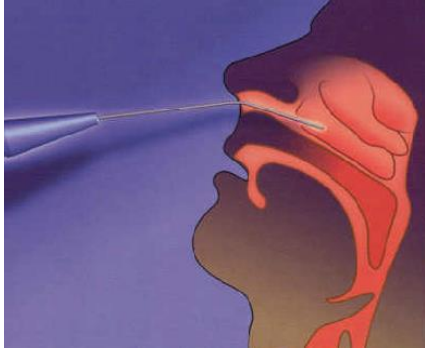
Surgical management

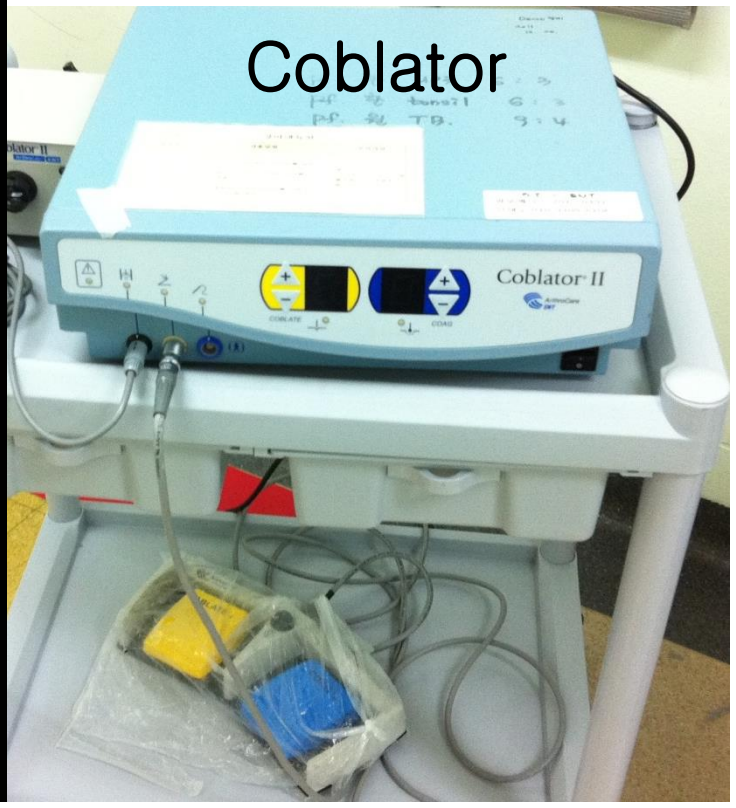
1. Turbinate surgery

2. Septoplasty

Radiofrequency ablation



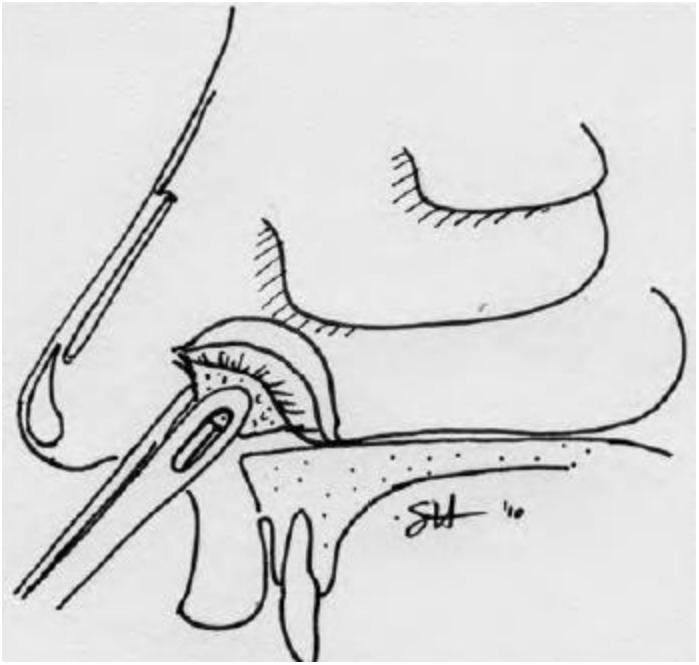


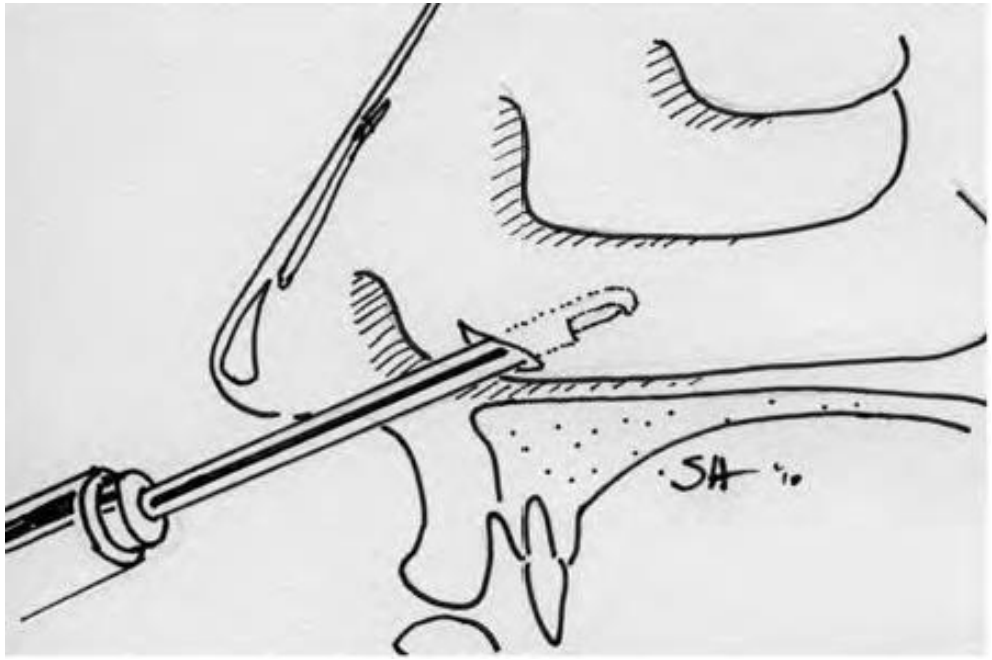


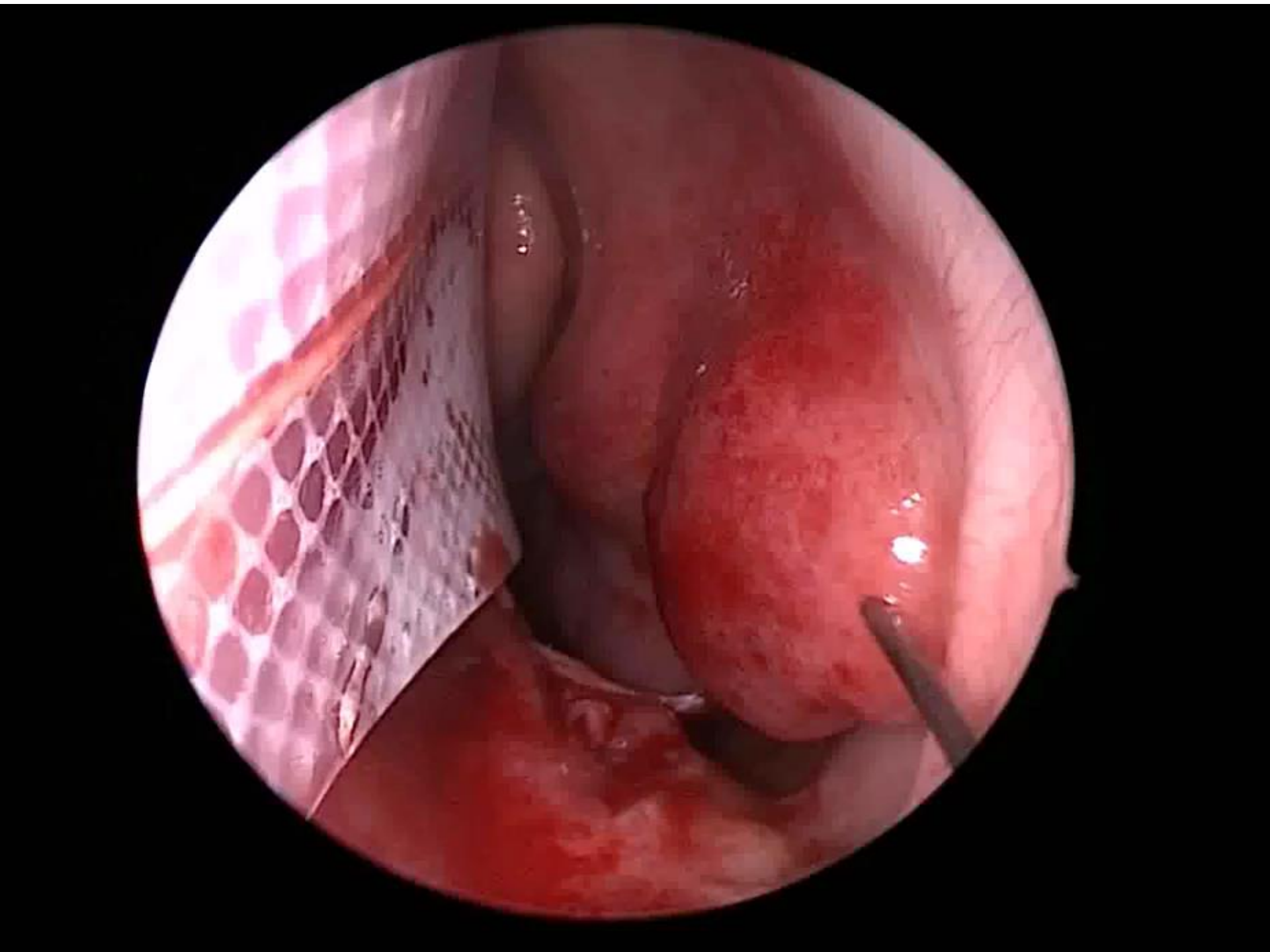
Microdebrider reduction

- To reduce bulky inflammatory tissue, while maximally preserving overlying mucosa

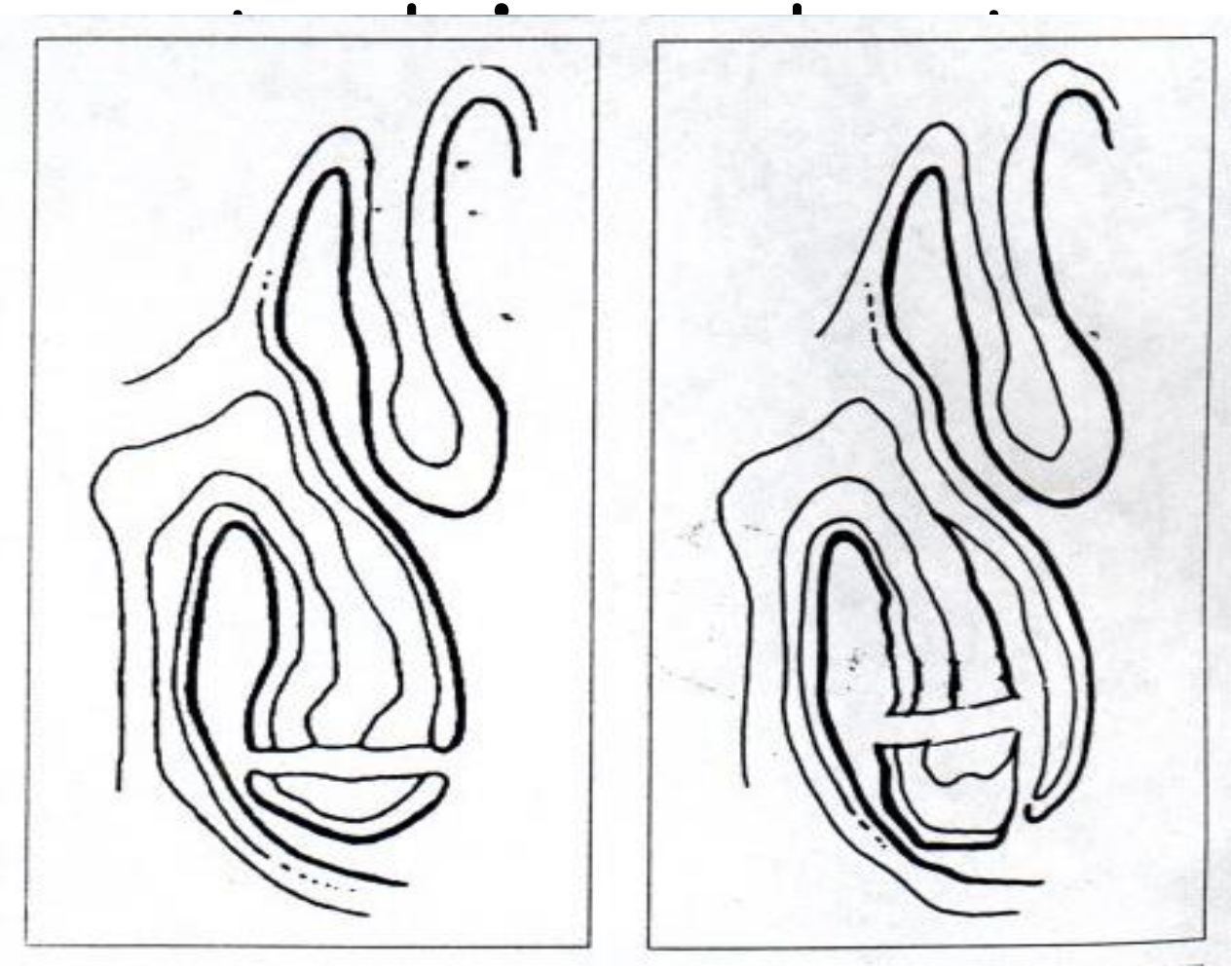
- Microdebrider technique

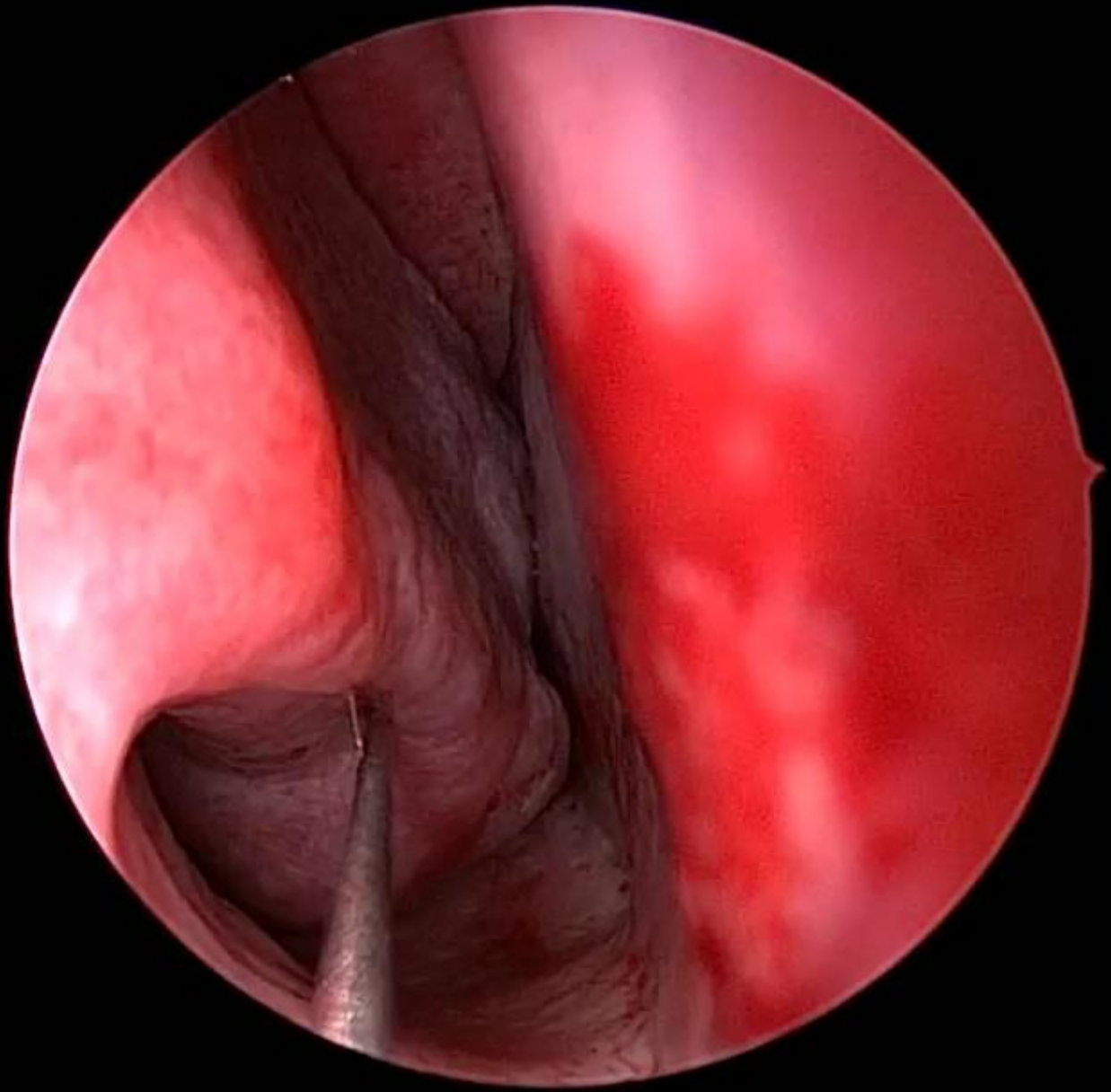




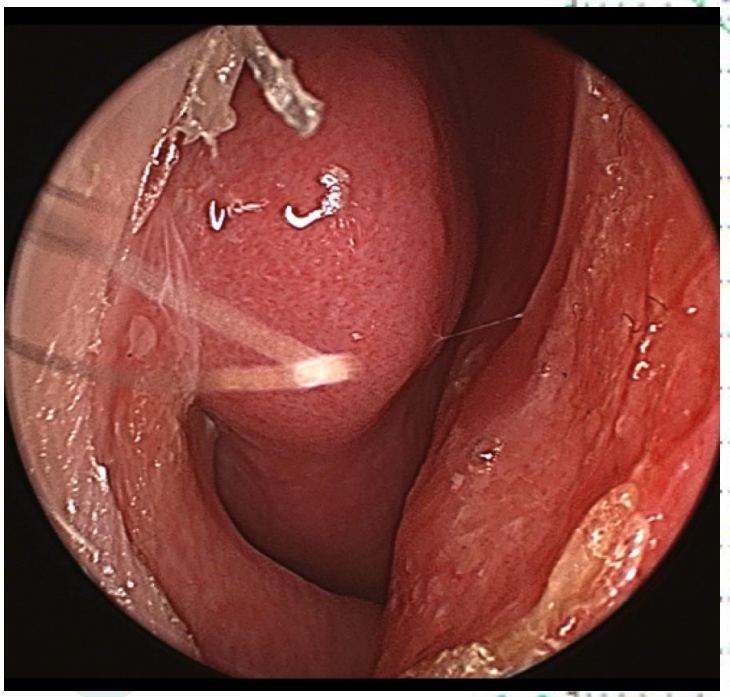


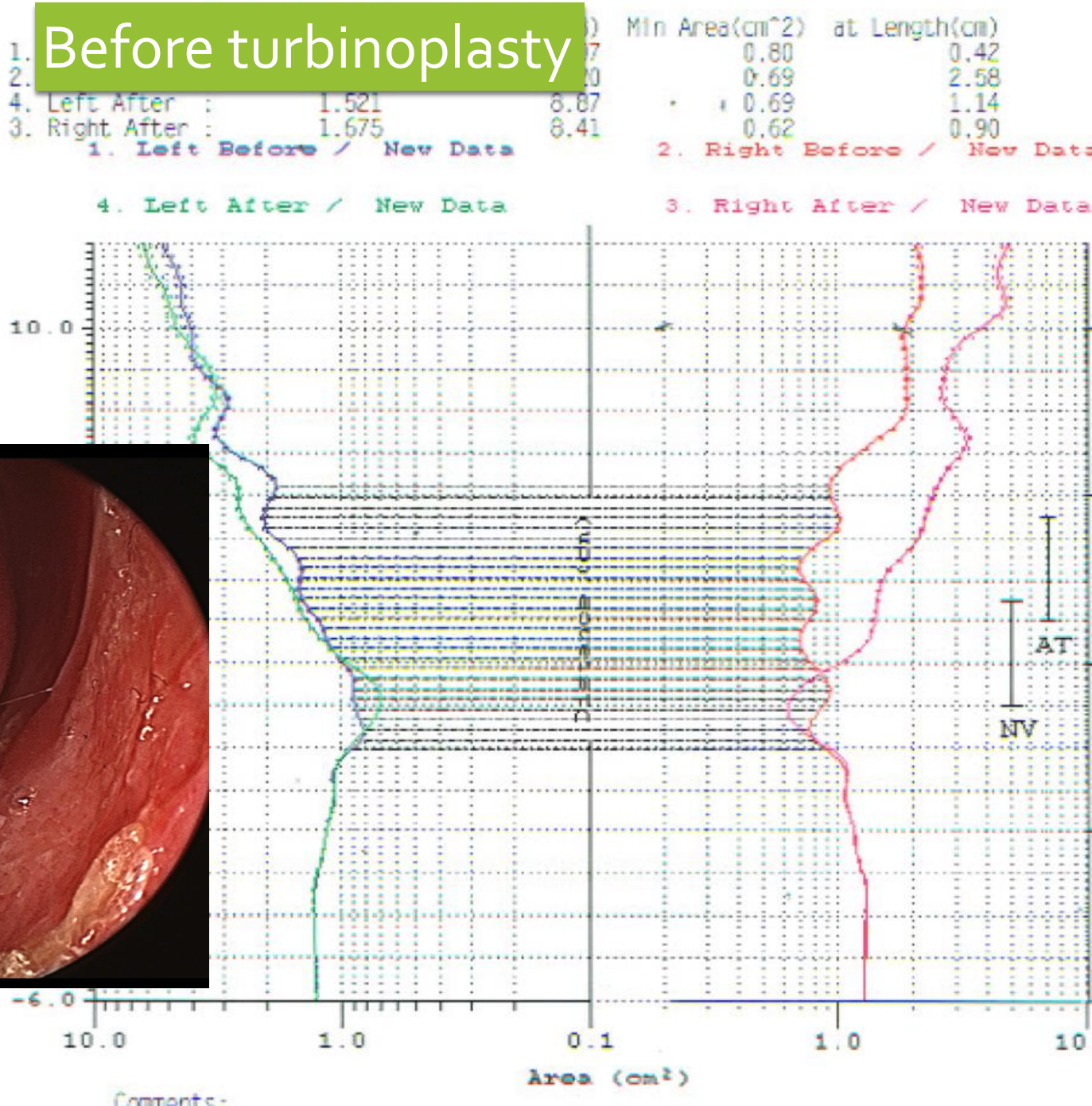
Submucosal



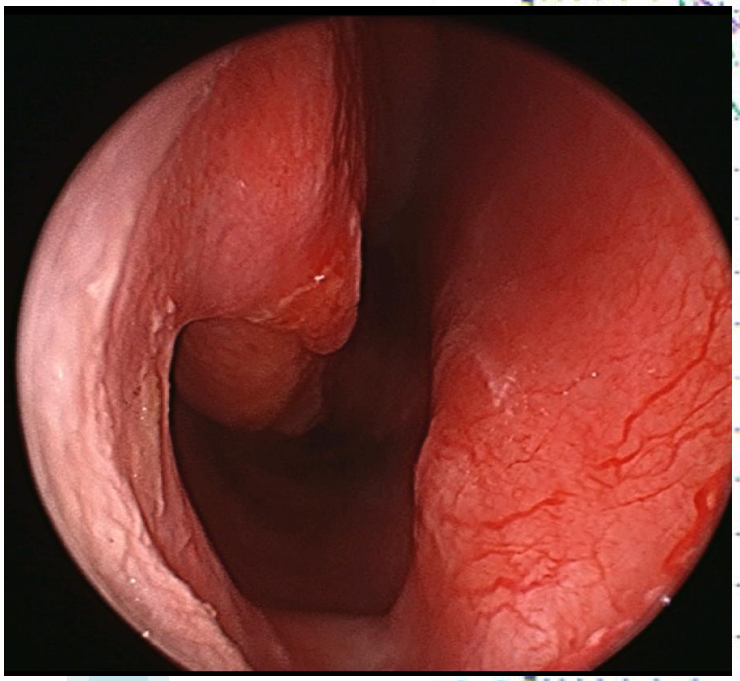


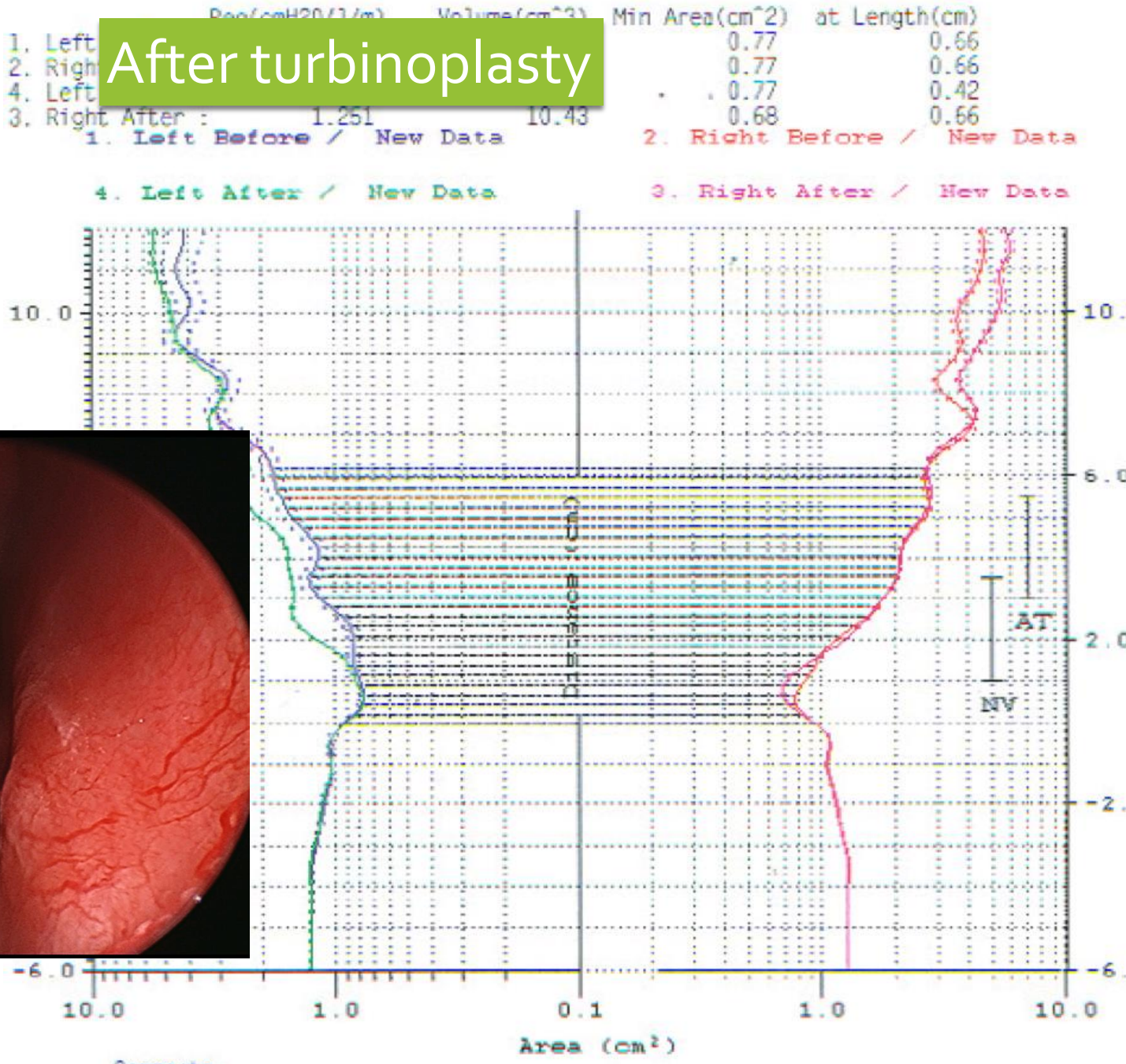
Before turbinoplasty



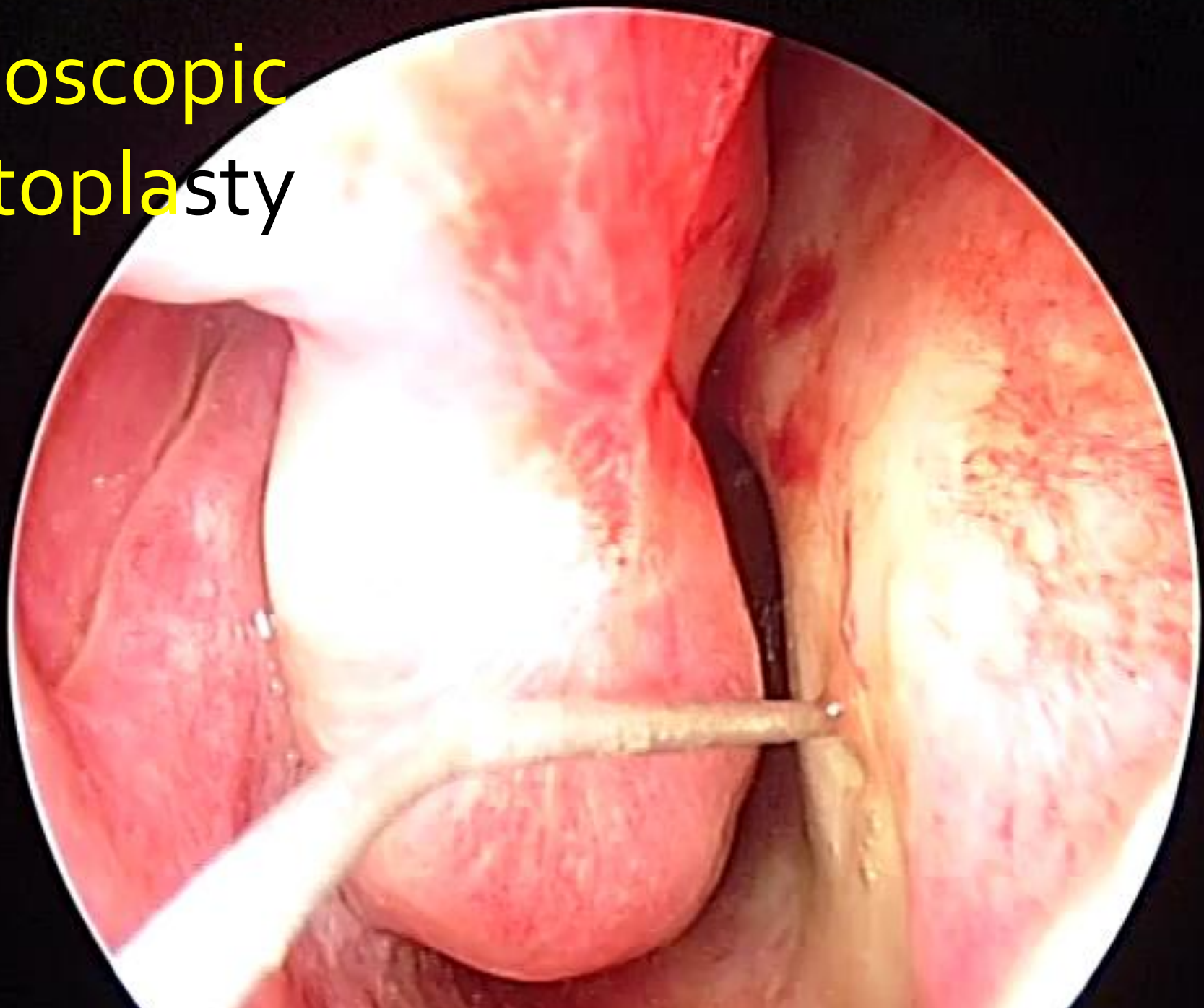


After turbinoplasty





Endoscopic septoplasty



The long term efficacy of turbinoplasty versus medication in allergic rhinitis

- 알레르기 비염 환자에서 수술적 치료와 약물 치료 시행 시 2년 이후의 치료 성적을 비교

Inclusion & Exclusion criteria

- 2010년 1월 ~ 2011년 12월

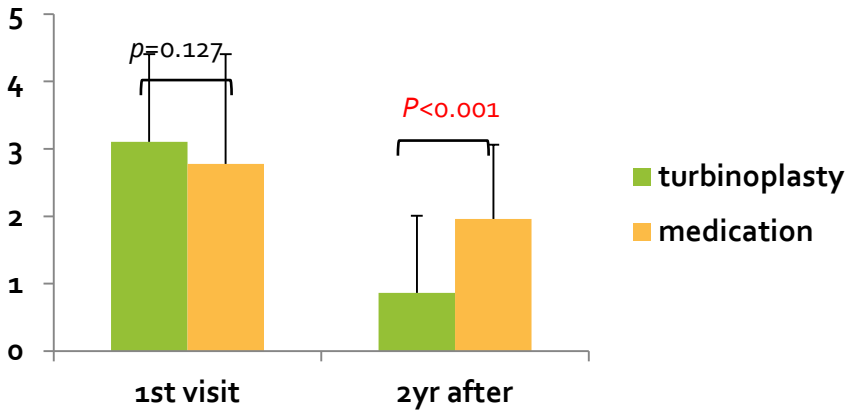
Allergic rhinitis 증상을 주소로 내원한 환자 중 skin test상 3+이상 혹은 3mm이상 보이는 환자

  - Group A (n=155) : Septoturbinoplasty or Turbinoplasty 를 시행한 환자
  - Group B (n=77) : medication 만 시행한 환자

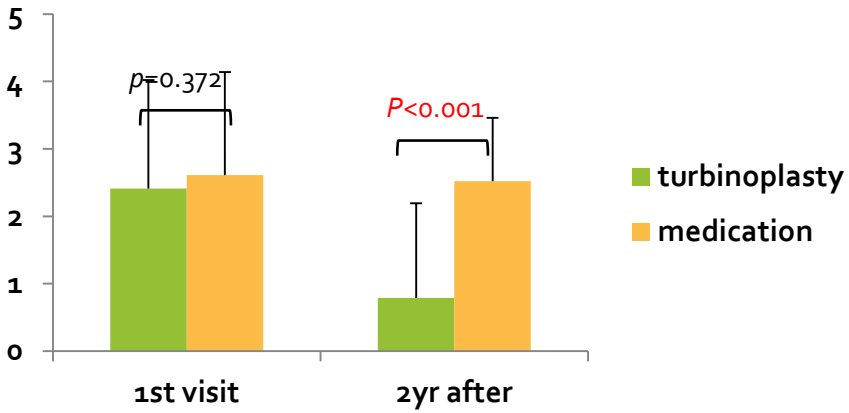
- ESS를 시행받은 환자는 제외함

Allergic symptoms

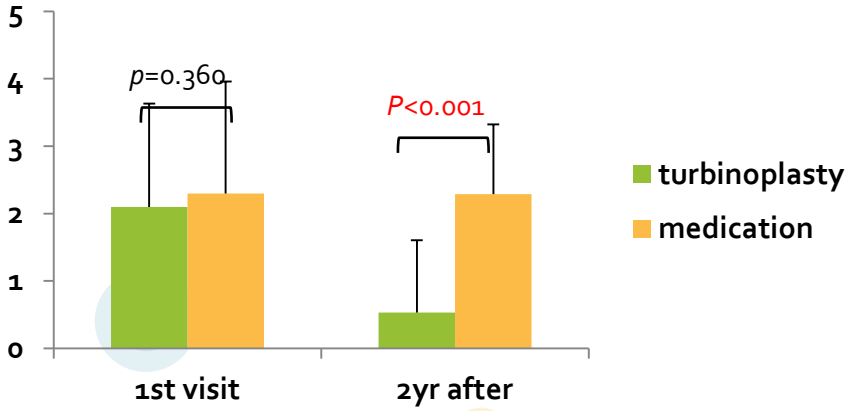
nasal obstruction



Rhinorrhea



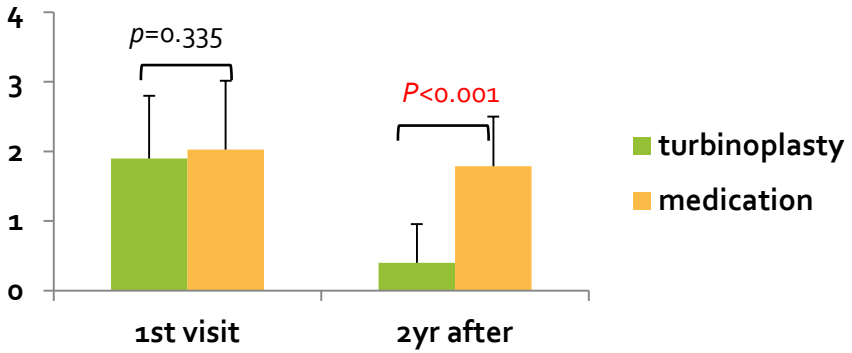
Sneezing



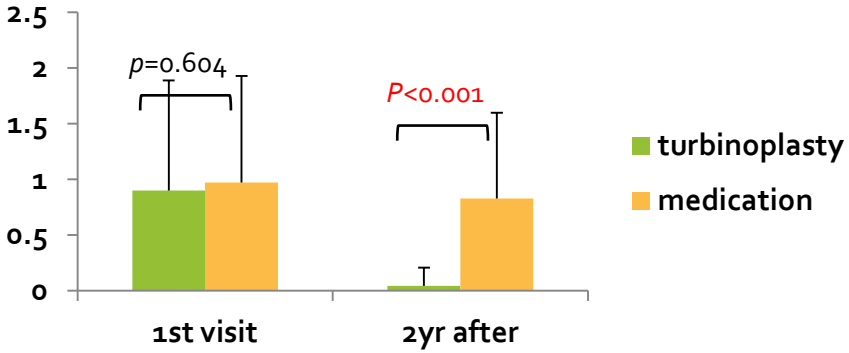
Independent t test

SNOT-20

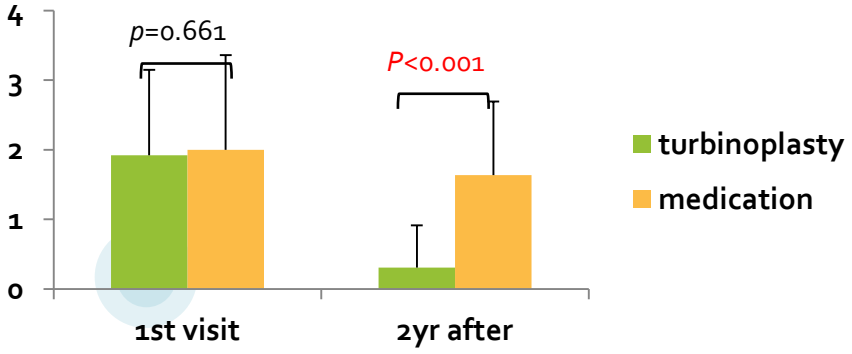
SNOT-20
-Rhinologic domain-



SNOT-20
-Otologic/facial domain-



SNOT-20
-Sleep domain-



Independent t test

Take Home Messages (II)

- Surgical management can be helpful in selected patients with AR

- Long term effects can be obtained with proper surgical management of AR

Thank You!