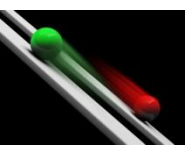


# **18. St. Galler Infekttag**

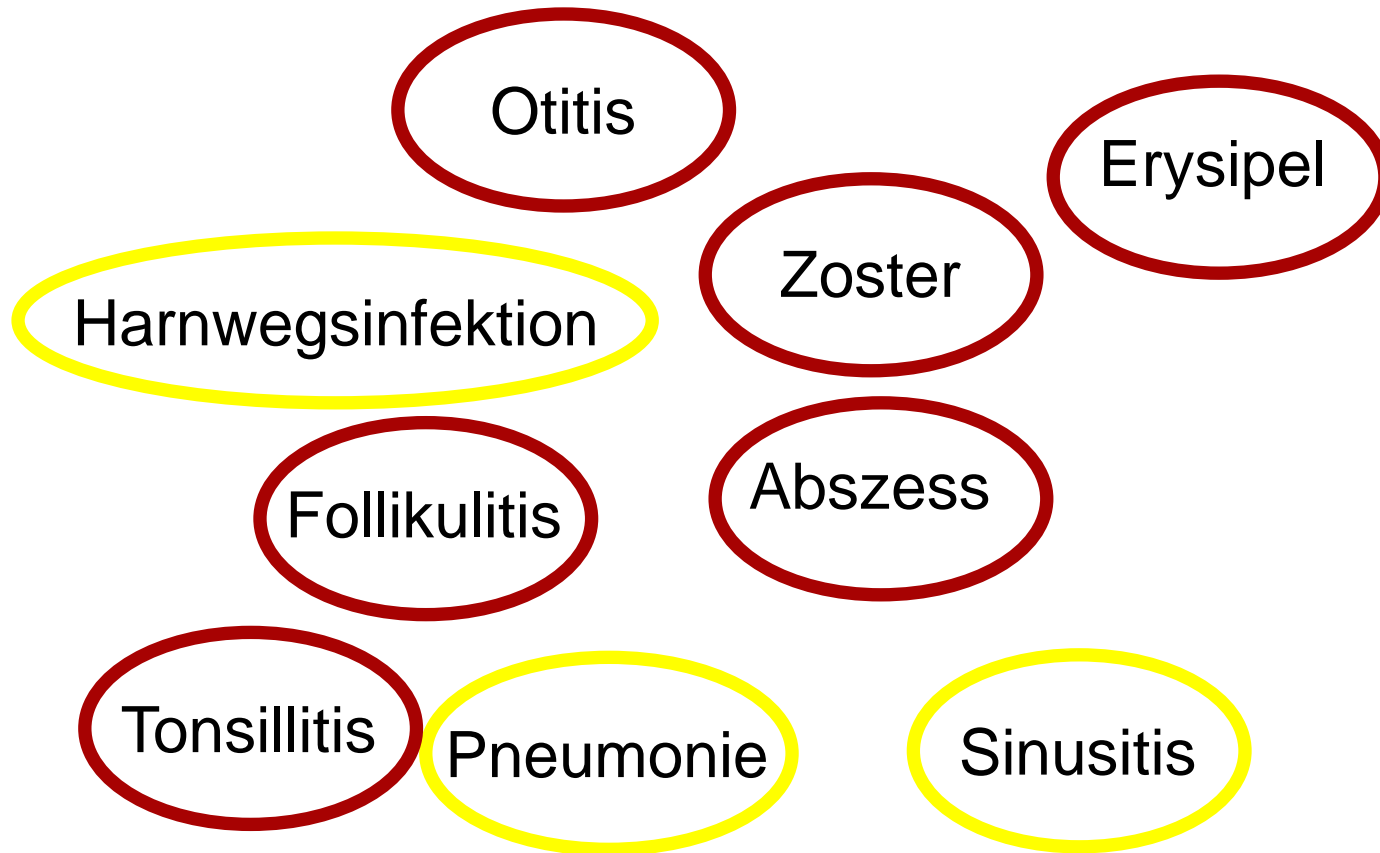
## **Rezidivierende Infekte in welche Richtung soll's gehen (Trends)**

**28. Februar 2013**

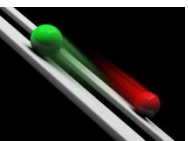
**Dr. Christine Gutmann**



# Was gibt es alles.....

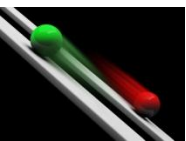


...und noch viel mehr....



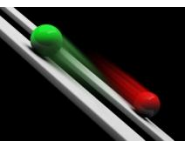
# Definitionen

- **Rezidivierende Infektionen (Definiert bei HWI)**
  - $\geq 2$  Infektionen in 6 Monaten
  - $\geq 3$  Infektionen in 12 Monaten
- **Relapse:** innerhalb 14 Tage nach Stopp einer adäquaten antibiotischen Therapie, gleicher Keim
- **Reinfektion:**  $\geq 14$  Tage nach Stopp einer adäquaten Therapie, gleicher oder anderer Keim



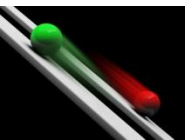
# Fallbeispiel:

- **30 - jährige Frau, seit 2 Tagen Dysurie, Pollakisurie, Urgesymptomatik, kein vaginaler Ausfluss, kein Fieber, keine Flankenschmerzen.**
- **Vor 1 Monat während 3 Tagen wegen einer Cystitis Bactrim per os eingenommen.**
- **Ansonsten gesund, aber 3 solche Episoden im letzten Jahr.**



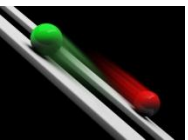
# Fallbeispiel:

- **62 – jährige Frau, seit 3 Tagen Dysurie, Pollakisurie, suprapubische Schmerzen, kein Fieber, keine Flankenschmerzen**
- **Diabetes mellitus**
- **Vor einem halben Jahr dieselben Beschwerden**



# Frage zu Fallbeispiel

**Was denken Sie bei diesen Anamnesen?**



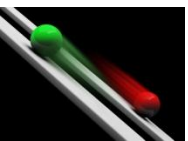
# Fallbeispiel

**A: Ein häufiges Problem, kenne ich aus meiner Praxis**

**B: Bei beiden Frauen liegen sicher anatomische Abnormitäten vor**

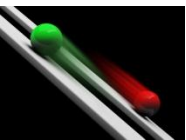
**C: Es handelt sich um multiresistente Erreger**

**D: Ich gebe nicht - steroidale Antirheumatika**



# **(Rezidivierende) Harnwegsinfektionen**

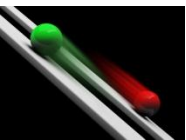
- **Mehr als die Hälfte aller Frauen hat mindestens 1 x in ihrem Leben eine Harnwegsinfektion**
  - **25% der Betroffenen haben eine 2. Infektion innerhalb 6 Monaten**
  - **25 bis 50% der Betroffenen haben eine 2. Infektion nach 12 Monaten**



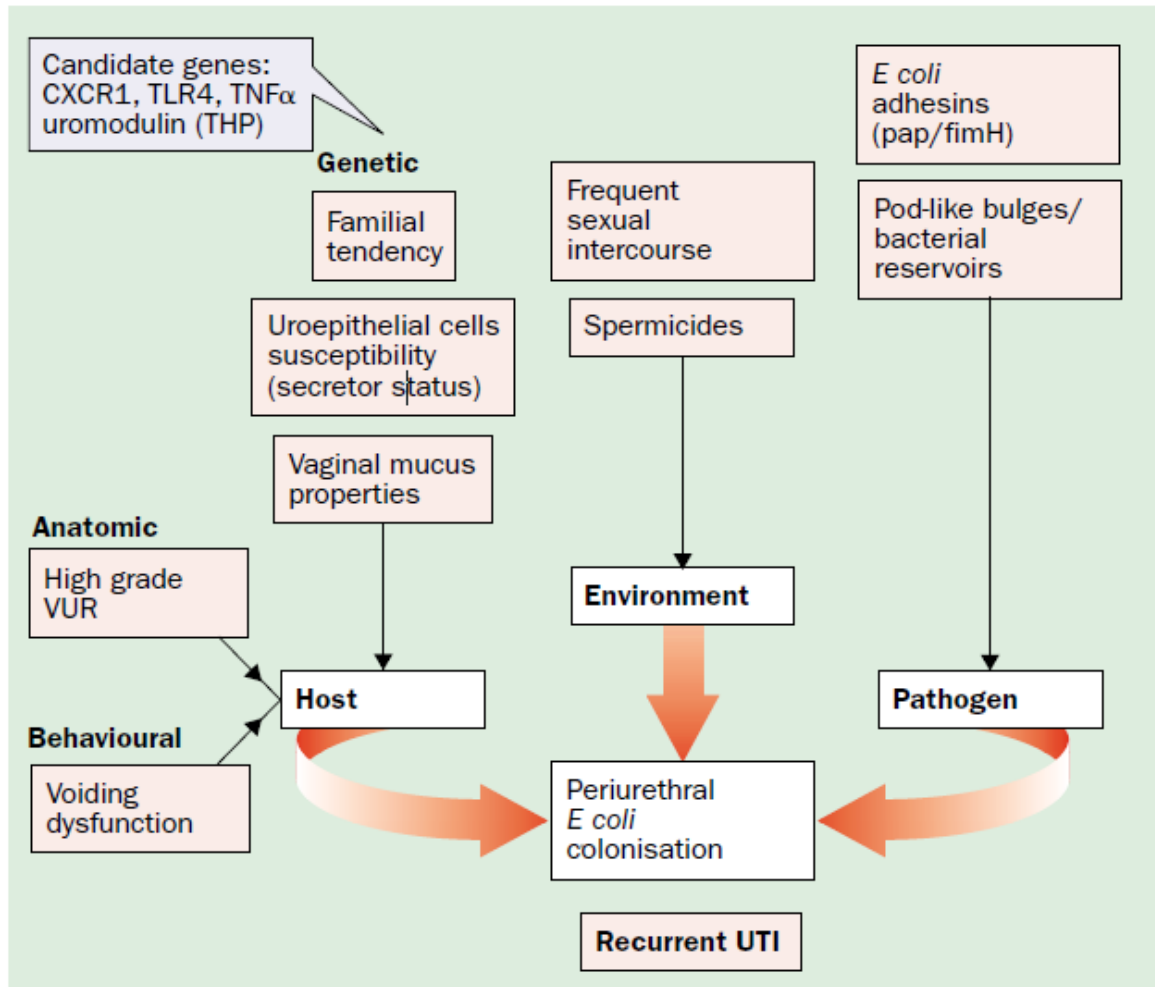


# Rezidivierende Harnwegsinfektionen

- **Problem für die betroffenen Frauen**  
(Weltbevölkerung am 01.01.2013: 7.111.960.000 Menschen)
- **Problem für den Hausarzt**
- **Problem Kosten: USA 3.5 Mrd \$ /J.**
- **Problem «Kollateralschaden»**  
(verursacht durch Behandlung)
- **Problem Resistenzen (verursacht durch Behandlung)**



# Pathophysiologie

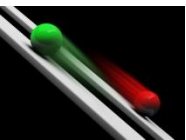
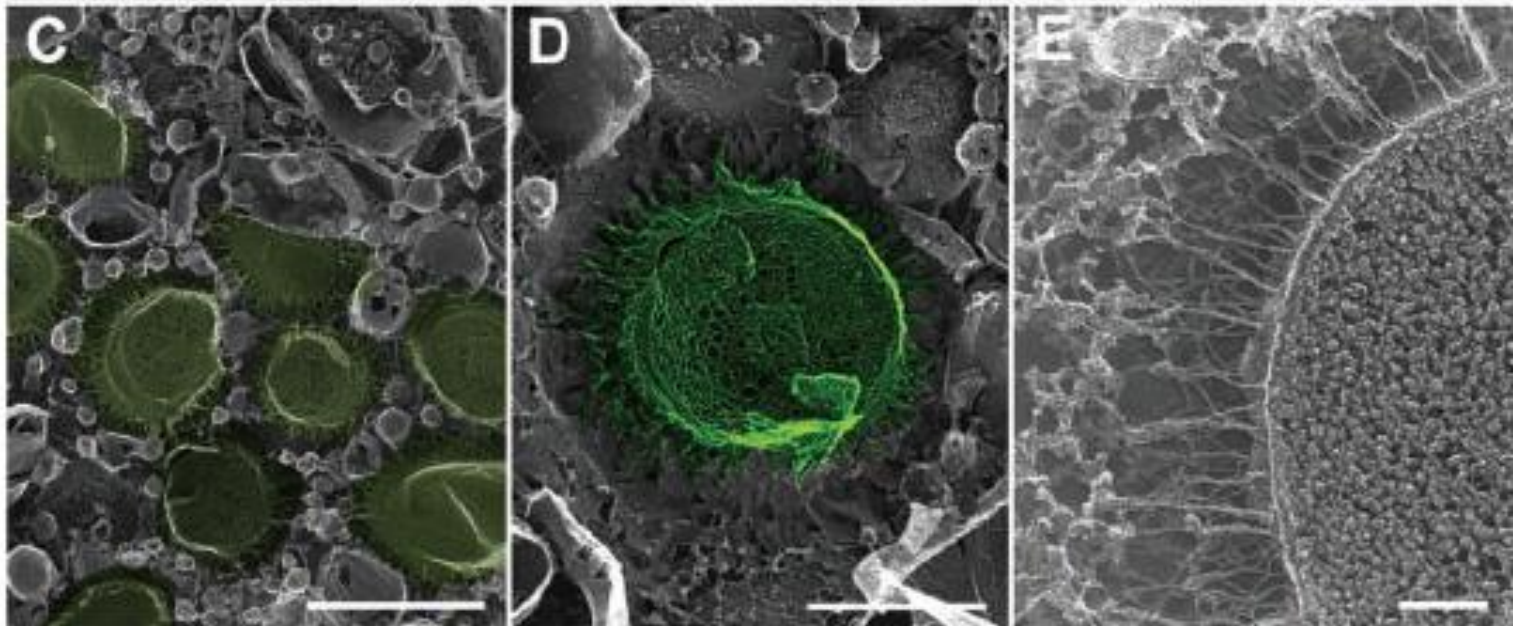


Pathophysiology model for recurrent UTI. CXCR1=interleukin-8 receptor; THP=Tamm Horsfall protein; TLR4=toll-like receptor-4; VUR=vesicoureteric reflux

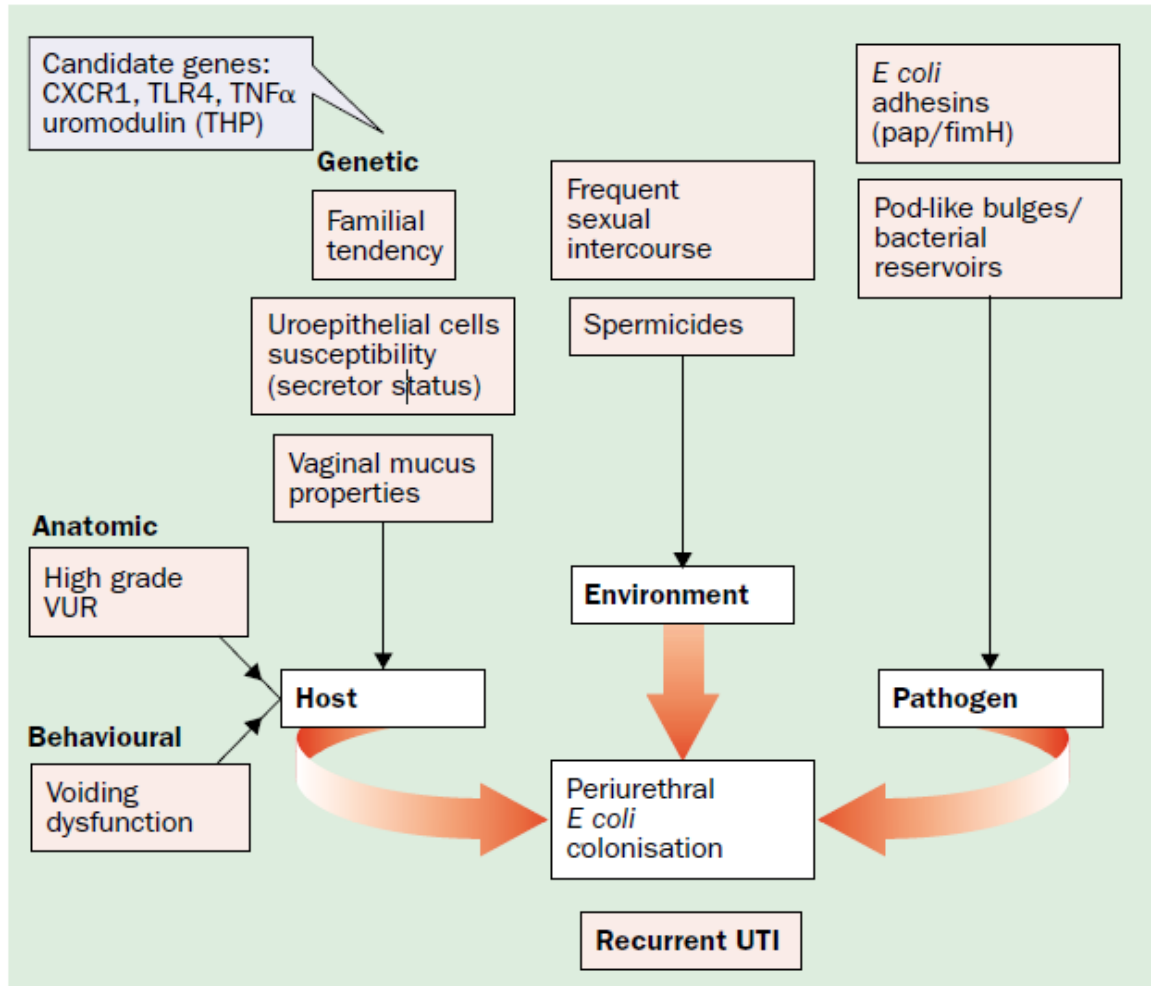
The Lancet Infectious Disease Vol 4, Oct.2004

# Trends

*E. coli*, fimH



# Pathophysiologie



Pathophysiology model for recurrent UTI. CXCR1=interleukin-8 receptor; THP=Tamm Horsfall protein; TLR4=toll-like receptor-4; VUR=vesicoureteric reflux

The Lancet Infectious Disease Vol 4, Oct.2004

# Risikofaktoren

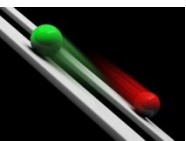
## Prämenopausal

- Geschlechtsverkehr
- Spermizide
- Neuer Sexualpartner
- St. n. HWI < 15 jährig
- HWI bei der Mutter

Anatomische  
Veränderungen  
Konkremente

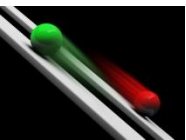
## Postmenopausal

- Vaginalschleimhaut-  
atrophie (Östrogenmangel)
- Inkontinenz
- Rekto-Zysto-  
Urethrozele
- Uterovaginaler  
Prolaps
- Restharn
- St. n. HWI
- D. mellitus



# Nicht bewiesene Risikofaktoren

- Prä - postkoitale Miktion
- Trinkmenge
- Miktionsfrequenz
- «Lange Halten»
- Tampon Gebrauch
- «Putzrichtung»
- Enge Unterwäsche
- Whirlpool
- Hoher BMI



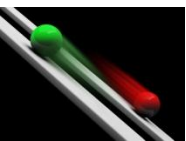
# Diagnostik bei erneuter Infektion

## Prämenopausal

- **Denken Sie auch an weitere Ursachen**  
(STD, Herpes genitalis, bakt. Vaginose...)
- **Urin Status**
- **Urin Kultur**

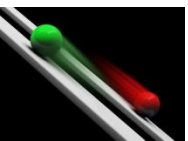
## Postmenopausal

- **Denken Sie auch an andere Ursachen**
- **Urin Status**
- **Urin Kultur**
- **Gynäkologie**
- **Urologie**



# Therapie

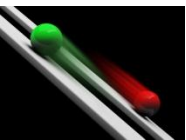
- **Rezidivierende Harnwegsinfektionen sind nicht per se komplizierte Harnwegsinfektionen**
- **Initiales Management gemäss Schema «unkomplizierte Zystitis»**





# Unkomplizierte Zystitis

- Frau (premenopausal)
  - TMP/SMX forte alle 12 h für 3 d (lokale Resistenzlage E.coli beachten, aktuell in der Ostschweiz für junge Frauen mit erstmaliger Symptomatik weiterhin 1. Wahl)
  - Fosfomycin 3 g als Einmaldosis
  - Nitrofurantoin 100mg alle 12 h für 5-7 d
- Frau (postmenopausal)
  - Daran denken, dass urogenitale Symptome nicht immer auf HWI weisen, deshalb Diagnostik wichtig!
  - Nitrofurantoin 100mg alle 12h für 7d (sofern keine Niereninsuffizienz)
- Mann
  - TMP/SMX forte alle 12 h für 10 d (auch hier Anpassung gemäss Urinkultur!)
  - Alternativ: Ciprofloxacin 500 mg alle 12 h 7-10 d
  - Dauer der Therapie mit 10-14 Tage länger, da meist Prostatamitbeteiligung

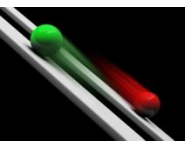


# Therapie

- **Bei Relapse Therapie verlängern**
- **Bei komplizierter Harnwegsinfektion\*  
Therapie angepasst an Keim und  
Resistenz für 7 bis 14 Tage  
(in Abhängigkeit der zugrunde liegenden  
Pathologie)**

\*

• The presence of an indwelling catheter, stent or splint (urethral, ureteral, renal) or the use of intermittent bladder catheterization
• A post-void residual urine of > 100 mL
• An obstructive uropathy of any aetiology, e.g. bladder outlet obstruction (including neurogenic urinary bladder), stones and tumour
• Vesicoureteric reflux or other functional abnormalities
• Urinary tract modifications, such as an ileal loop or pouch
• Chemical or radiation injuries of the uroepithelium



# Prophylaxe

**Table 4. Strategies for Nonantimicrobial Prevention of Recurrent Acute Uncomplicated Cystitis.\***

Strategy	Comments
<b>Behavioral counseling</b>	
Recommend abstinence or reduction in frequency of intercourse	Sexual intercourse is the strongest risk factor for uncomplicated UTIs; often this behavioral strategy is not feasible
If spermicides are used, recommend changing to another method for contraception or prevention of infection	Spermicide use, including use of spermicide-coated condoms, is a strong risk factor, especially if used with a diaphragm; spermicides alter the vaginal flora and favor the colonization of uropathogens
Recommend that patient urinate soon after intercourse, drink fluids liberally, not routinely delay urination, wipe front to back after defecation, avoid tight-fitting underwear, avoid douching	In case-control studies, none of these strategies have been shown to be associated with a reduced risk of recurrent UTIs, and none have been studied prospectively; however, it is reasonable to suggest them to the patient, since they pose a low risk and might be effective
<b>Biologic mediators</b>	
Cranberry juice, capsules or tablets	Biologic plausibility is based on the inhibition of uropathogen adherence to uroepithelial cells; clinical data supporting a protective effect have been limited by design flaws <sup>40</sup> ; a recent randomized, placebo-controlled trial showed no benefit from cranberry juice <sup>41</sup>
Topical estrogen	In some postmenopausal women, topical estrogen normalizes the vaginal flora and reduces the risk of recurrent UTIs <sup>42</sup> ; oral estrogens are not effective
Adhesion blockers (D-mannose, available in health-food stores and online, is occasionally used as preventive therapy)	UTIs caused by <i>E. coli</i> are initiated by adhesion of the bacteria to mannose receptors in the uroepithelium by means of FimH adhesin located on type 1 pili; theoretically, mannosides could block adhesion; however, D-mannose has not been evaluated in clinical trials

\* Counseling about the pros and cons of these strategies is appropriate for women who have one or more recurrent UTIs or who have questions about any of the strategies.

# Trends

Bleidorn et al. *BMC Medicine* 2010, 8:30  
http://www.biomedcentral.com/1741-7015/8/30



## RESEARCH ARTICLE

Open Access

### Symptomatic treatment (ibuprofen) or antibiotics (ciprofloxacin) for uncomplicated urinary tract infection? - Results of a randomized controlled pilot trial

Jutta Bleidorn<sup>1</sup>, Ildikó Gágyor<sup>\*†2</sup>, Michael M Kochen<sup>2</sup>, Karl Wegscheider<sup>3</sup> and Eva Hummers-Pradier<sup>1</sup>

### Presentation, pattern, and natural course of severe symptoms, and role of antibiotics and antibiotic resistance among patients presenting with suspected urinary tract infection in primary care: observational study

*Journal of Infection* (2009) 58, 91–102

P Little, professor of primary care research,<sup>1</sup> R Merriman, medical student,<sup>1</sup> S Turner, medical student,<sup>1</sup> K Rumsby, study data coordinator,<sup>1</sup> G Warner, general practitioner,<sup>2</sup> J A Lowes, consultant microbiologist,<sup>3</sup> H Smith, professor of primary care,<sup>4</sup> C Hawke, public health physician,<sup>5</sup> G Leydon, senior research fellow,<sup>1</sup> A Arscott, research assistant,<sup>1</sup> D Turner, health economics research fellow,<sup>6</sup> M Mullee, senior lecturer in medical statistics and director of RDSU<sup>7</sup>



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www.elsevierhealth.com/journals/jinf

## REVIEW

### Antibiotics versus placebo in the treatment of women with uncomplicated cystitis: A meta-analysis of randomized controlled trials

Matthew E. Falagas<sup>a,b,c,\*</sup>, Ioannis K. Kotsantis<sup>a</sup>, Evridiki K. Vouloumanou<sup>a</sup>, Petros I. Rafailidis<sup>a,b</sup>

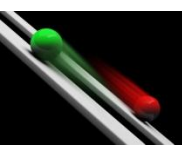
### Effectiveness of five different approaches in the management of urinary tract infection: randomised controlled trial

P Little, professor of primary care research,<sup>1</sup> M V Moore, senior lecturer,<sup>1</sup> S Turner, trial manager,<sup>1</sup> K Rumsby, trial data coordinator,<sup>1</sup> G Warner, general practitioner,<sup>2</sup> J A Lowes, consultant microbiologist,<sup>3</sup> H Smith, professor of primary care,<sup>4</sup> C Hawke, public health physician,<sup>5</sup> G Leydon, senior research fellow,<sup>1</sup> A Arscott, research assistant,<sup>1</sup> D Turner, health economics research fellow,<sup>6</sup> M Mullee, senior lecturer in medical statistics and director of RDSU<sup>7</sup>

BMJ

BMJ

FB Infektiologie / Spitalhygiene



# Trends: Antibiotika vs. Placebo

Study or Subgroup	Antibiotics		Placebo		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Dubi 1982	30	43	8	18	20.4%	2.88 [0.93, 8.97]
Asbach 1991	50	57	5	19	17.6%	20.00 [5.50, 72.77]
Christiaens 2002	13	35	7	35	21.6%	2.36 [0.81, 6.93]
Ferry 2007	388	643	53	212	40.4%	4.56 [3.22, 6.47]
<b>Total (95% CI)</b>		<b>778</b>		<b>284</b>	<b>100.0%</b>	<b>4.67 [2.34, 9.35]</b>
Total events	481		73			
Heterogeneity: Tau <sup>2</sup> = 0.28; Chi <sup>2</sup> = 7.09, df = 3 (P = 0.07); I <sup>2</sup> = 58%						
Test for overall effect: Z = 4.36 (P < 0.0001)						

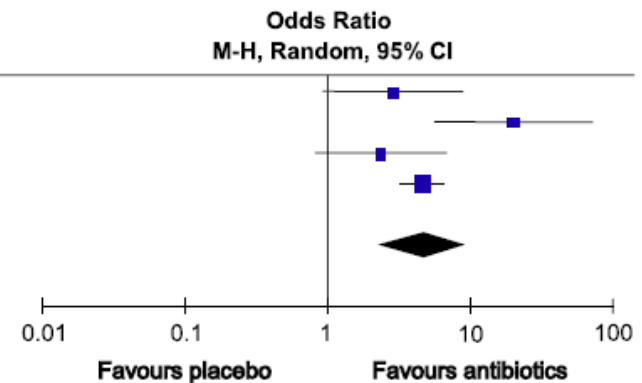
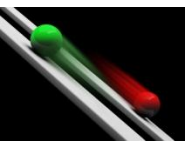


Figure 2 Clinical cure in women with acute uncomplicated cystitis who were treated with antibiotics compared to placebo. Vertical line indicates no difference between the compared treatment groups. Pooled odds ratios (95%CI) are shown by diamond shapes. 95%CIs are shown by horizontal lines. Squares indicate point estimates. The size of the squares indicates the weight of each individual study in the meta-analysis.



# Trends: Antibiotika vs. Placebo

Study or Subgroup	Antibiotics		Placebo		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Brooks 1972	2	25	1	20	2.6%	1.65 [0.14, 19.65]
Dubi 1982	5	43	1	18	3.2%	2.24 [0.24, 20.63]
Christiaens 2002	9	40	10	38	14.7%	0.81 [0.29, 2.29]
Ferry 2007	131	657	27	227	79.5%	1.84 [1.18, 2.88]
<b>Total (95% CI)</b>		<b>765</b>		<b>303</b>	<b>100.0%</b>	<b>1.64 [1.10, 2.44]</b>
Total events	147		39			
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.11, df = 3 (P = 0.55); I <sup>2</sup> = 0%						
Test for overall effect: Z = 2.45 (P = 0.01)						

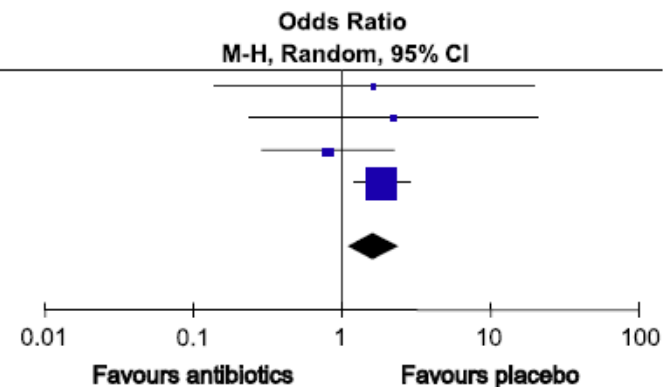
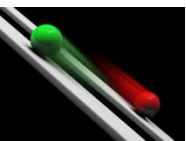
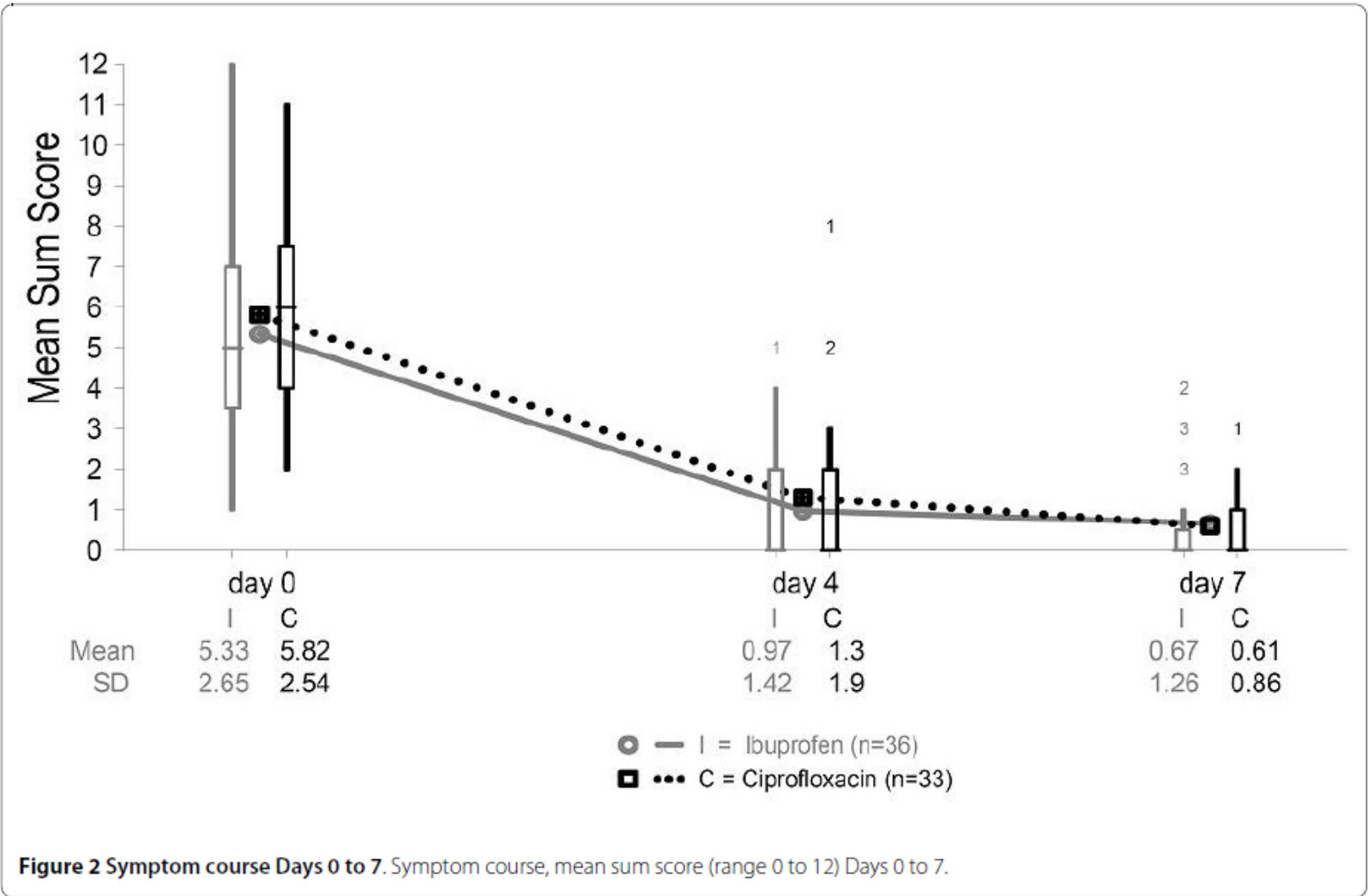


Figure 4 Total adverse events occurring in women with acute uncomplicated cystitis who were treated with antibiotics compared to placebo. Vertical line indicates no difference between the compared treatment groups. Pooled odds ratios (95%CI) are shown by diamond shapes. 95%CIs are shown by horizontal lines. Squares indicate point estimates. The size of the squares indicates the weight of each individual study in the meta-analysis.

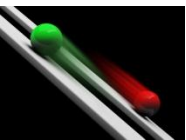


# Trends: Antibiotika vs. NSAR



# Trends

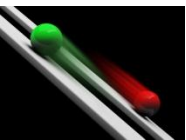
- **Clinical cure in 25 bis 42% mit Placebo** (Falagas et al., Journal of Infection 2009)
- **Milde Symptome mit NSAR, Spasmolytika behandeln**
- **Nur minimales Risiko einer Progression in Pyelonephritis**  
(Christiaens et al., Journal of women's health 2011)





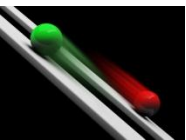
# Zum Mitnehmen...

- **Komplexe Pathophysiologie**
- **Beeinflussung der Risikofaktoren bei rezidivierenden Harnwegsinfektionen hat einen sehr hohen Stellenwert**
- **Restriktiver Antibiotika Einsatz**
- **Neue Therapieansätze in Entwicklung**



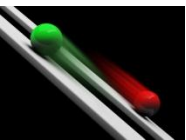
# Themenwechsel, neues Fallbeispiel

- **37 jähriger Mann**
  - **4–6 x / Jahr Sinusitis und Pneumonie**
  - **Antibiotika Therapie**
  - **Episoden mit jedem Mal länger und stärker ausgeprägt**



# Rezidivierende Infektionen

- **Anatomische Veränderungen**
- **Sekundäre Immunerkrankung**
- **Primäre Immunerkrankung**



# Anatomische und Physiologische Prädisposition

## Lungs

### Bronchopneumonia

Smoking

Acute exacerbations of chronic bronchitis

Intrinsic airway disorders:

Bronchiectasis, foreign body, bronchial stenosis, bronchomalacia, tracheobronchial fistula

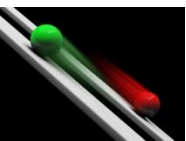
Recurrent aspiration (alcohol/drug use, seizure disorder)

Esophageal disease (gastroesophageal reflux, Zenker's diverticulum, achalasia)

Bronchial obstruction (extrinsic versus intrinsic obstruction)

Unrecognized cystic fibrosis

Unrecognized ciliary dyskinesia



# Anatomische und Physiologische Prädisposition

## Head and neck

### Recurrent otitis media

Cholesteatoma

Tympanic membrane perforation

Eustachian tube dysfunction due to allergy or viral infection

### Sinusitis

Ostiomeatal obstruction

Nasal polyps

Mucocele

Allergic rhinitis

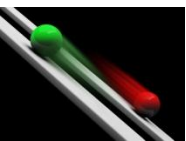
Viral infection

Inadequate therapy for acute sinusitis

### Cervical lymphadenitis

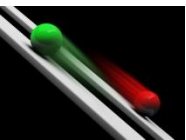
Unrecognized branchial cleft cyst

Inadequately treated dental disease



# Sekundäre Immunschwäche

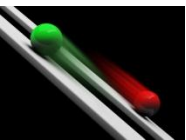
- Immunsuppressive Therapie
- Infektionen
- Malignome
- Metabolische Störungen
- Autoimmunerkrankungen
- Trauma (Barrierefunktion↓)
- Asplenie, Alter, Stress



# Iatrogene Prädisposition

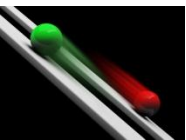
## Protonenpumpeninhibitor (PPI)

- In letzten 30 Tagen: **+ 65%** erhöhtes Pneumonie-Risiko
- Selbst niedrig dosiert: **+ 17% !**
- Risiko für Clostridien Colitis erhöht



# Primäre Immunerkrankung

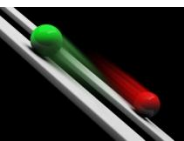
- Die meisten Erkrankungen werden bereits im Kindesalter diagnostiziert
- Prävalenz bei Erwachsenen aber viel höher als angenommen (1:1200)
- Infektionen
- Autoimmunerkrankungen
- Malignome





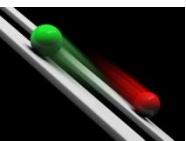
# Primäre Immunerkrankung; «Warning signs»

- 1) Four or more new ear infections within 1 year.
- 2) Two or more serious sinus infections within 1 year.
- 3) Two or more months on antibiotics with little effect.
- 4) Two or more pneumonias within 1 year.
- 5) Failure of an infant to gain weight or grow normally.
- 6) Recurrent, deep skin or organ abscesses.
- 7) Persistent thrush in mouth or fungal infection on skin.
- 8) Need for intravenous antibiotics to clear infections.
- 9) Two or more deep-seated infections including septicemia.
- 10) A family history of PI.



# Common variable immunodeficiency

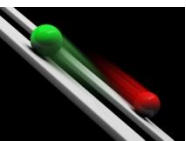
- Defekt in B – Lymphozyten Zellreihe, fehlende Plasmazellbildung  
→ Immunglobulin Produktion ↓
- Alter bei Diagnosestellung bei Männern früher; im Durchschnitt bei 25 Jahren
- Bei Frauen im Durchschnitt bei 36 Jahren



# Common variable immunodeficiency

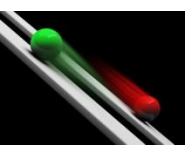
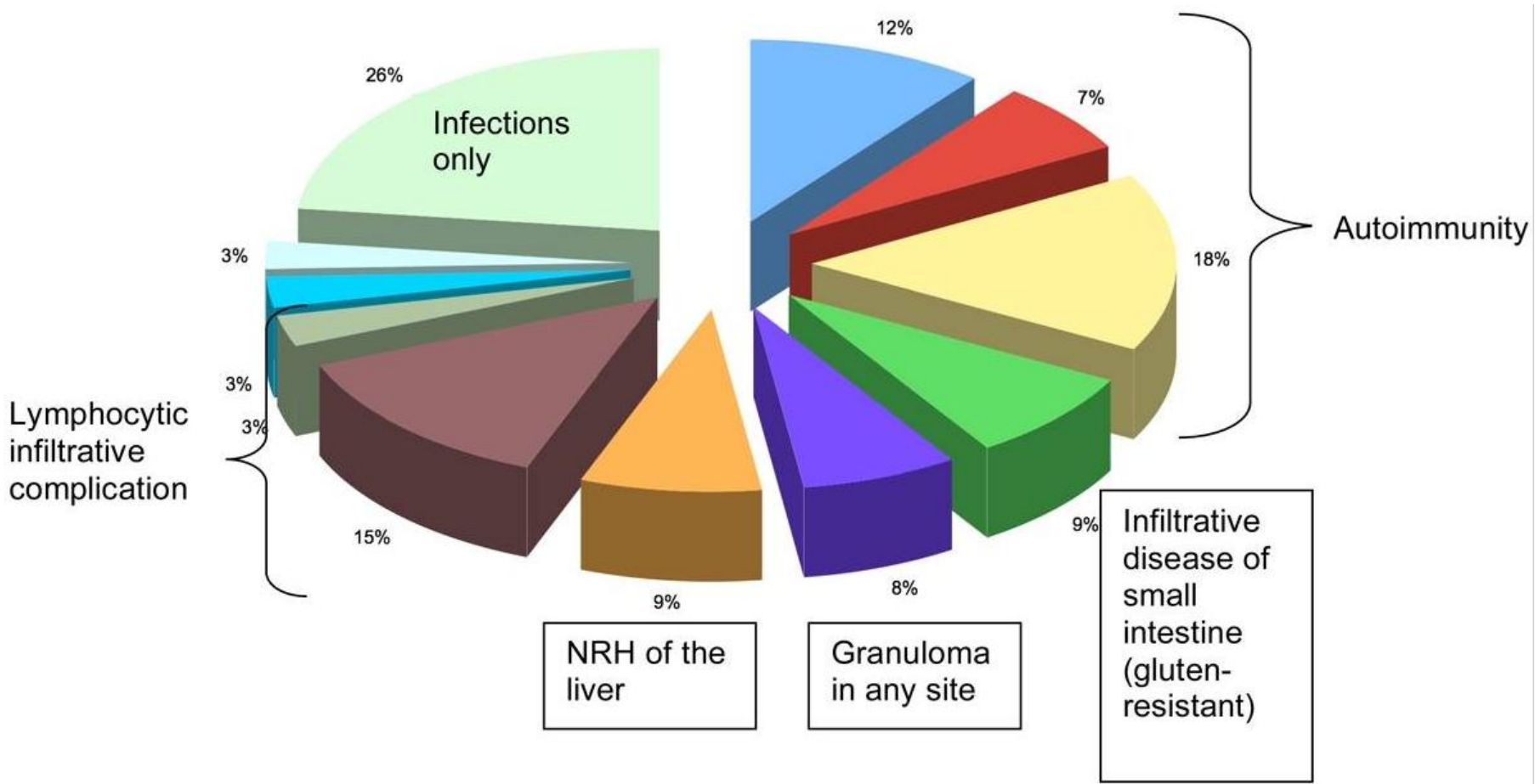
Table 5. Clinical phenotypes: variation of prevalences between countries

Phenotype	Czech Republic, no. patients (%)	Germany, no. patients (%)	Sweden, no. patients (%)	United Kingdom, no. patients (%)	<i>P</i>
Polyclonal lymphocytic infiltration	22 (54)	21 (31)	15 (12)	37 (39)	< .001
Infections only	14 (34)	27 (40)	79 (61)	36 (37)	< .001
Autoimmunity	12 (29)	26 (38)	35 (27)	46 (48)	.02
Enteropathy	6 (15)	7 (10)	4 (3)	12 (13)	.03
Lymphoid malignancy	0	4 (6)	1 (0.8)	5 (5)	.07
Total	41	68	129	96	



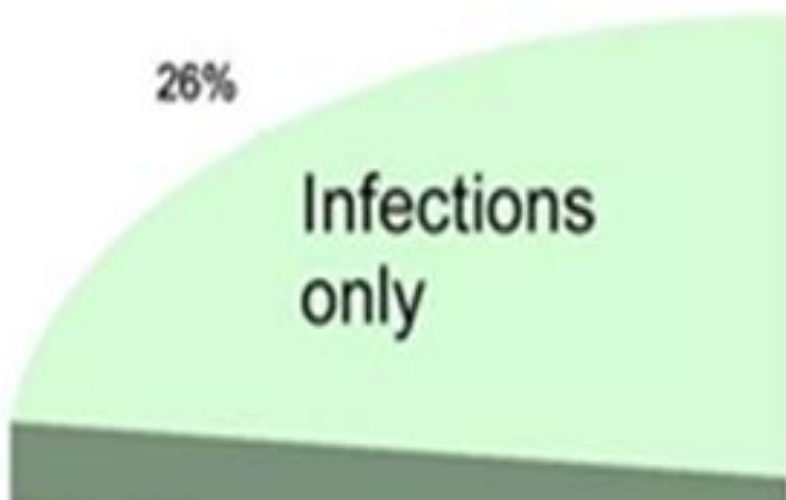
## Complications in patients with CVIDs

- Cytopenia
- Skin
- Organ specific
- Enteropathy
- Granuloma
- Hepatomegaly
- Persistent L/N
- LIP
- Lymphoid malignancy
- Cancers
- Infections only



# Common variable immunodeficiency

- **Infektionen:**



**Sinusitis, Bronchitis,  
Pneumonie, Otitis**



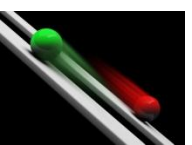
**Gastrointestinale  
Infektionen**



**Septische Arthritis**



**Meningitis**

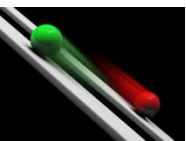


# Common variable immunodeficiency; Diagnostik

*Panel:* Laboratory investigations for CVID in the patients who are HIV-negative in whom other causes of recurrent infections have been ruled out

## Phase I

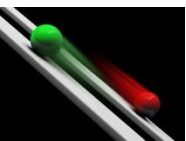
- Complete blood count with differential
- Serum immunoglobulins—IgG, IgA, and IgM
- Urine protein analysis (to rule out loss of immunoglobulins due to nephrotic syndrome)



# Diagnostik beim Spezialist

## Phase 2

- IgG subclasses (IgG1 to IgG4; useful for patients with IgA deficiency or history of recurrent sinopulmonary infections)<sup>49</sup>
- Functional antibody tests
  - Protein: diphtheria toxoid, tetanus toxoid, *H influenzae* B, isohaemagglutinins
  - Polysaccharide antigen: *S pneumoniae*
- T-cell, B-cell, and natural-killer cell quantitation by flow cytometry
- Possibly test for lymphocyte proliferation for mitogens and antigens (tetanus toxoid and *Candida*)



## Phase 3

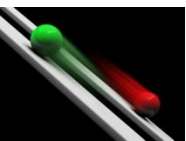
- B-cell subsets by flow cytometry\* (to determine if there is a reduction in class-switched memory B cells, and changes in other B-cell subsets that correlates with certain clinical presentations<sup>35,50</sup>)
- Class-switched memory B cells (CD27+ IgD- IgM-)
- Non-switched memory B cells (CD27+ IgD+ IgM+)
- IgM-memory B cells (CD27+ IgM+ IgD<sup>dull</sup>)
- Transitional B cells (CD38+++ IgM++)
- Plasmablasts (CD38+++ M-)
- Mature B cells (CD19+ CD21+)
- CD21<sup>lo</sup> B cells (CD19+ CD21<sup>lo</sup>)

# Diagnostik beim Spezialist

### Optional testing\*

- Protein expression for BAFF-R, † TACI, † and CD19† on B cells and ICOS† on activated T cells by flow cytometry
- Mutation analysis by gene sequencing for *TNFRSF13B*† and *ICOS*†
- Mutation analysis for *TNFRSF13C* and *CD19* are presently available only in specific research laboratories

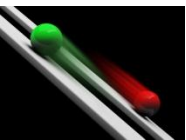
\*Tests may not affect diagnosis or management decisions but will provide additional information on the underlying basis for the CVID presentation. †Tests are clinically available in specialised reference laboratories.





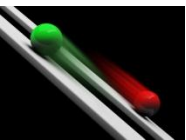
# Common variable immunodeficiency; Therapie

- **Substitution von Immunglobulinen  
(IVIG 1 x / Mt oder SCIG 1 x / Wo)**



# Auflösung Fallbeispiel

- **Diagnose: CVID mit**
  - **absolutem IgG Mangel**
  - **B-Zell Lymphopenie**



# Zum Mitnehmen...

- **Bei rezidivierenden Infektionen an eine mögliche zugrunde liegende anatomische Veränderung denken**
- **Prädisponierende Faktoren beeinflussen**
- **Sekundäre Immundefekte ausschliessen**
- **Auch wenn im Erwachsenenalter eher selten, gibt es sie doch auch, die primären Immundefekte**

