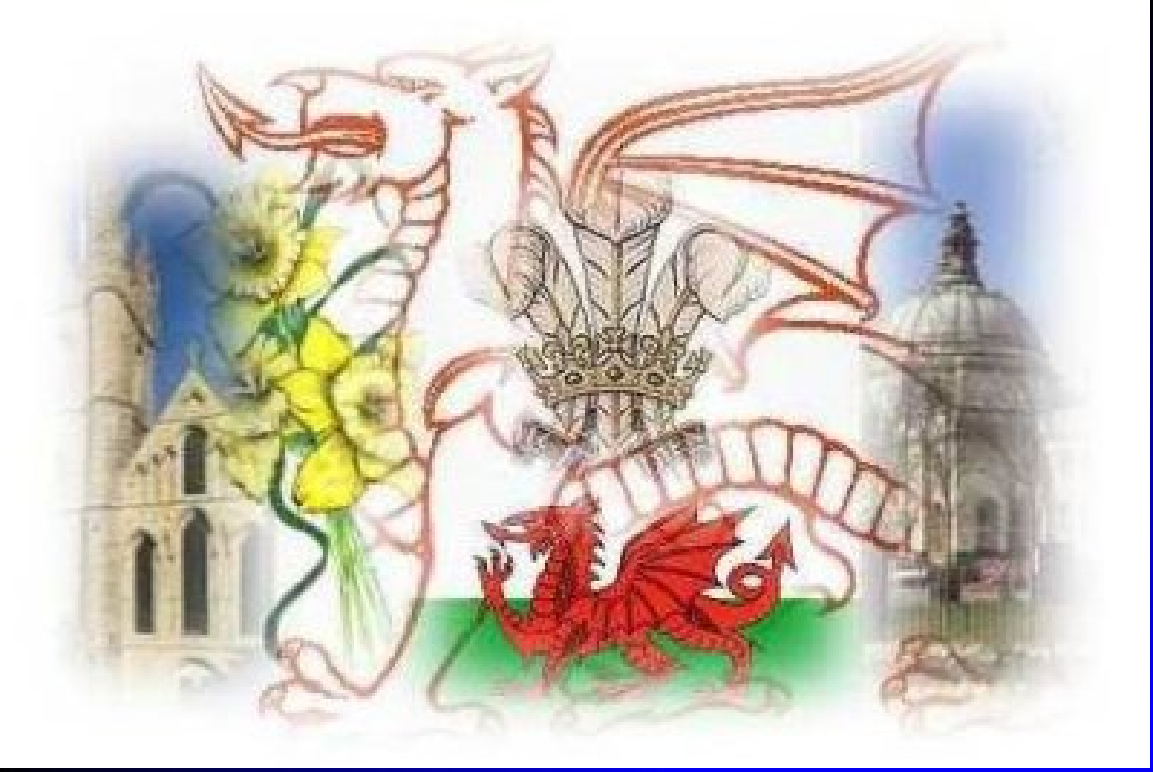


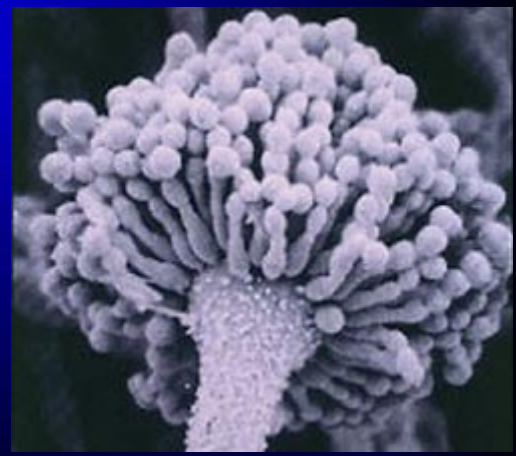
Haematological and Immunological aspects of invasive fungal infection in leukaemia

Dr. Chris Poynton

Department of Haematology

University Hospital of Wales,

Cardiff



ACP Prague 2008

Changing spectrum of risk factors in the development of IFI in haematological malignancy

- Type of malignancy: AML>ALL>lymphoma>myeloma
- State of remission/relapse
- Neutropenia: depth and duration

- Not just degree, but type of immunosuppression
  - Graft vs Host Disease – especially chronic GvHD
  - Purine analogues
  - Monoclonal antibody therapy (especially Alemtuzumab and Infliximab))

ARE ANTIFUNGAL DRUG TRIALS REALLY THE WAY FORWARD?

HOW COMMON IS INVASIVE FUNGAL INFECTION?

1987-1998: Retrospective studies of 11,802 patients - overall incidence 4.6%

AML - 12%

ALL - 6.5%

CML - 2.5%

CLL - 0.5%

NHL - 1.6%

HL - 0.7%

Myeloma 0.5%

1999-2003: Overall IFI incidence - 6.1%

2003-2007: Overall IFI incidence - 12.7%

Pagano L et al CID (2007) 44: 1524-1525

ARE WE IMPROVING THE MANAGEMENT OF INVASIVE ASPERGILLOSIS OVER TIME?

Time period	Incidence of Aspergillosis	Attributable mortality	Deaths/1000 pts
1987-1998	4.7%	48%	22
1999-2003	6.1%	38.5%	23
2003-2007	12.6%	14%	18

Data in Pagano L et al CID (2007) 44: 1524-1525

Comparative Studies of Amphotericin preparations in Febrile Neutropenia

Reference	Type of Study	Comparison	Patients n=	Clinical response	Survival	RenalToxicity
Pizzo (1982) PID	Empiric	cAmpho 1 vs placebo	N/A	Superior	Superior	N/A
Anaissie (1995) Abstr	Therapy	ABLC 5 vs cAmpho0.6-1	231	Same	Same	N/A
Viscoli (1996) EuJC	Empiric	cAmpho 1 vs flu	112	Same	Same	Flu Superior
White (1998) CID	Empiric	ABCD 4 = cAmpho 0.8	213	Same	Same	ABCD Superior
Leenders (1998) BJH	Therapy	LAmBi 5 vs cAmpho 1	106	Superior (5 pts)	Same	LA Superior
Ellis (1998) CID	Therapy	LAmBi 1 vs LAmBi 4	89	Same	Same	Same
Walsh (1999) NEJM	Empiric	LAmBi 3 vs cAmpho 0.6	687	Same	Same	LA Superior
Prentice (1999) BJH	Empiric	LAmBi 3 vs 1 vs cAmpho 1	338	LA3 superior	Same	LA Superior
Winston (2000) CID	Empiric	LAmBi5 vs 3 vs ABLC 5	244	Same	Same	LA Superior
Winston (2000)CID	Empiric	Flu 400 vs cAmpho 0.5	317	Same	Same	Flu Superior
Fleming (2001) LL	Therapy	LAmBi3-5 vs ABLC 3-5	75	Same	Same	Same
Walsh (2001) AAC	Therapy	LAmBi 15 vs 12.5 vs 10 vs 7.5	44	Same	Same	Same
Boogaerts (2001)AIMed	Empiric	cAmpho1 vs Itraconazole	384	Same	Same	Itra Superior
Cagnoni (2002) JAC	Empiric	LAmBi3 vs ABLC5 vs cAmpho	414	Same	Same	LA Superior
Bowden (2002) CID	Therapy	ABCD6 vs cAmpho1-1.5	174	Same	Same	ABCD Superior
Walsh (2002) NEJM	Empiric	Voriconazole vs AmBi 3-6	837	NNI	Same	Vori superior
Herbrecht (2002) NEJM	Therapy	Voriconazole vs cAmpho	277	Vori superior	superior	Vori superior
Mora-Duarte(2002)	Therapy	Caspofungin vs LAmBi3	224	Same	Same	Caspo superior
Walsh (2004) NEJM	Empiric	Caspofungin vs LAmBi3	1095	Same	Superior	Caspo superior

COMMON MISTAKES THAT ARE MADE IN TRIALS

☹ THE USE OF HISTORICAL COMPARISONS

How not to compare treatments historical controls:

SAB – a promising new treatment for AML in the elderly?

Treatment	Number of pts	CR rate	Induction deaths	Resistant disease
DAT	167	47%	30%	23%
SAB	284	61%	15%	24%

p=0.00007

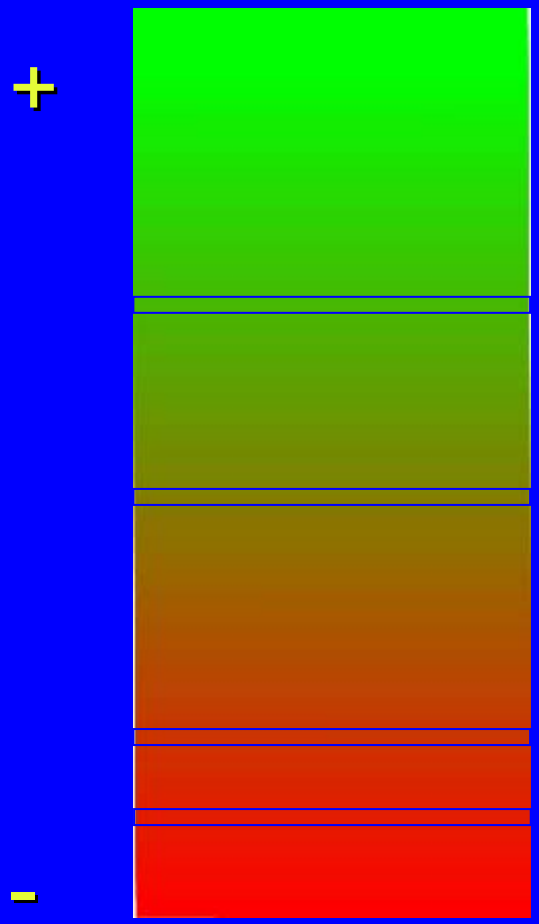
COMMON MISTAKES THAT ARE MADE IN TRIALS

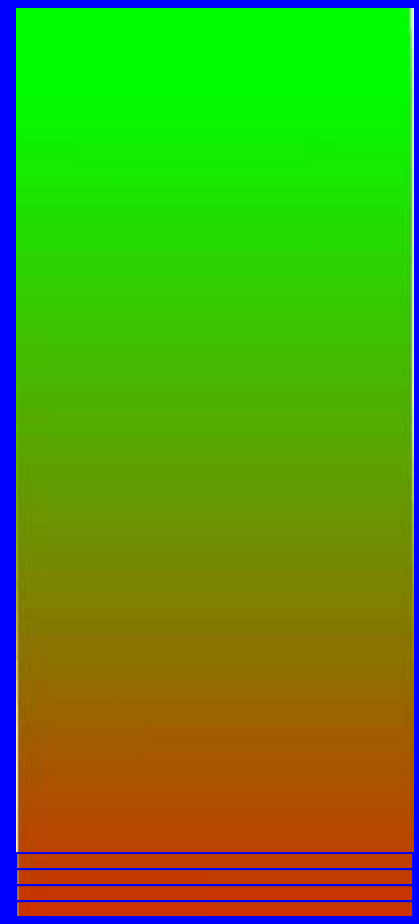
☹ THE USE OF HISTORICAL COMPARISONS

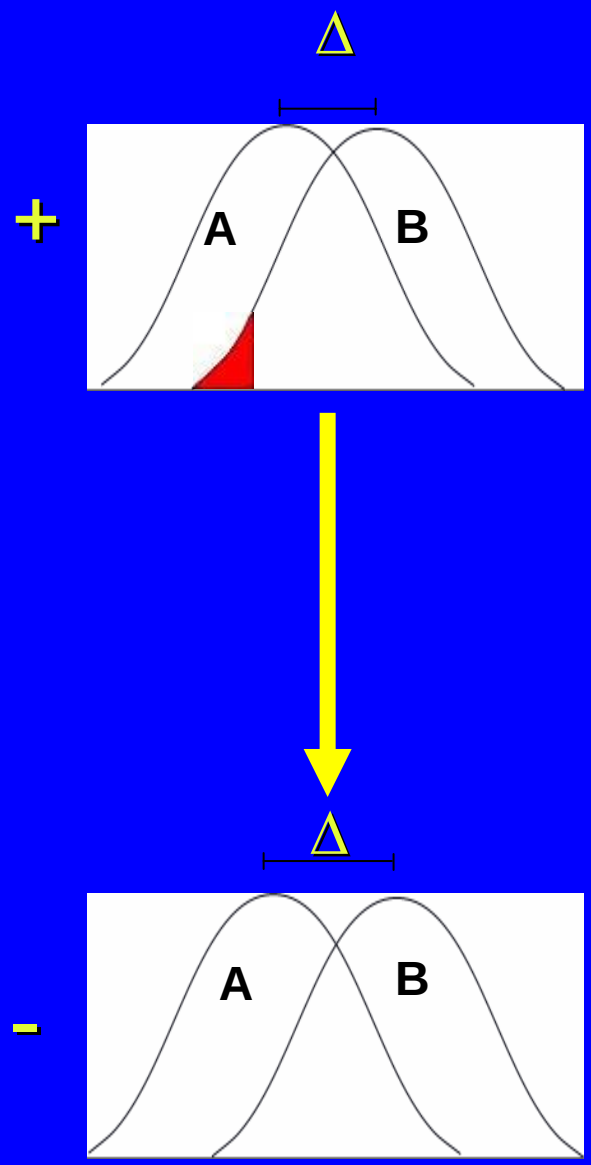
☹ THE UNEQUAL REORGANISATION OF SUBGROUPS AFTER THE TRIAL RESULTS ARE KNOWN

DRUG A RESULTS

DRUG B RESULTS







COMMON MISTAKES THAT ARE MADE IN TRIALS

- ☹ THE USE OF HISTORICAL COMPARISONS
- ☹ THE UNEQUAL REORGANISATION OF SUBGROUPS AFTER THE TRIAL RESULTS ARE KNOWN
- ☹ UNDERPOWERING TO REDUCE NUMBER OF PATIENTS NEEDED AND NONINFERIORITY BASED ON INTENTION TO TREAT

STATISTICAL CONSIDERATIONS IN TRIAL DESIGN

A: Numbers of patients required

Assuming a success rate of around 50% (the choice that is easiest to prove)

To have a 90% chance of detecting a difference of 10% in success

with a 95% significance p value (<0.05)

you would need 1000 patients

You would need only 260 patients to detect a 20% difference with the same p value

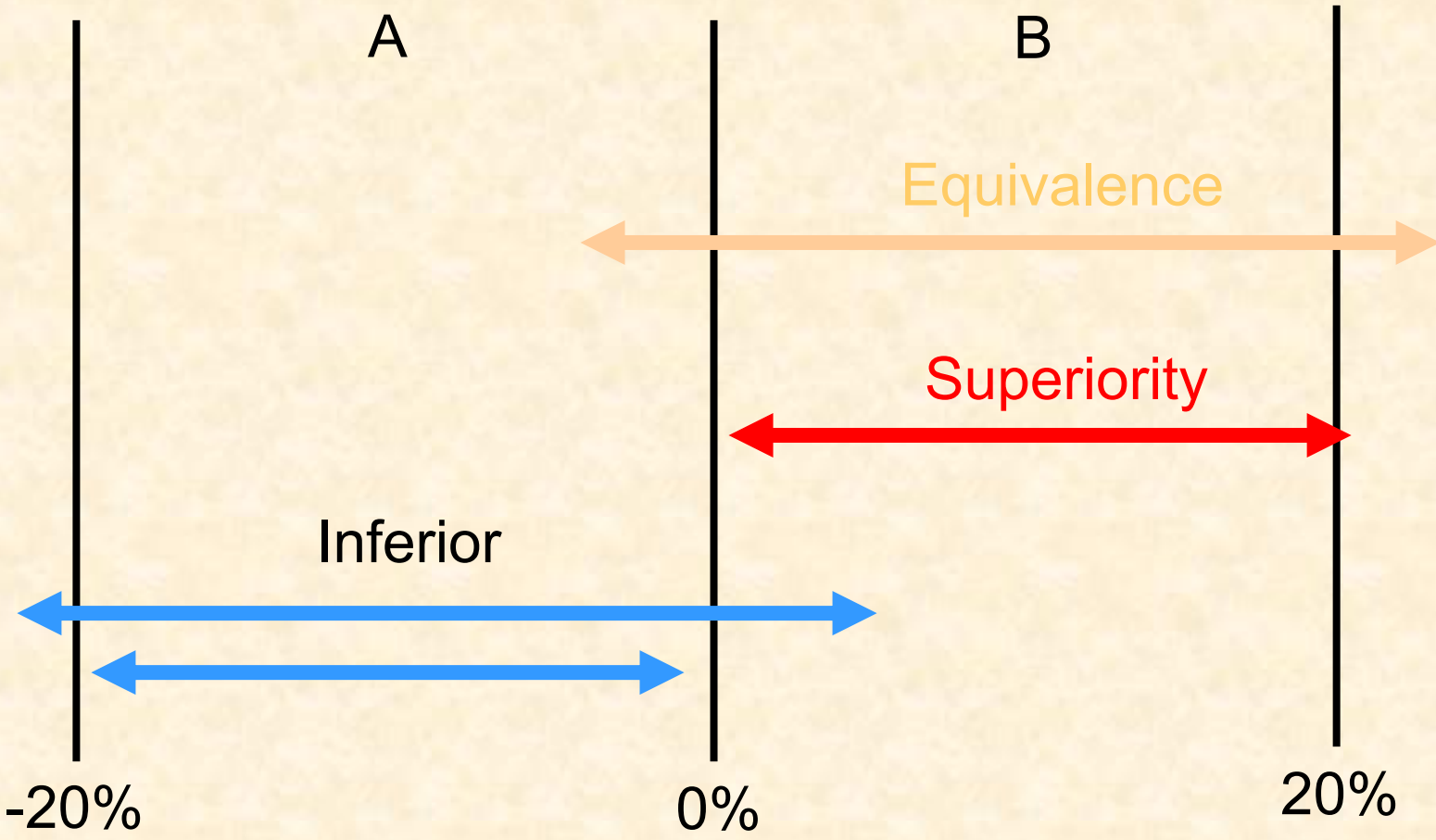
B: Design

In non inferiority trials, intention to treat is not the correct way to analyse the effect of the drugs. Compliance and actual delivery of drug is the issue

In a trial with central randomisations that balance subgroups (minimization technique) you cannot then go back and analyse different subgroups accurately

Non-inferiority analysis

95% confidence re. differences between groups
if upper CI limit > 0 and lower CI>-20%



VORICONAZOLE (n=144) vs AMPHOTERICIN B (n=133)

Drug	Success at 12 weeks	Full Compliance	
Voriconazole	53%	73%	
c Ampho B	32%	20%	

Voriconazole intolerance

n=52 (36%)

- cAmphotericin B (38%)
- Lipid Amphotericin (27%)
- Itraconazole (33%)
- Combination (2%)

cAmphoterin B intolerance

n=107 (96%)

- Lipid Amphotericin B (44%)
- Itraconazole (36%)
- Other (20%)

data in Walsh T et al N Engl J Med (2002) 347: 408-415

VORICONAZOLE (n=144) vs AMPHOTERICIN B (n=133)

A: Overall response (CR+PR)

	Voriconazole	cAmphotericin B
Country A	57%	37%
Country B	47%	23%

B: Complete response (CR only)

	Voriconazole	cAmphotericin B
Country A + B	20.8%	16.5%

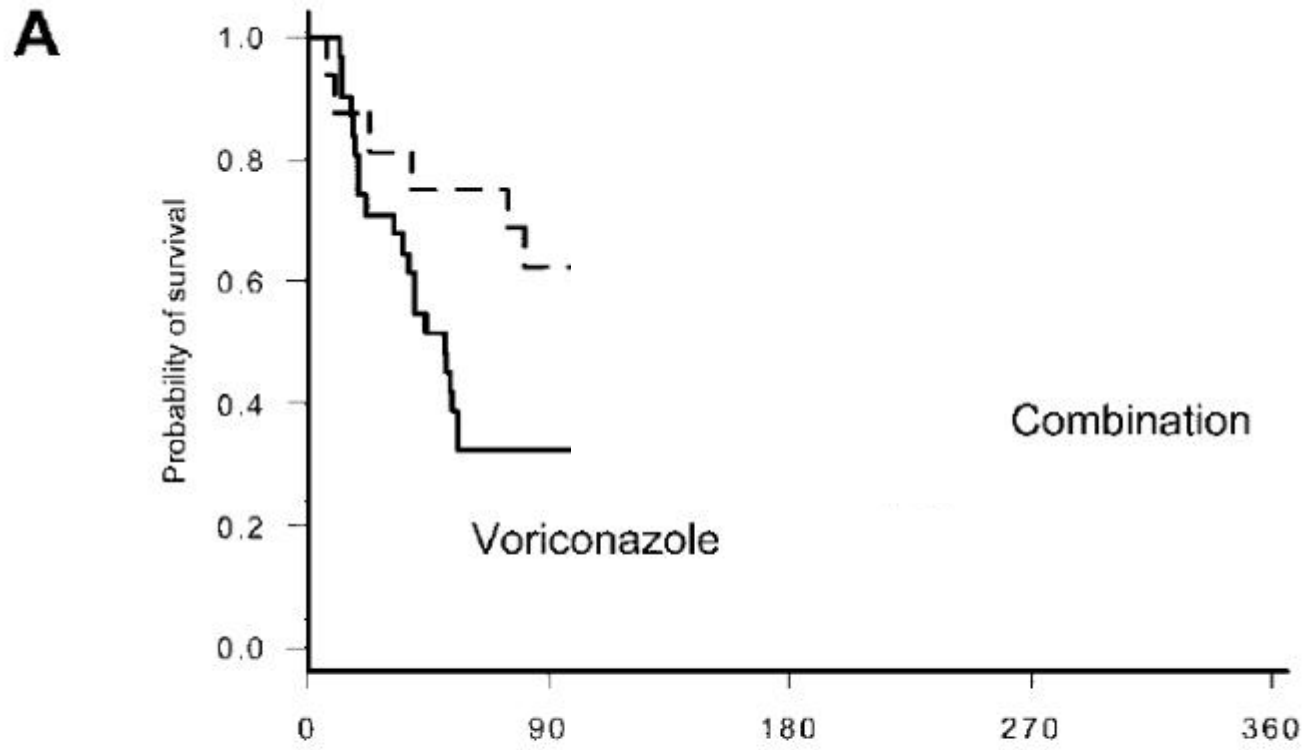
data in Walsh T et al N Engl J Med (2002) 347: 408-415

COMMON MISTAKES THAT ARE MADE IN TRIALS

- ☹ THE USE OF HISTORICAL COMPARISONS
- ☹ THE UNEQUAL REORGANISATION OF SUBGROUPS AFTER THE TRIAL RESULTS ARE KNOWN
- ☹ UNDERPOWERING TO REDUCE NUMBER OF PATIENTS NEEDED AND NONINFERIORITY BASED ON INTENTION TO TREAT
- ☹ RESULTS ANALYSED AT TOO EARLY A TIMEPOINT

EFFECT OF TIME ON TRIAL RESULT

Voriconazole vs Voriconazole+Caspofungin

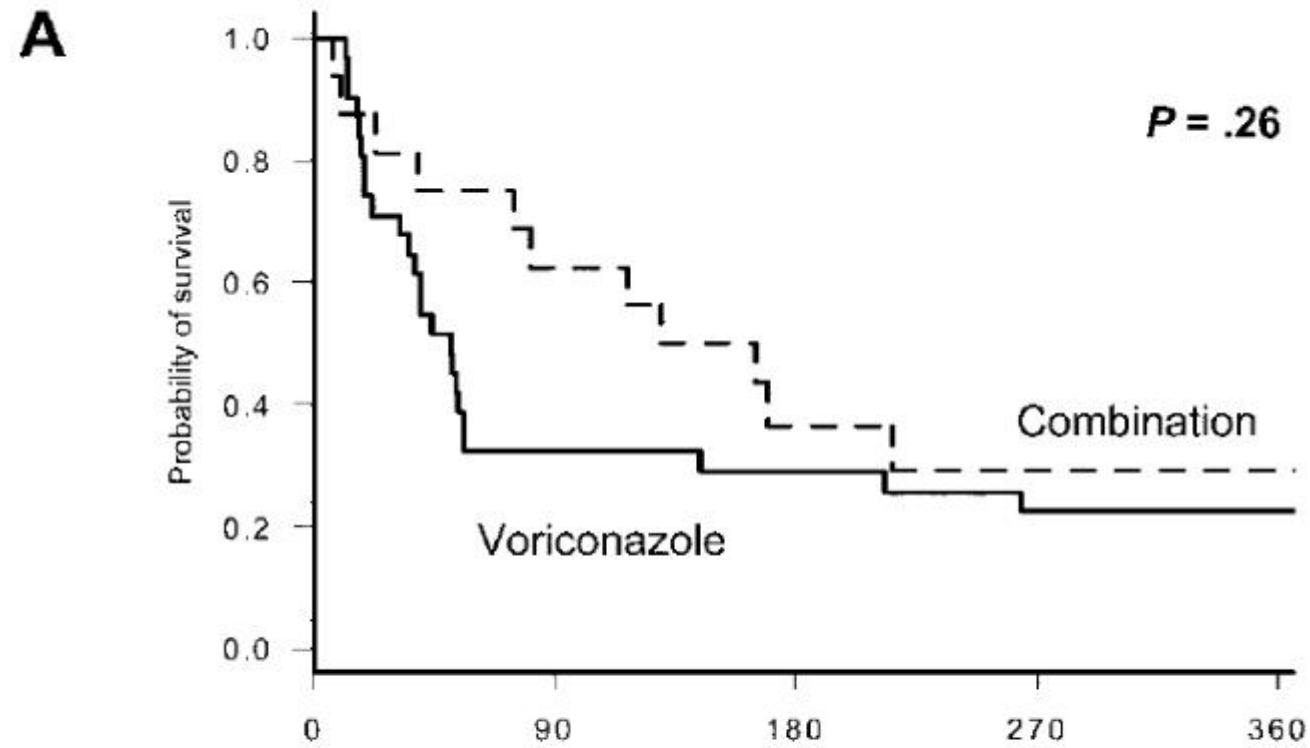


Patients (no.)					
Voriconazole	31	10	9	7	7
Combination	16	10	5	1	1

Marr K et al Clin Inf Dis (2005) 40: 1074-6

EFFECT OF TIME ON TRIAL RESULT

Voriconazole vs Voriconazole+Caspofungin



Patients (no.)					
Voriconazole	31	10	9	7	7
Combination	16	10	5	1	1

Marr K et al Clin Inf Dis (2005) 40: 1074-6

Minor or stable short term outcomes do not necessarily translate into long term benefit

Cause of death at 1 year	Voriconazole n=31	Voriconazole+caspofungin n=16
Invasive Aspergillosis	18 (58%)	3 (19%)
Bacterial pneumonia/sepsis	4 (18%)	3 (19%)
CMV pneumonitis	0	1 (6%)
RSV pneumonitis	0	1 (6%)
GvHD with organ failure	2 (6.5%)	0
Relapsed malignancy	2 (6.5%)	2 (13%)
Unknown	0	1 (6%)

Marr K et al Clin Inf Dis (2005) 40: 1074-6

The father of the modern clinical randomised controlled trial

David Davies Chair of Tuberculosis and Diseases of the Chest
MRC Unit - Welsh National School of Medicine 1960

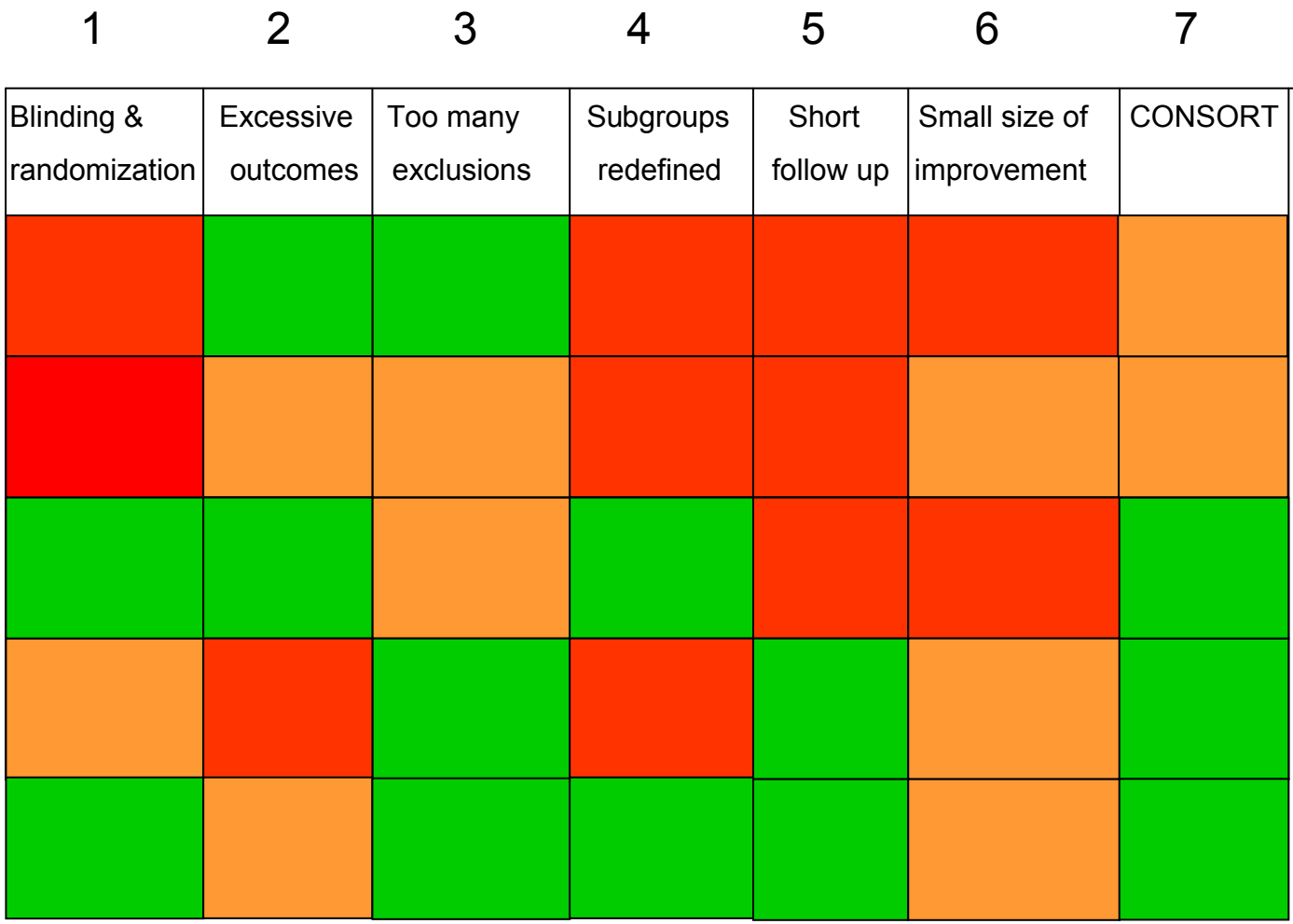
Professor Archie Cochrane

1908-1988

"The main idea of a clinical trial is to distinguish small, clinically not relevant effects from moderate but still clinically useful ones"

"Effectiveness and Efficiency: Random Reflections on Health Services"

ADHERENCE OF RECENT ANTIFUNGAL TRIALS TO BEST STATISTICAL PRACTICE



1. Double blind randomised centrally with minimization technique. The best method BUT you cannot do a non inferiority study on intention to treat!! Compliance is then the big issue.

2. The more outcomes the more likelihood of finding a significant one.

3. Too many exclusions means treatment not applicable to "real life" patients.

4. Modified Intention to treat analysis (MITT) is a common post trial analysis mistake (data dredging).

Guidelines for Antifungal Therapy for Invasive Fungal Infection

Infectious Diseases Society of America

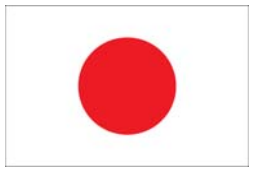
Australasian Society for Infectious Diseases

University of Manitoba Canadian Mycoses Group

European Conference on Infections in Leuaemia (ECIL)

Groupe de travail de CHRU de Lille

Japanese Society for Medical Mycology



National Comprehensive Cancer Care Network

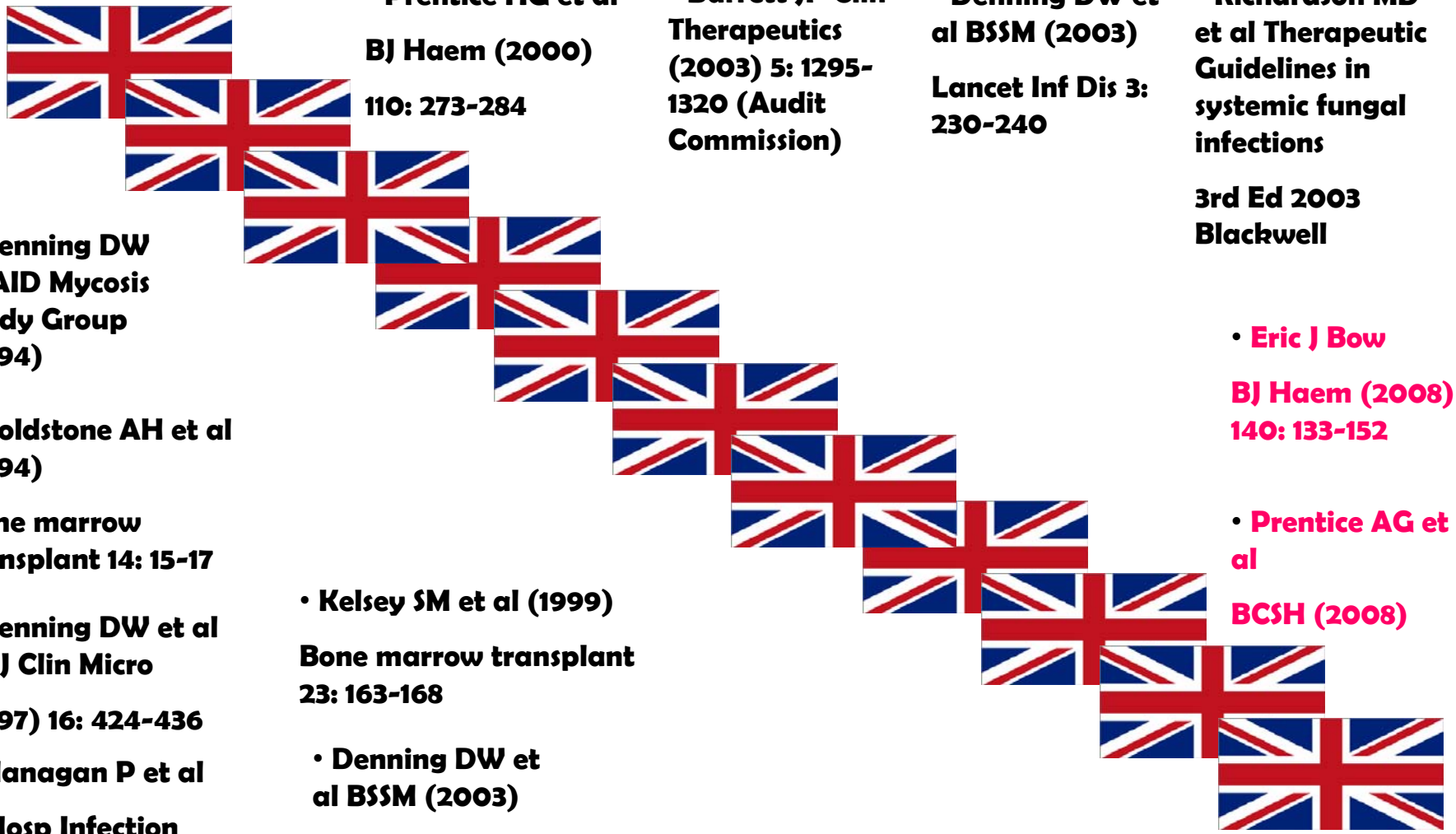
Guidelines of the New South Wales Infectious Diseases Group

Infectious Diseases working party of the German Society of Hematology and Oncology

Fungal Infection network of Switzerland (FUNGINOS)

Grupos de Estudio infeccion fungica

Guidelines for Antifungal Therapy for Invasive Fungal Infection



- Denning DW NIAID Mycosis Study Group (1994)
- Goldstone AH et al (1994)

  Bone marrow transplant 14: 15-17
- Denning DW et al Eu J Clin Micro

  (1997) 16: 424-436
- Flanagan P et al

  J. Hosp Infection 91998) 38: 163-177
- Prentice HG et al

  BJ Haem (2000)

  110: 273-284
- Kelsey SM et al (1999)

  Bone marrow transplant 23: 163-168
- Denning DW et al BSSM (2003)

  Lancet Inf Dis 3: 230-240
- Barrett JP Clin Therapeutics (2003) 5: 1295-1320 (Audit Commission)
- Denning DW et al BSSM (2003)

  Lancet Inf Dis 3: 230-240
- Richardson MD et al Therapeutic Guidelines in systemic fungal infections

  3rd Ed 2003 Blackwell
- Eric J Bow

  BJ Haem (2008) 140: 133-152
- Prentice AG et al

  BCSH (2008)

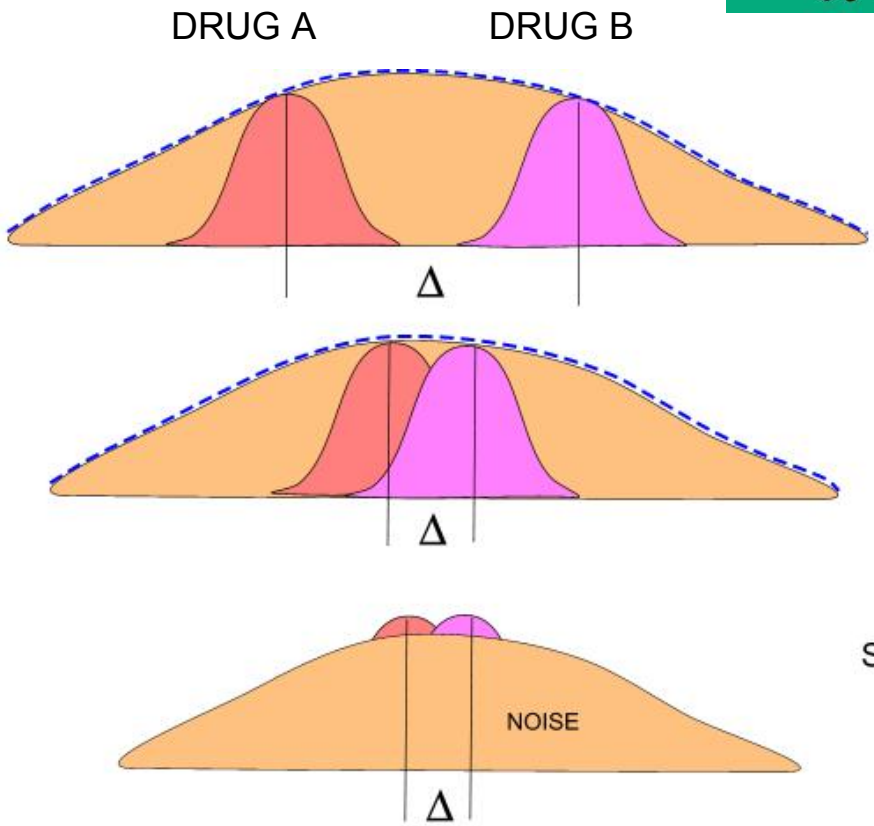
Without proper evidence, evidence based practice is impossible.

Antifungal guidelines are largely a non evidence based exercise that represent simply expert opinion and experience.

More statistics

Large effects hide small effects

Δ = days until fever resolution



STD DIFF	n
1	50
0.5	200
0.33	400
0.25	700

$$\text{Standard Difference} = \frac{\Delta}{\text{Standard Deviation}}$$

Last statistics

effect of diagnostic uncertainty

Trial A

20% had SFI 80% did not

DRUG A cures 50%. Success= 90%

DRUG B cures 75% Success =95%

} n=1200

Trial B

40% had SFI 60% did not

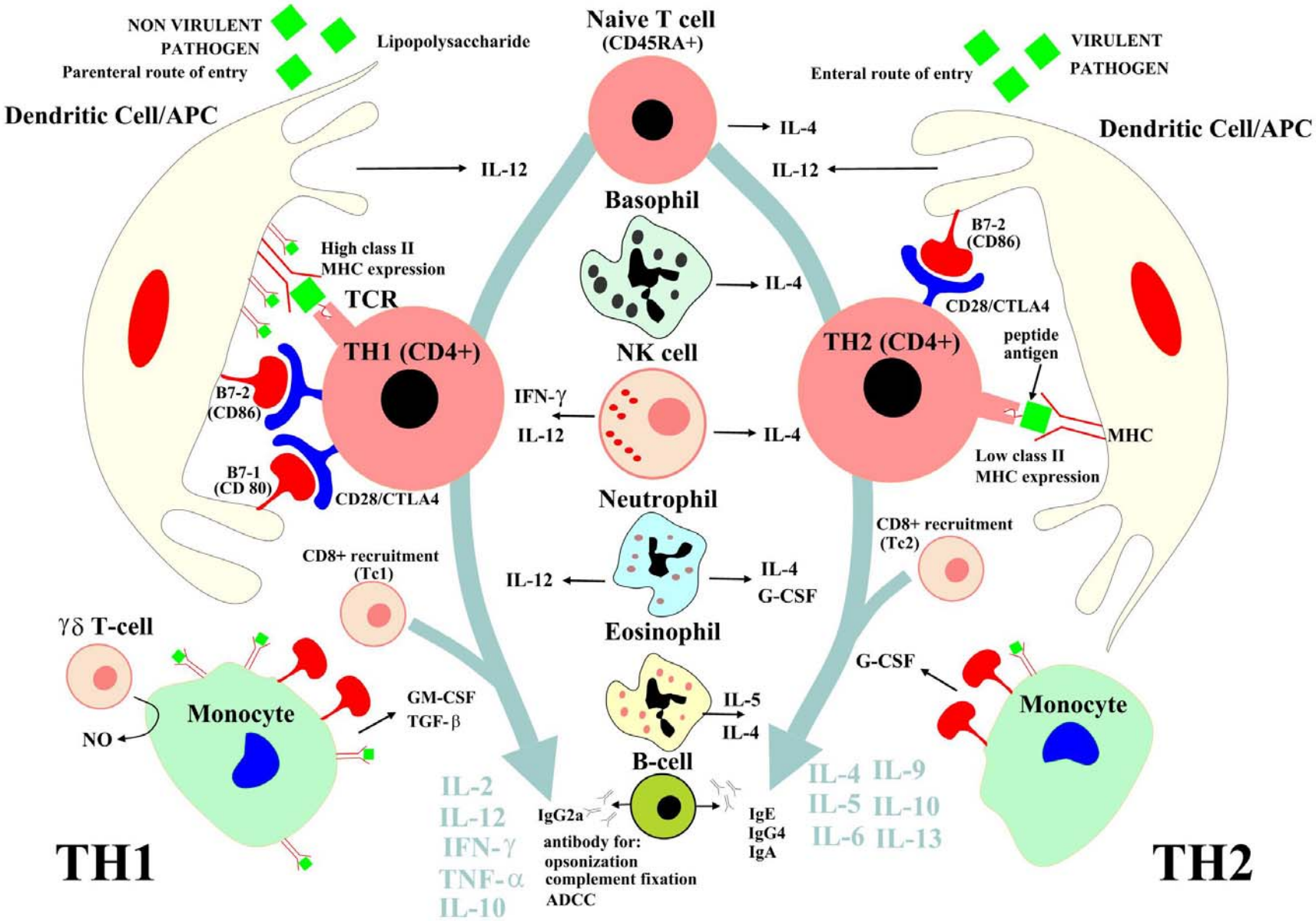
DRUG A cures 50%. Success= 80%

DRUG B cures 75% Success =90%

} n=500

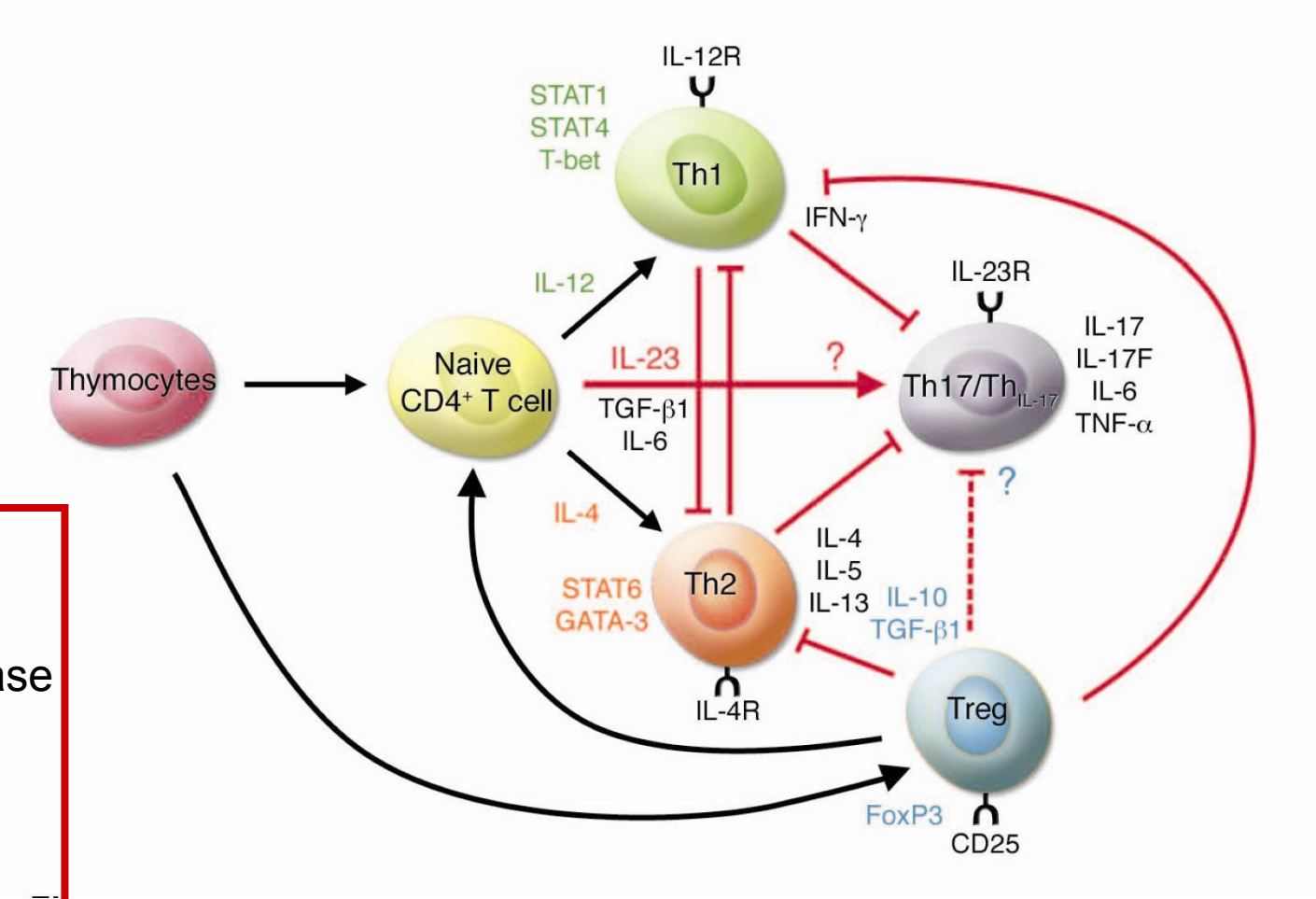
IMMUNE SUPPRESSION IN HAEMATOLOGY PATIENTS WITH SERIOUS FUNGAL INFECTION IS NOT ALWAYS THE SAME

THE CLASSIC T-HELPER CELL CYTOKINE PARADIGM - T_H1 and T_H2



IL23 promotes the development of IL17 producing CD4+ helper cells

IL17 is also produced by CD8+ T cells, γδ T cells, and neutrophils

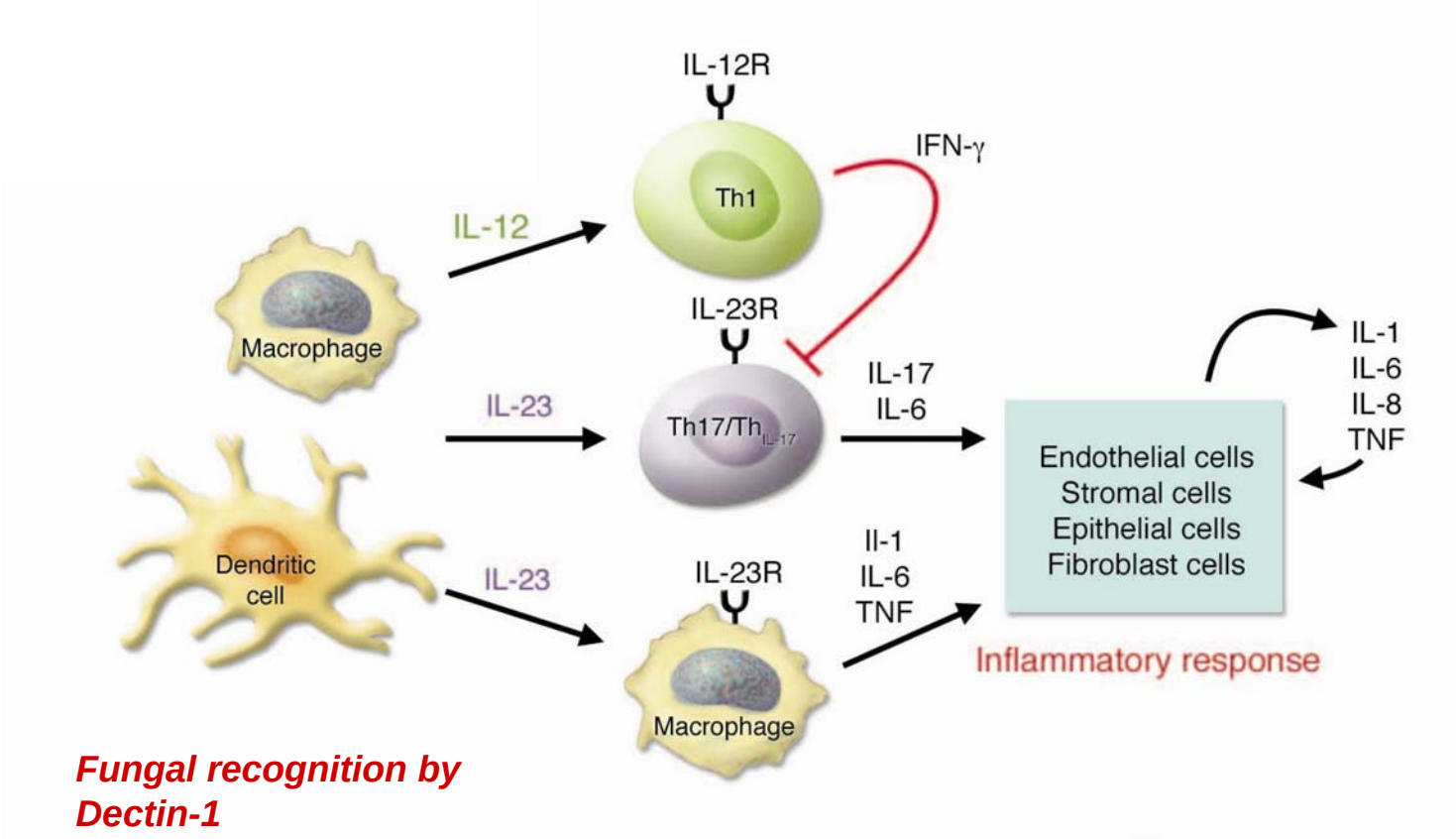


IL-17 increased in:

- Rheumatoid disease
- MS
- IBD
- asthma

Iwakura Y et al J. Clin Invest (2006) 116:1218-1222

CHRONIC INFLAMMATORY CYTOKINE PROFILE - T_H1 and T_H17



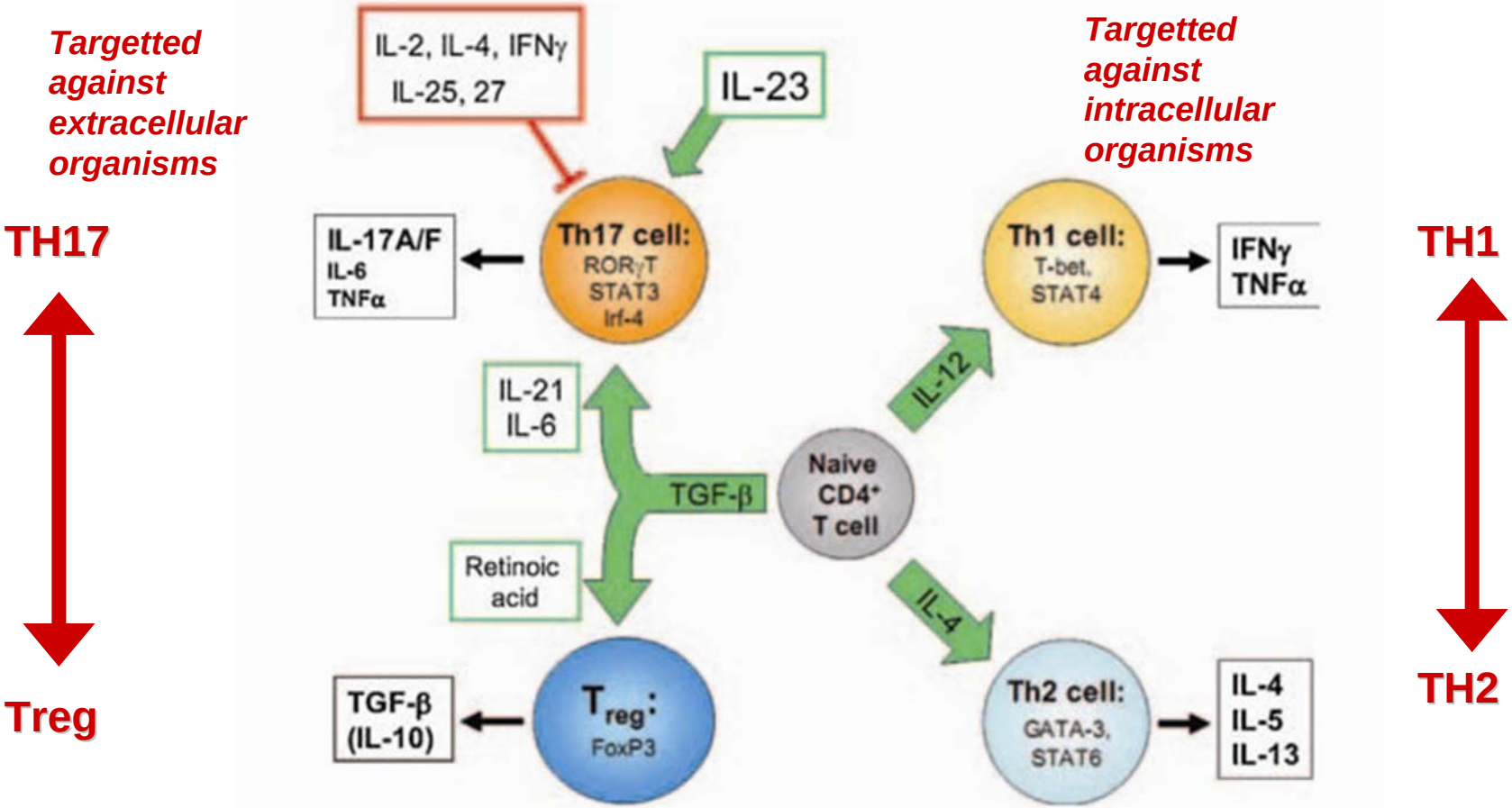
Iwakura Y et al J. Clin Invest (2006) 116:1218-1222

TWO MUTUALLY INTERDEPENDENT SPECTRUMS OF ACTIVITY:

TH1/TH2 AND TH17/Treg

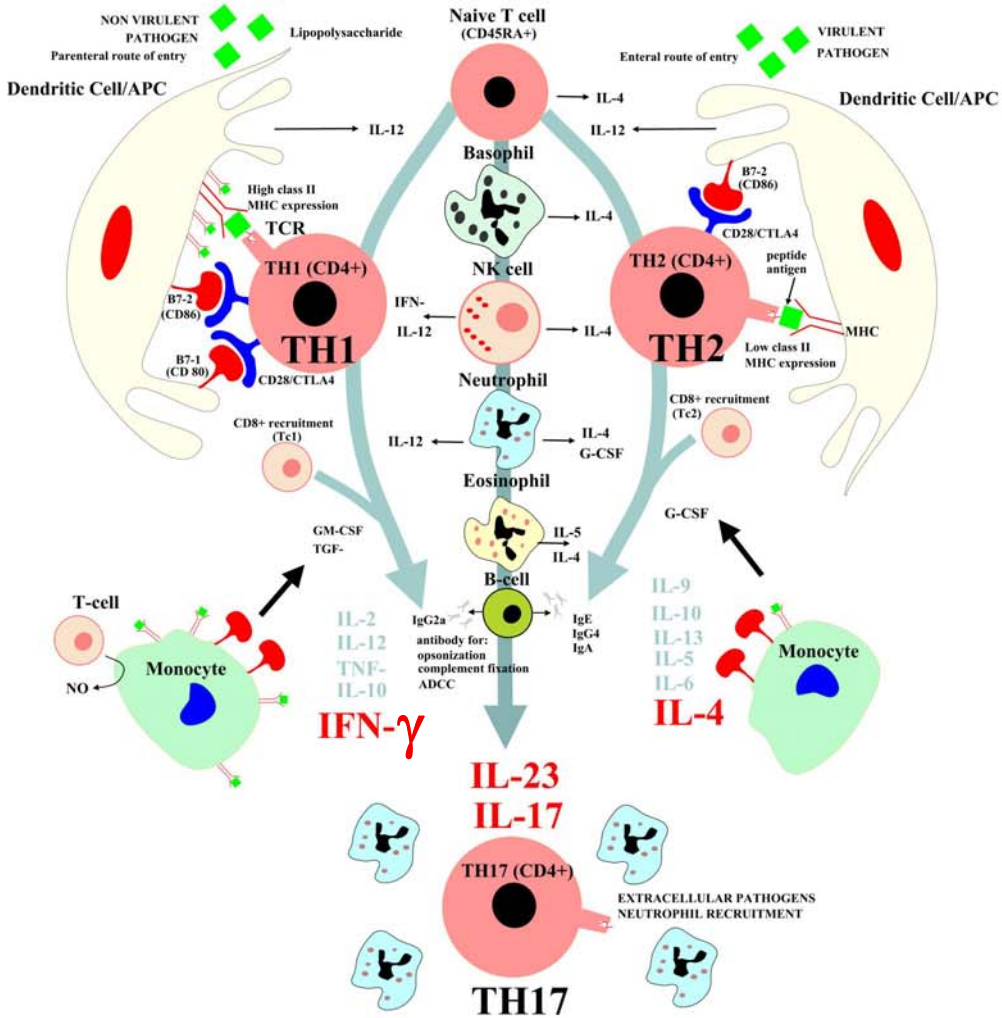
Targetted against extracellular organisms

Targetted against intracellular organisms



Kurtz C et al Neprol Dial Transpl (2007) 23: 816-819

THE NEW PARADIGM OF T_H1/T_H2 and T_H3 (now called TH17)



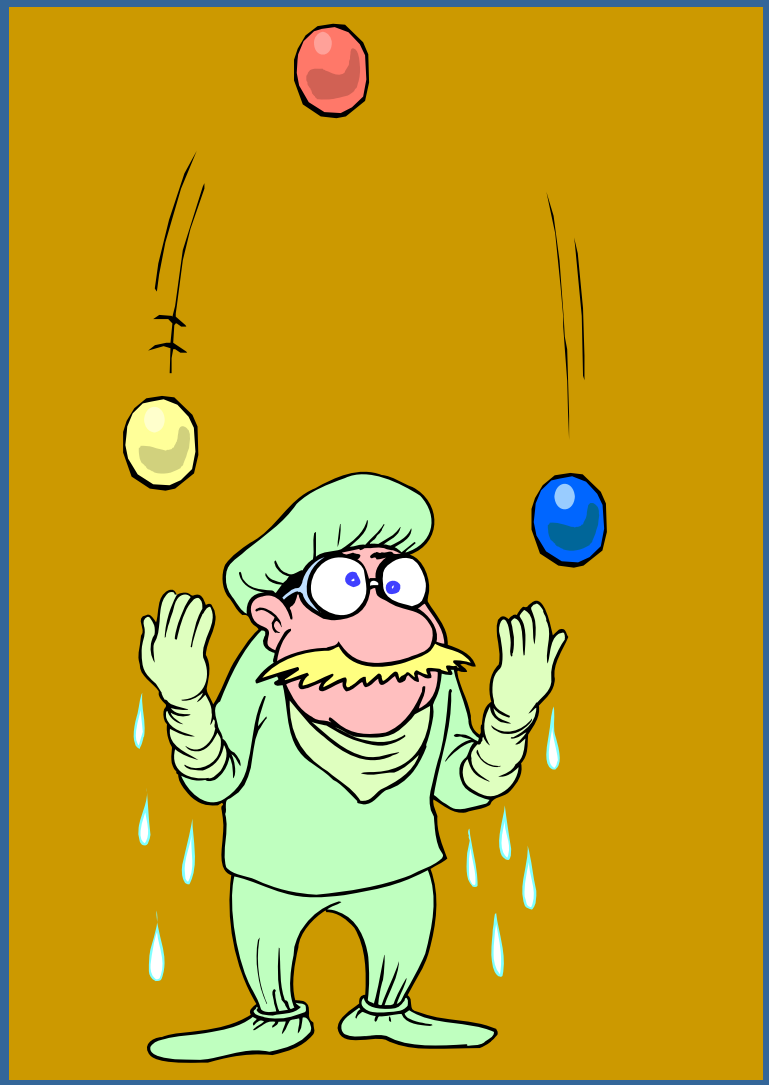
- DEFECTIVE PATHOGEN CLEARANCE
- ONGOING INFLAMMATION
- FAILURE OF PROTECTIVE RESPONSES TO FUNGI
- INCREASES TISSUE DAMAGE BY NEUTROPHILS

CONCLUSIONS:

TH17 activation is associated with:

- Ongoing inflammation
- Defective pathogen clearance
- Failure of protective responses to *Aspergillus* and *Candida*
- Increased neutrophil inflammatory activity causing tissue damage
- Blockade of IL23 and IL17 may be have therapeutic potential

VOLTAIRE'S IDEAL PHYSICIAN



The ideal doctor entertains his patient while nature does its work

"Thank God! A panel of experts!"