# Infezioni e Trapianto di CSE

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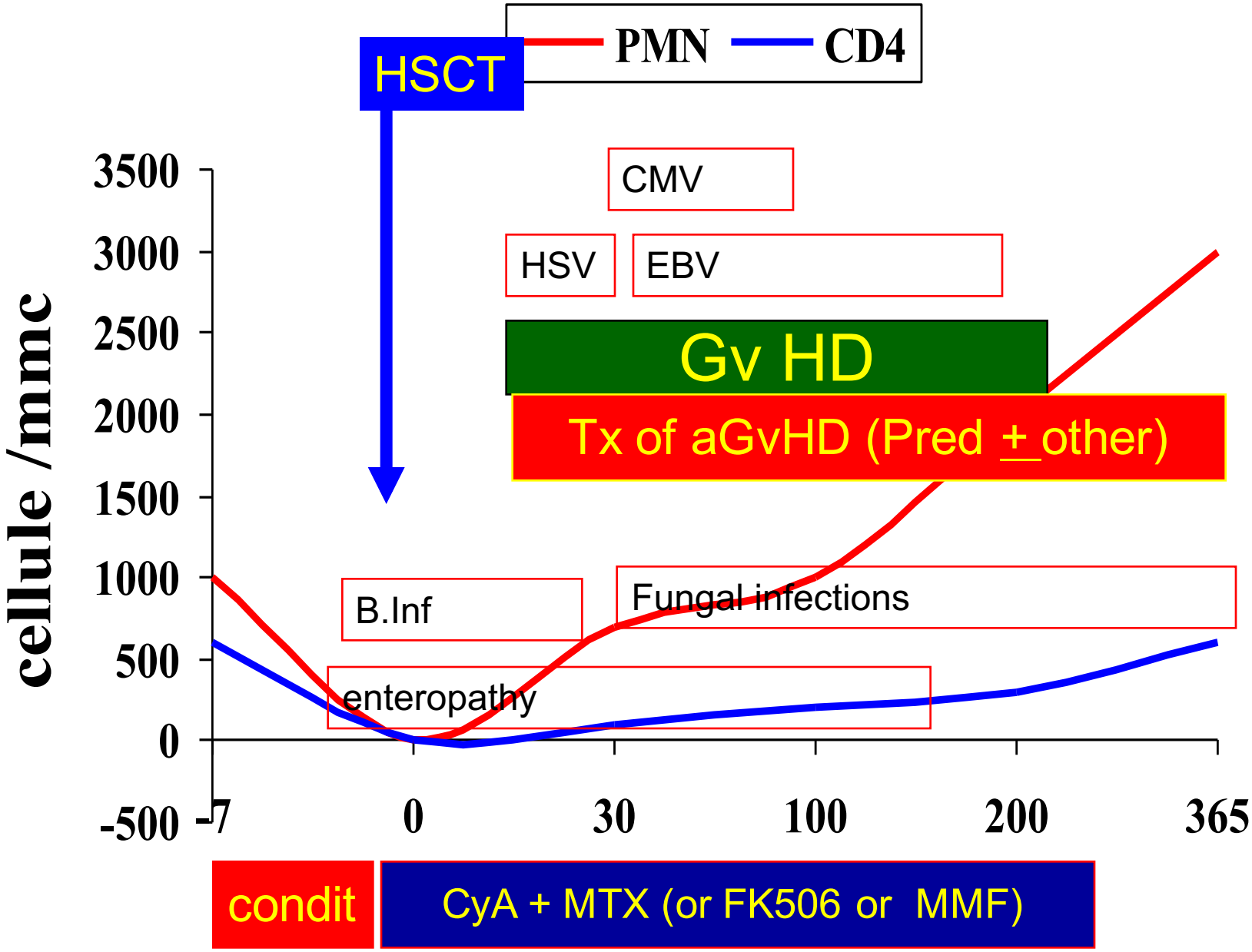
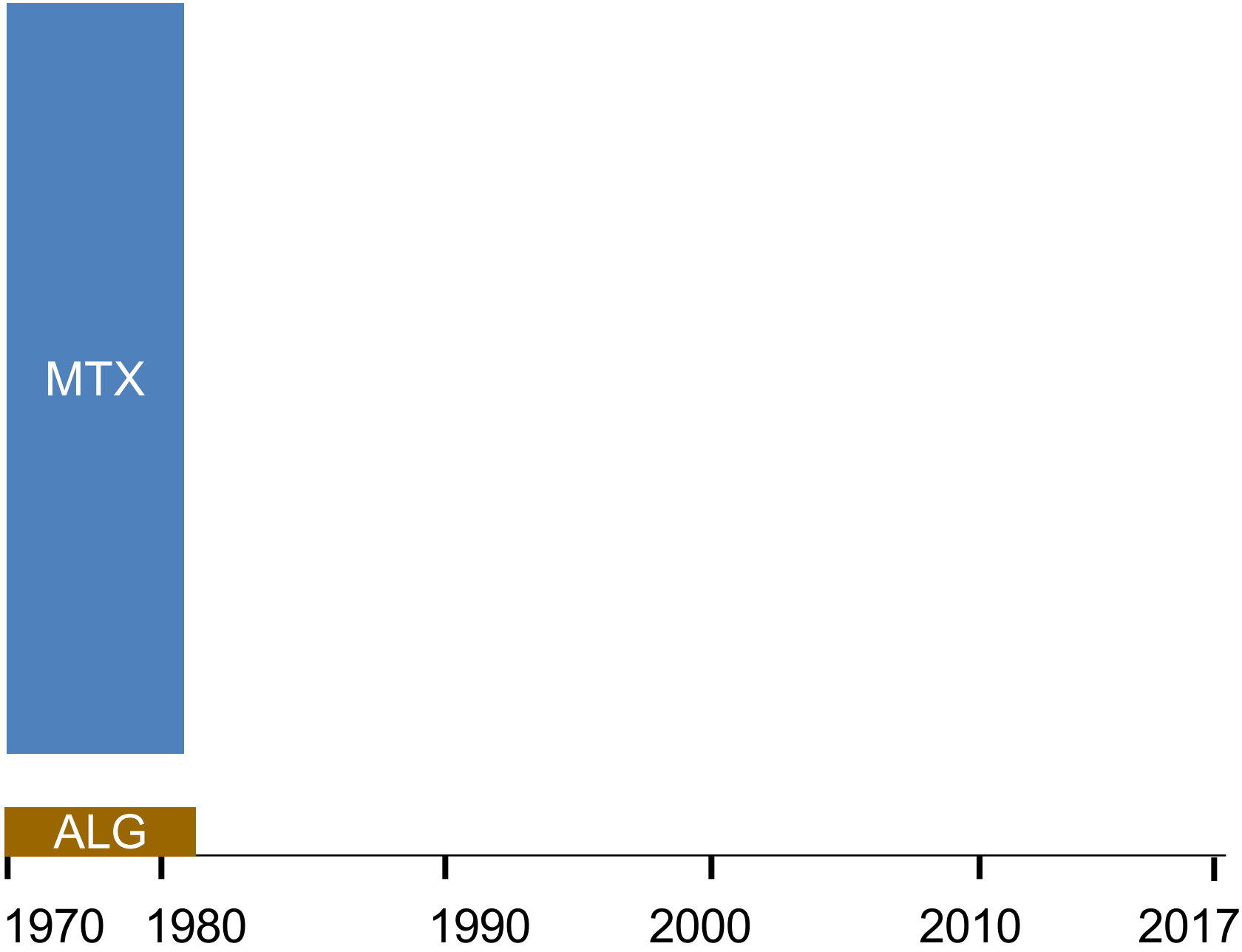
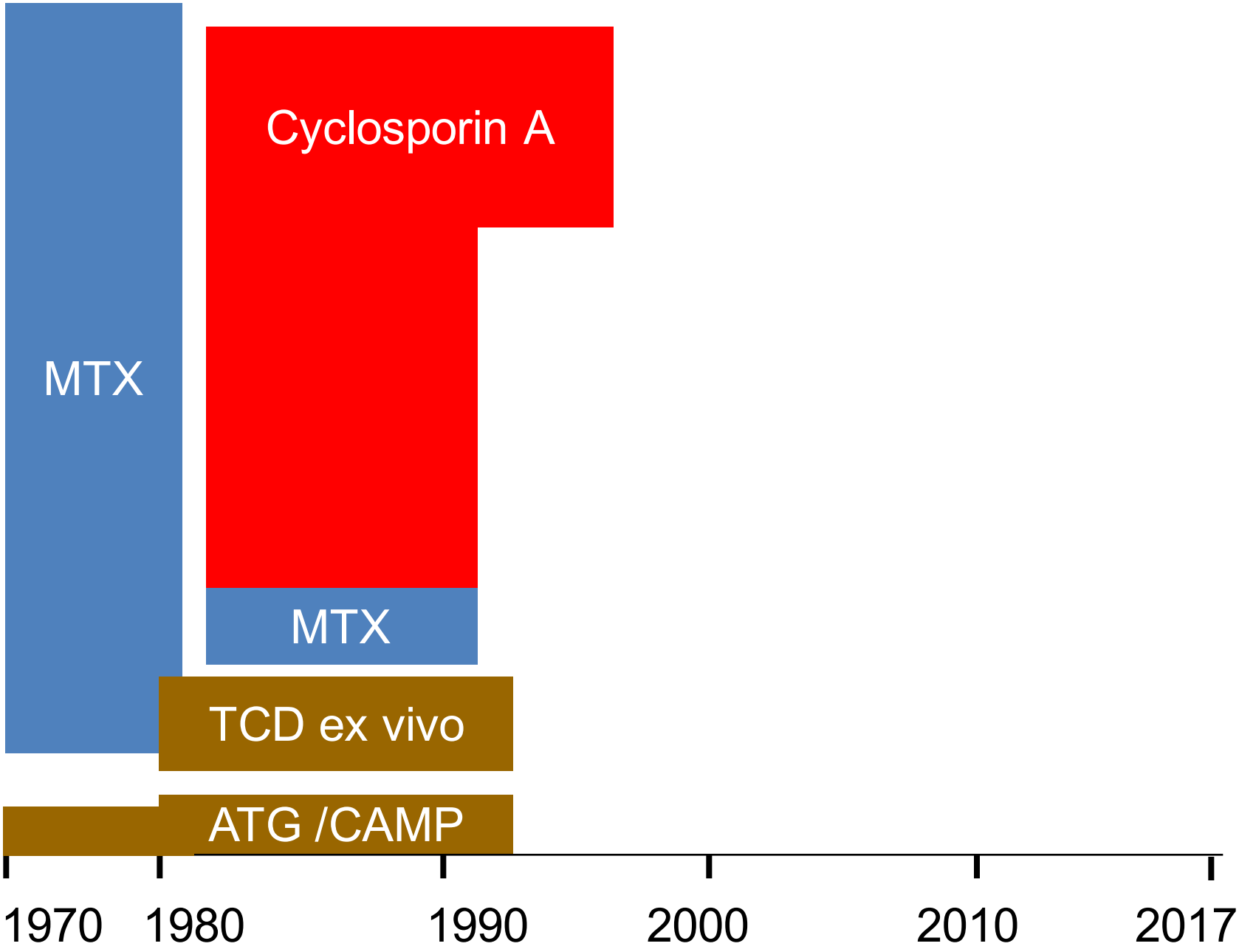

PMN
CD4
HSCT
CMV
HSV
EBV
Gv HD
Tx of aGvHD (Pred + other)
B.Inf
Fungal infections
enteropathy
cellule /mmc
3500
3000
2500
2000
1500
1000
500
0
-500
-7
0
30
100
200
365
condit
CyA + MTX (or FK506 or MMF)

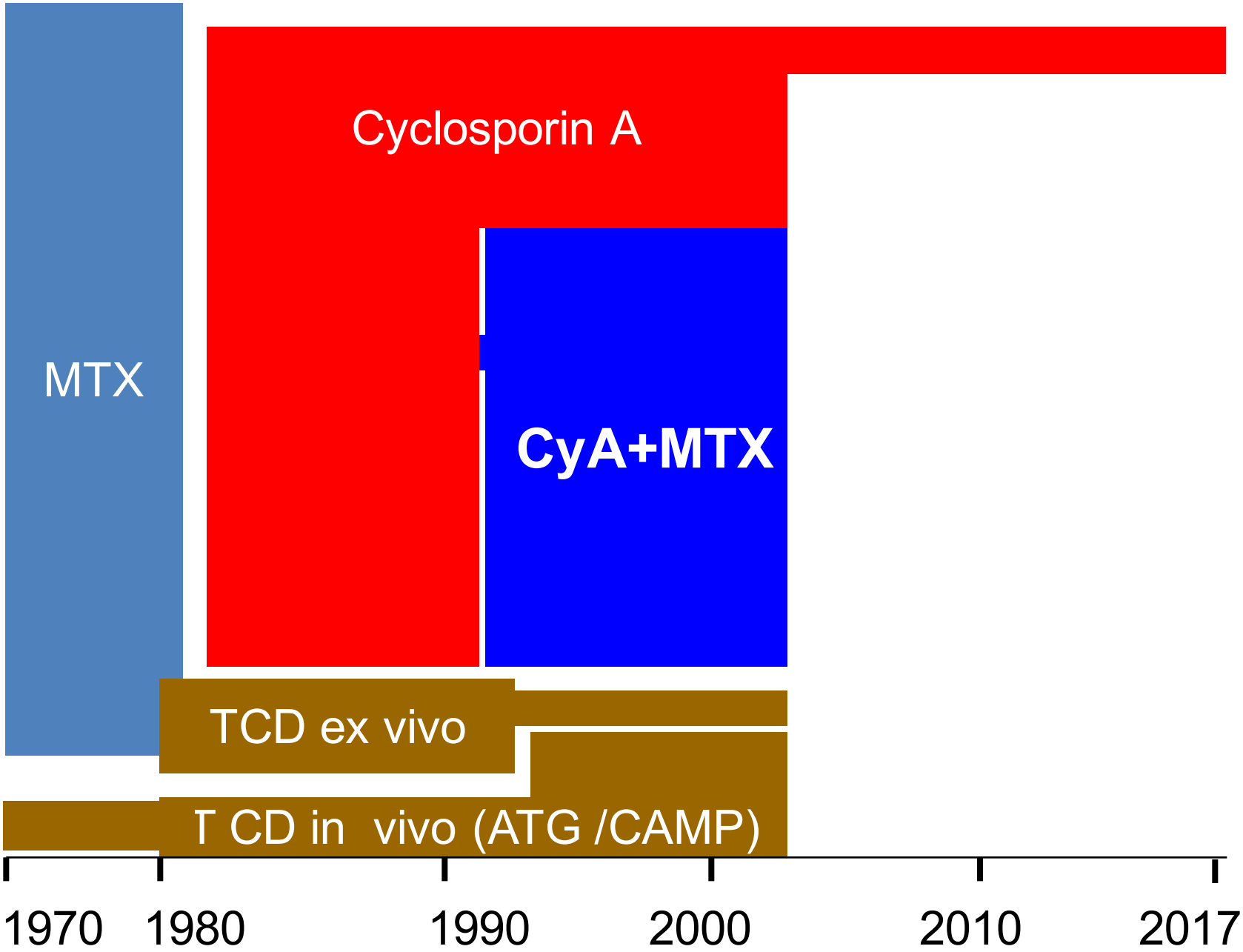
# 1. Infections and GvHD

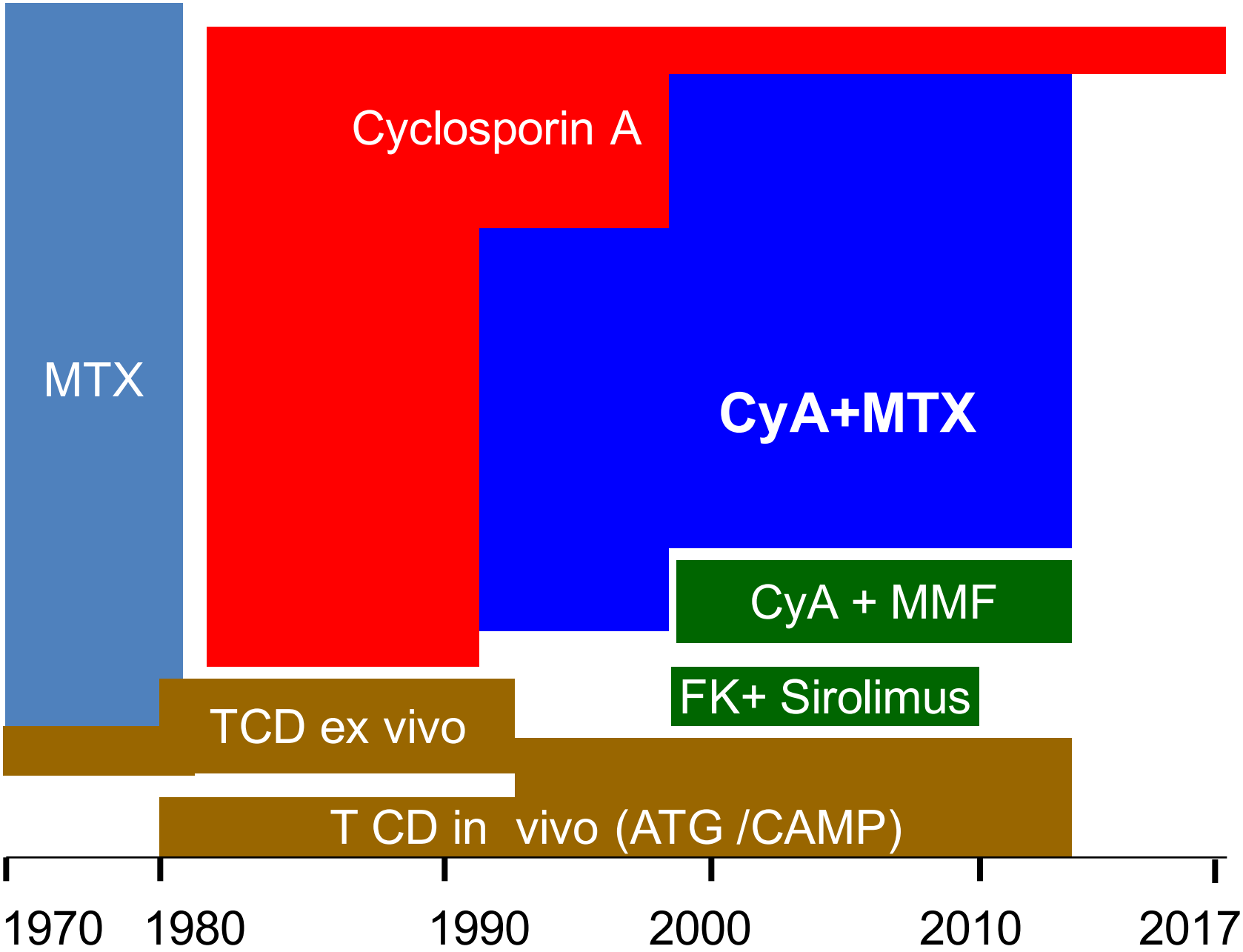
**GvHD (clinical and subclinical) plays a major role in post-transplant infections**

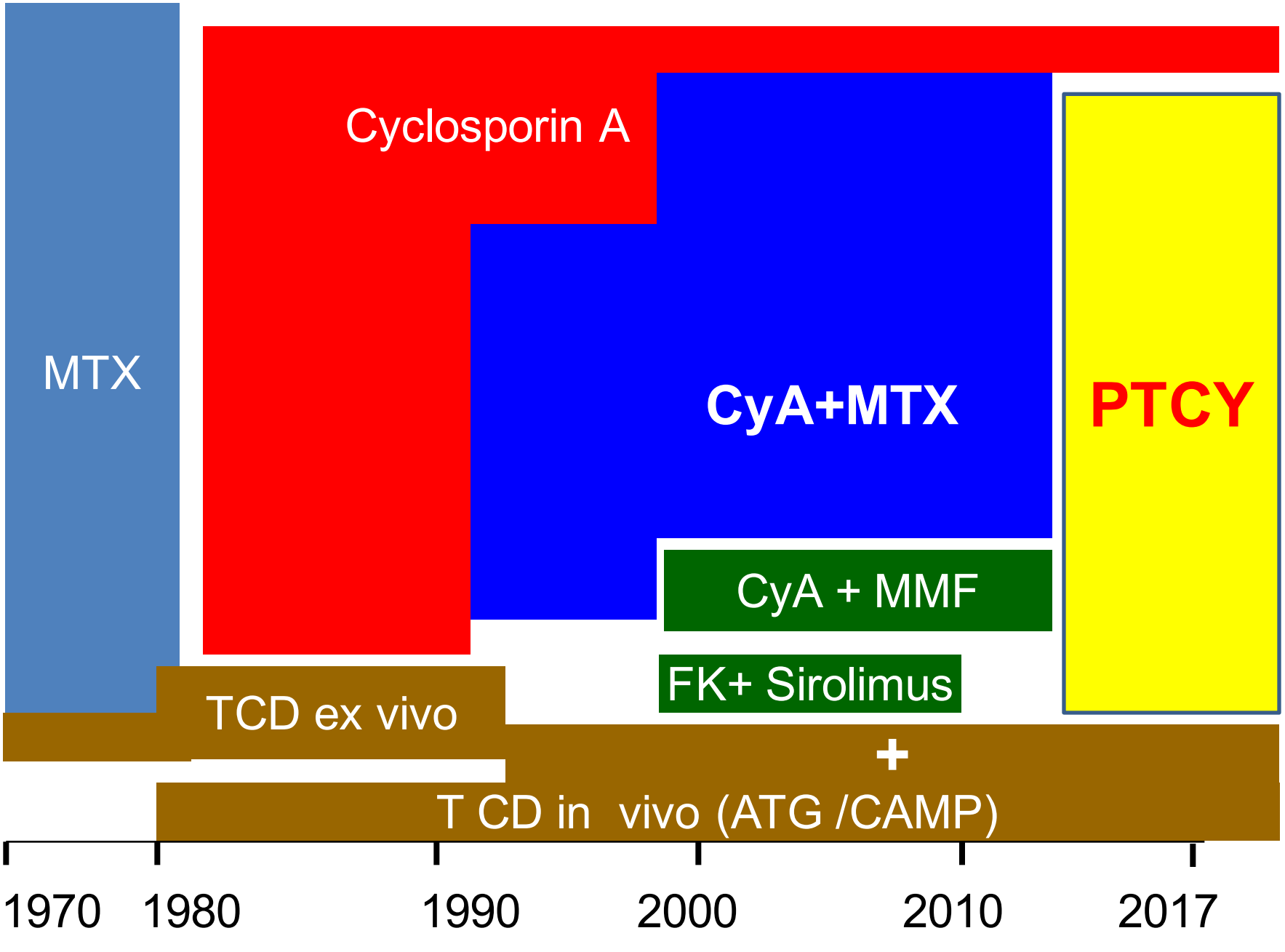
**GvHD needs to be PREVENTED**


MTX
ALG
1970
1980
1990
2000
2010
2017

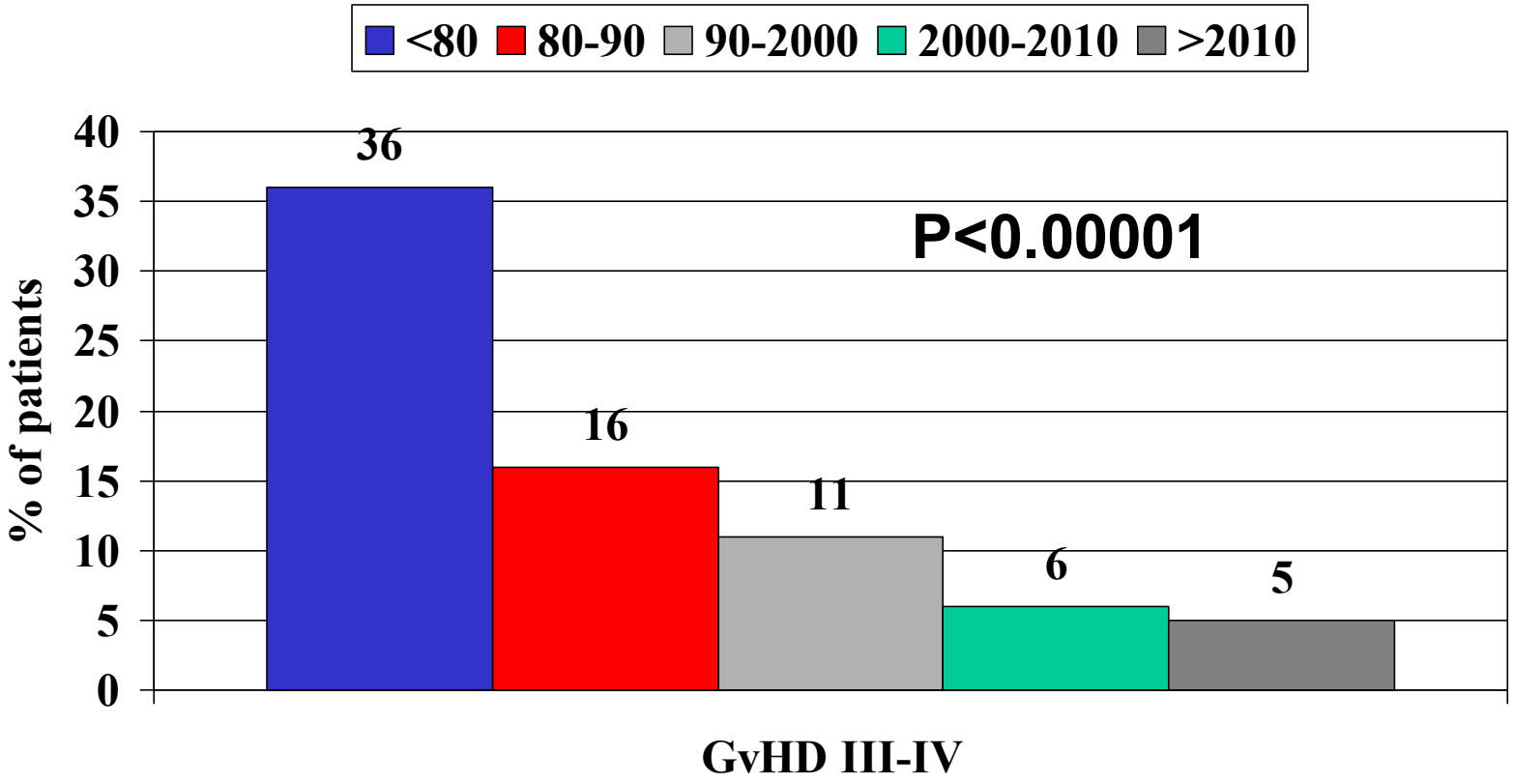

Cyclosporin A
MTX
MTX
TCD ex vivo
ATG /CAMP
1970
1980
1990
2000
2010
2017


Cyclosporin A
MTX
CyA+MTX
TCD ex vivo
T CD in vivo (ATG /CAMP)
1970
1980
1990
2000
2010
2017


Cyclosporin A
MTX
CyA+MTX
CyA + MMF
FK+ Sirolimus
TCD ex vivo
T CD in vivo (ATG /CAMP)
1970
1980
1990
2000
2010
2017


MTX
Cyclosporin A
CyA+MTX
PTCY
CyA + MMF
FK+ Sirolimus
TCD ex vivo
+
T CD in vivo (ATG /CAMP)
1970
1980
1990
2000
2010
2017

# Reduced incidence of severe GvHD

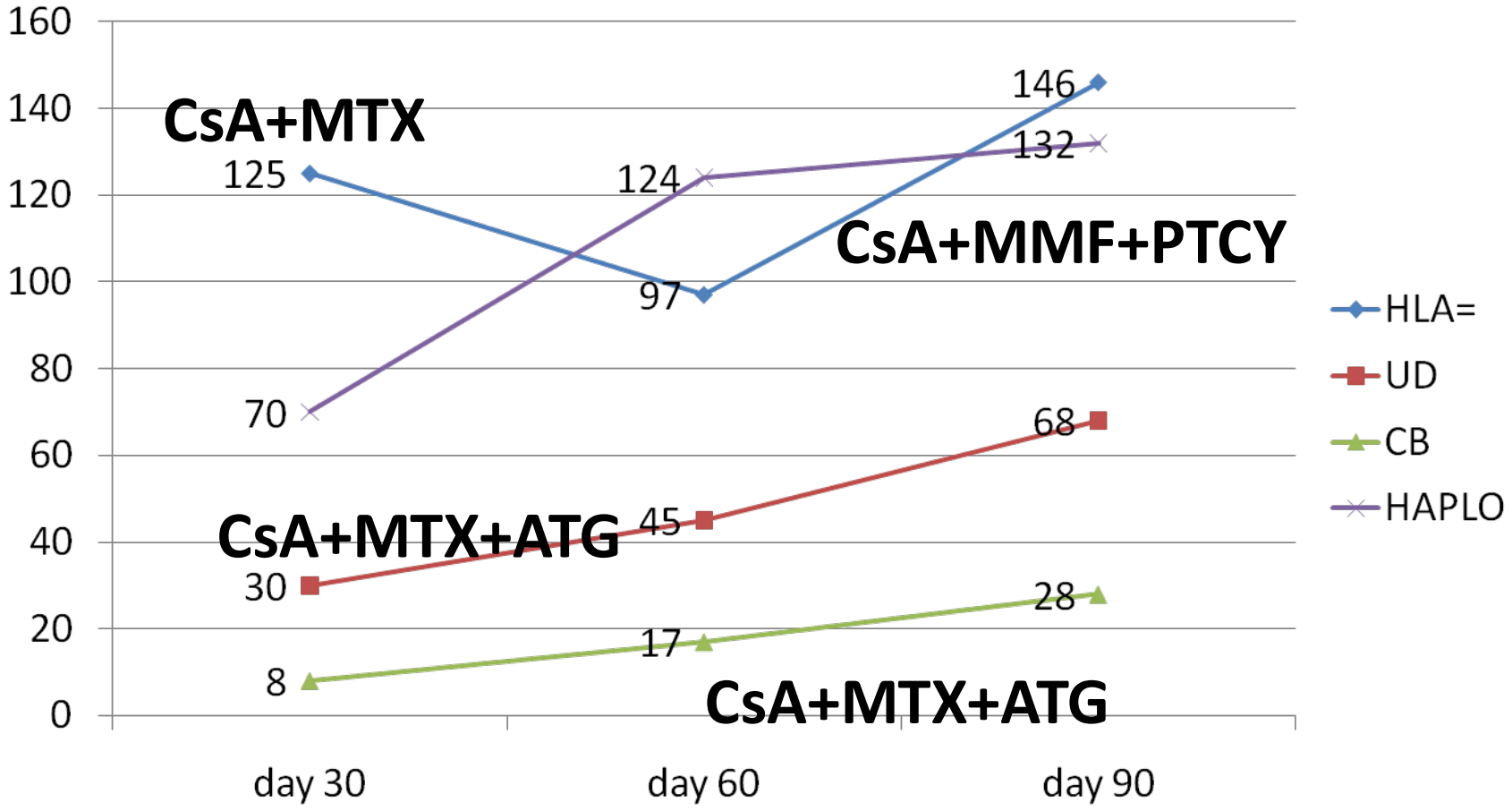


# 2. Infections and GvHD

## Significant reduction of severe GvHD with time

# CD4 recovery after HSCT

## median counts



# 3. Infections and GvHD

**Immune reconstitution depends on GvHD prophylaxis, and donor**

**Incidence ? Severity ?**

Biol Blood Marrow Transplant 23 (2017) 522–528

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

# Infectious Risk after Allogeneic Hematopoietic Cell Transplantation Complicated by Acute Graft-versus-Host Disease

Holly K. Miller [1,2,*], Thomas M. Braun [3], Terri Stillwell [4], Andrew C. Harris [1], Sung Choi [1], James Connelly [1], Daniel Couriel [1], Steven Goldstein [1], Carrie L. Kitko [1], John Magenau [1], Attaphol Pawarode [1], Pavan Reddy [1], Mary Riwes [1], Gregory A. Yanik [1], John E. Levine [1,4,5]

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[2] *Pediatric Hematology/Oncology, Phoenix Children's Hospital, Phoenix, Arizona*
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[5] *Blood and Marrow Transplant Program, Icahn School of Medicine at Mount Sinai, New York, New York*

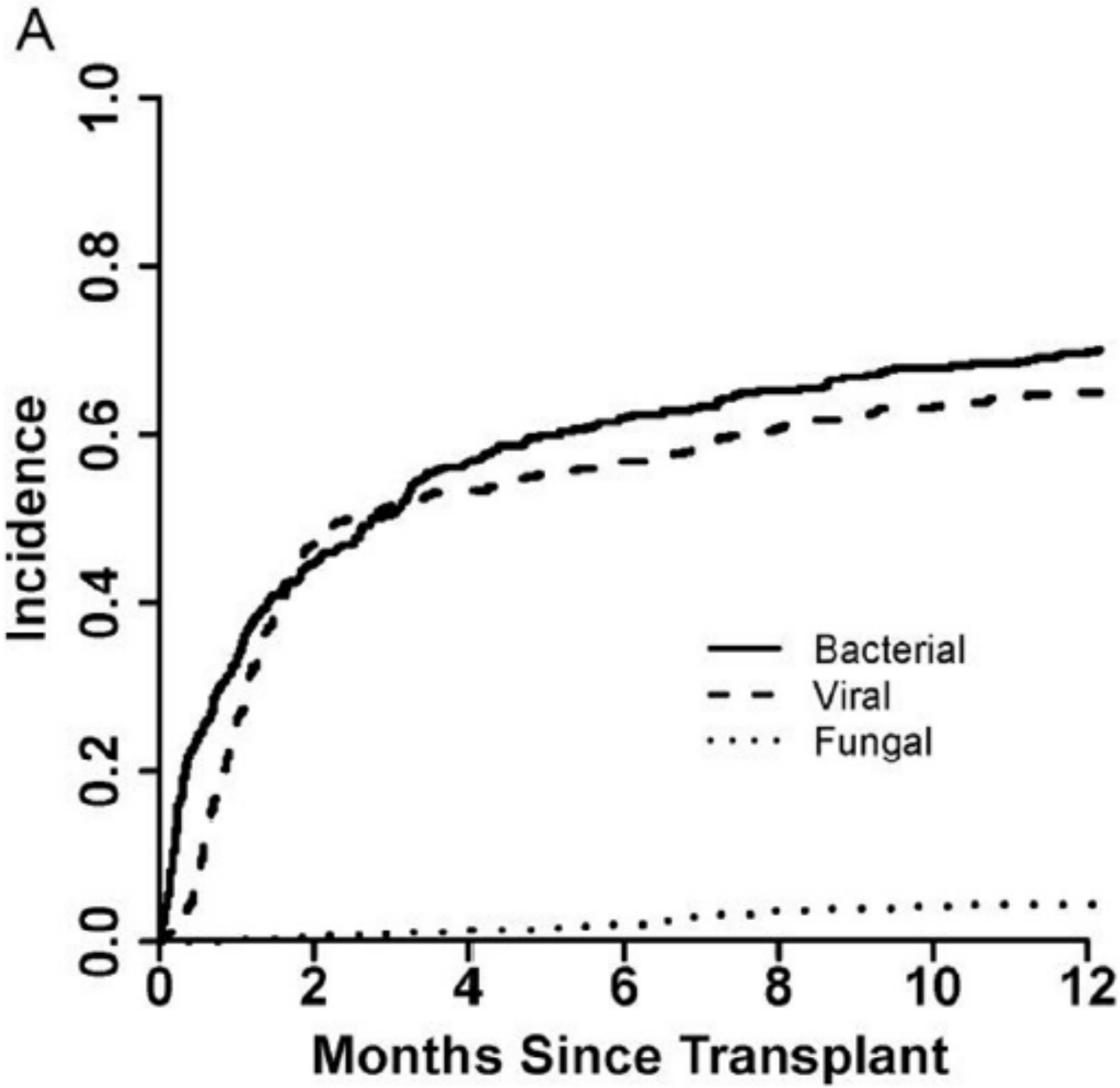
**Table 1**
Infectious Contribution to Mortality Scoring System

| Score | Definition |
|---|---|
| 0 | No infection present just before or at the time of death. The cause of death is clearly attributable to noninfectious causes (eg, relapse). |
| 1 | Documented infection just before death, with or without meeting sepsis/SIRS criteria, **but** another definitive cause of death is present (eg, aGVHD). |
| 2 | Sepsis and/or SIRS criteria are present **without** a documented infection just before or at the time of death. There is **no other** definitive cause of death present (eg, quiescent GVHD, no relapse). |
| 3 | Sepsis/SIRS **with** documented infection just before or at the time of death and **no other** definitive cause of death present. |

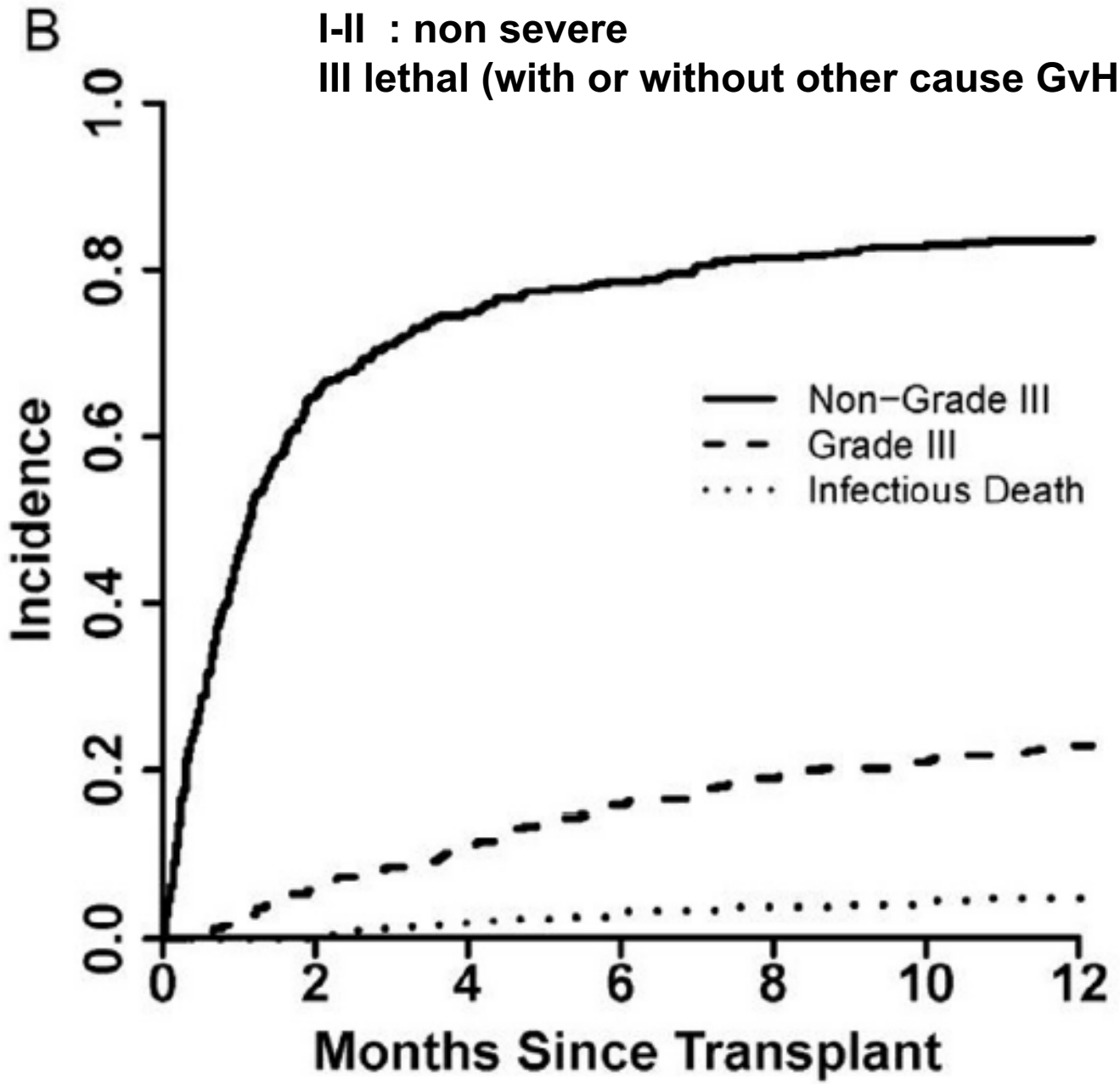
A score of 2 or 3 defined death from infection.
SIRS indicates systemic inflammatory response syndrome.

**Table 2**
Demographics

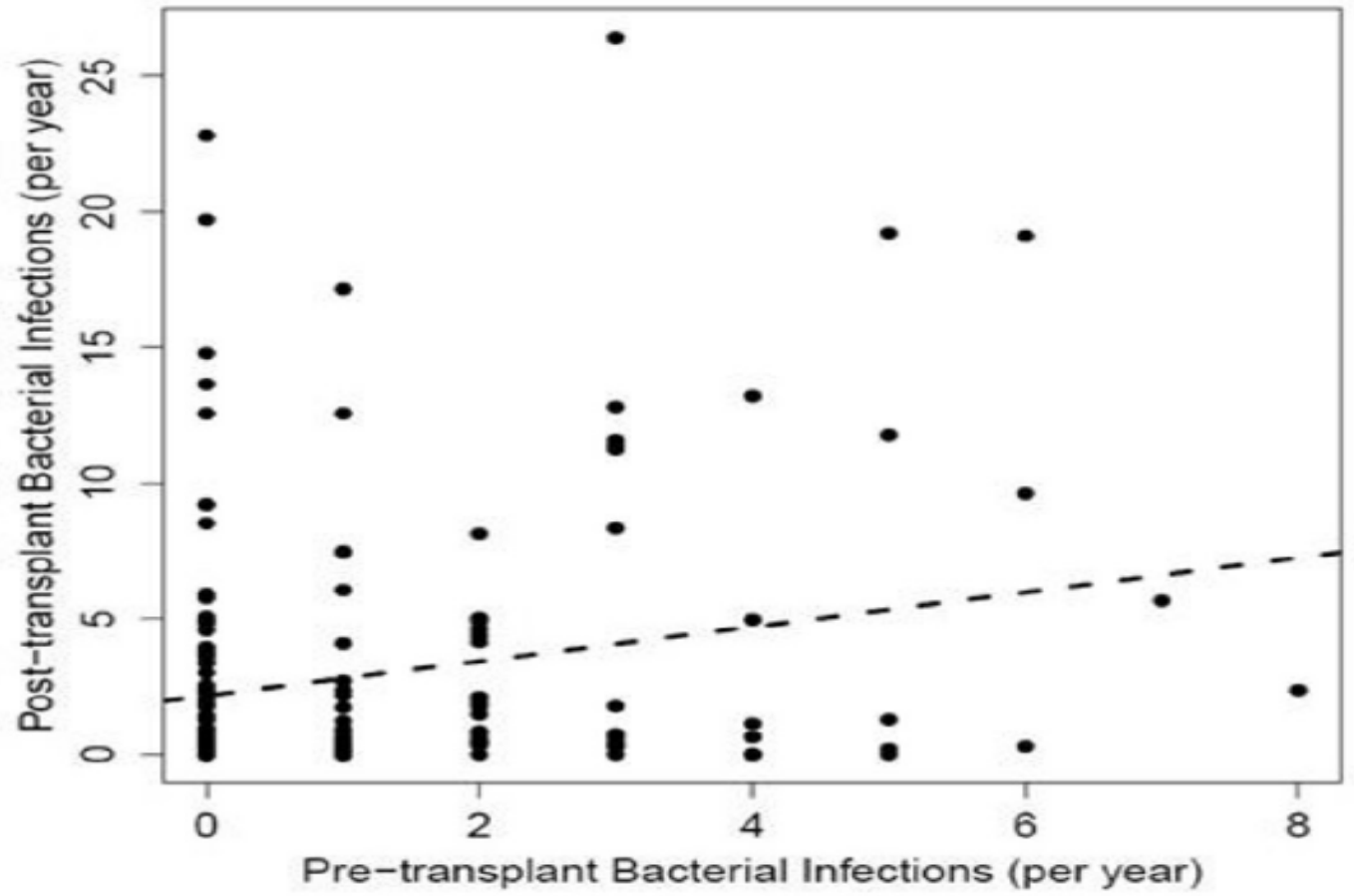
| Characteristic | aGVHD (n = 256) | No aGVHD (n = 175) |
|---|---|---|
| Age, median, (range), yr | 53.6 (.6-71.1) | 48.8 (.6-73.2) |
| Sex | | |
| Male | 57% (145) | 59% (104) |
| Female | 43% (111) | 41% (71) |
| Donor | | |
| Related | 38% (98) | 62% (108) |
| Unrelated | 62% (158) | 38% (67) |
| Stem Cell Source | | |
| BM | 8% (21) | 16% (28) |
| PBSC | 83% (211) | 75% (132) |
| CB | 9% (24) | 8% (14) |
| BM + CB | 0% (0) | 1% (1) |
| Preparative regimen | | |
| Full | 72% (184) | 74% (130) |
| Reduced | 28% (72) | 26% (45) |
| Day of aGVHD onset, median (range) | 35 (7-273) | N/A |
| Follow-up, median (range) | 616 d (25 d-6.5 yr) | 953 d (16 d-6.6 yr) |


A
Incidence
0.0
0.2
0.4
0.6
0.8
1.0
0
2
4
6
8
10
12
Months Since Transplant
Bacterial
Viral
Fungal

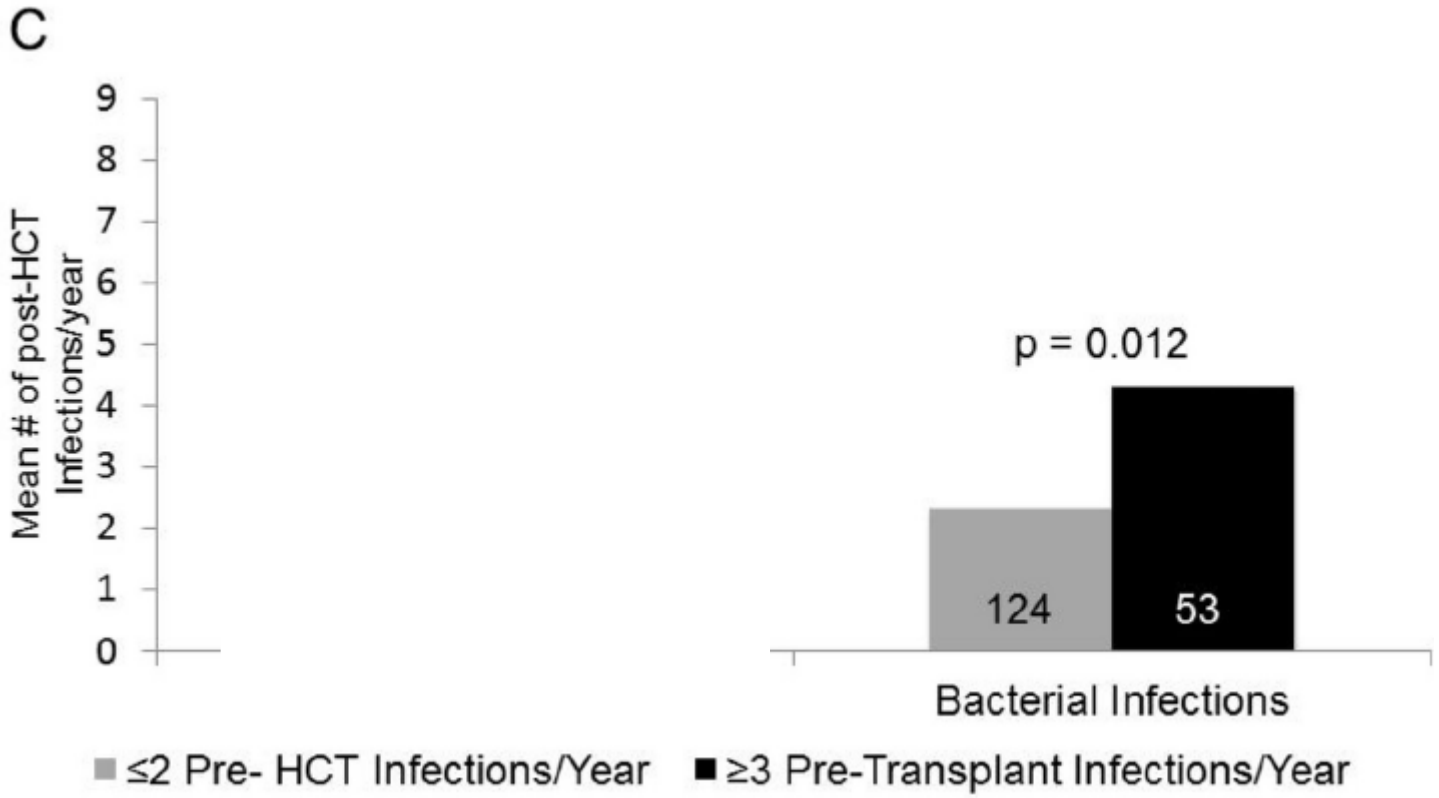
**CI of infections**
**I-II : non severe**
**III lethal (with or without other cause GvHD)**



# Predisposing factors?

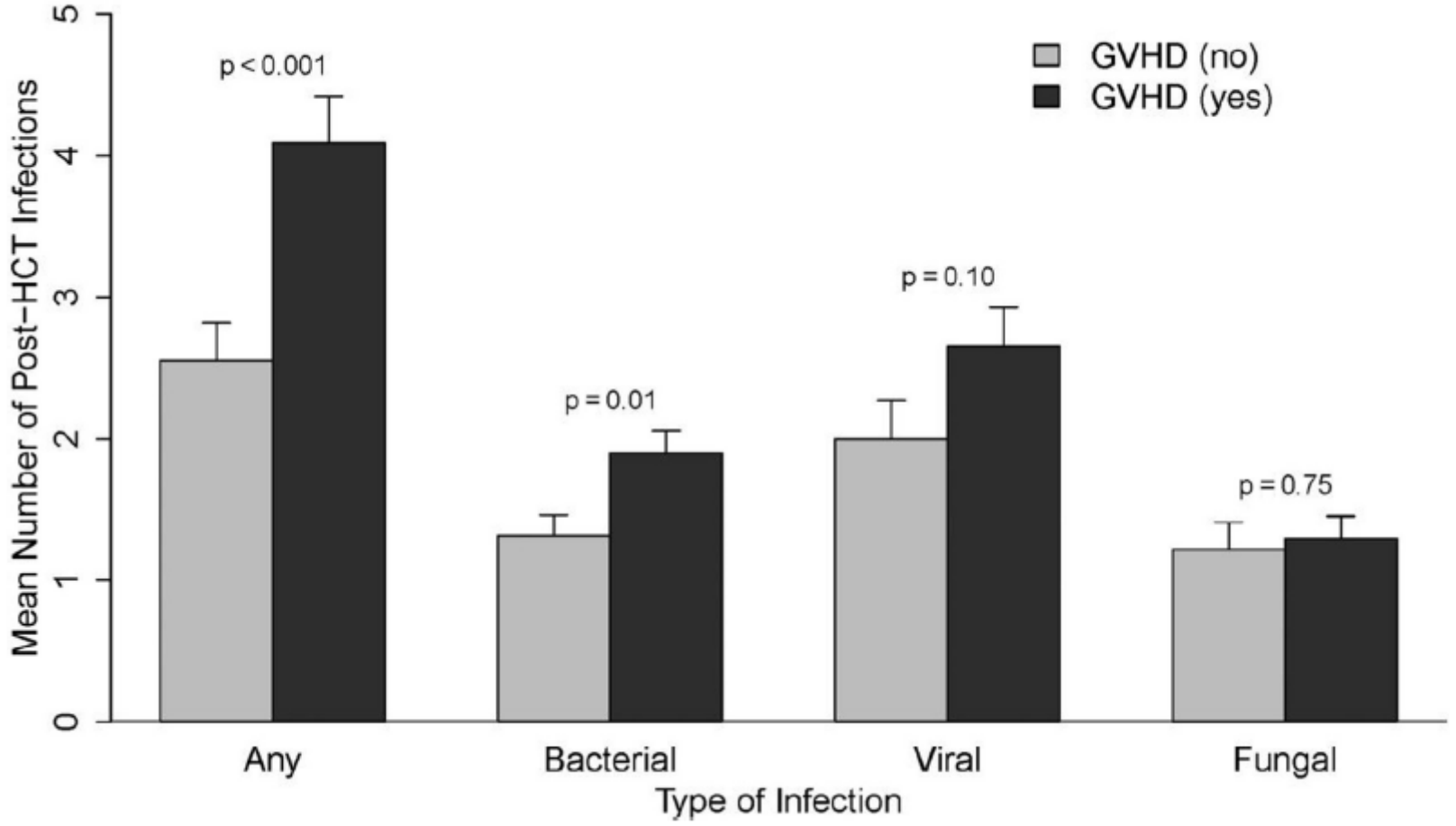



**Each pre-transplant bacterial infection/year leads to an additional 2.15 post-HSCT bacterial infection year (p=0.004)**

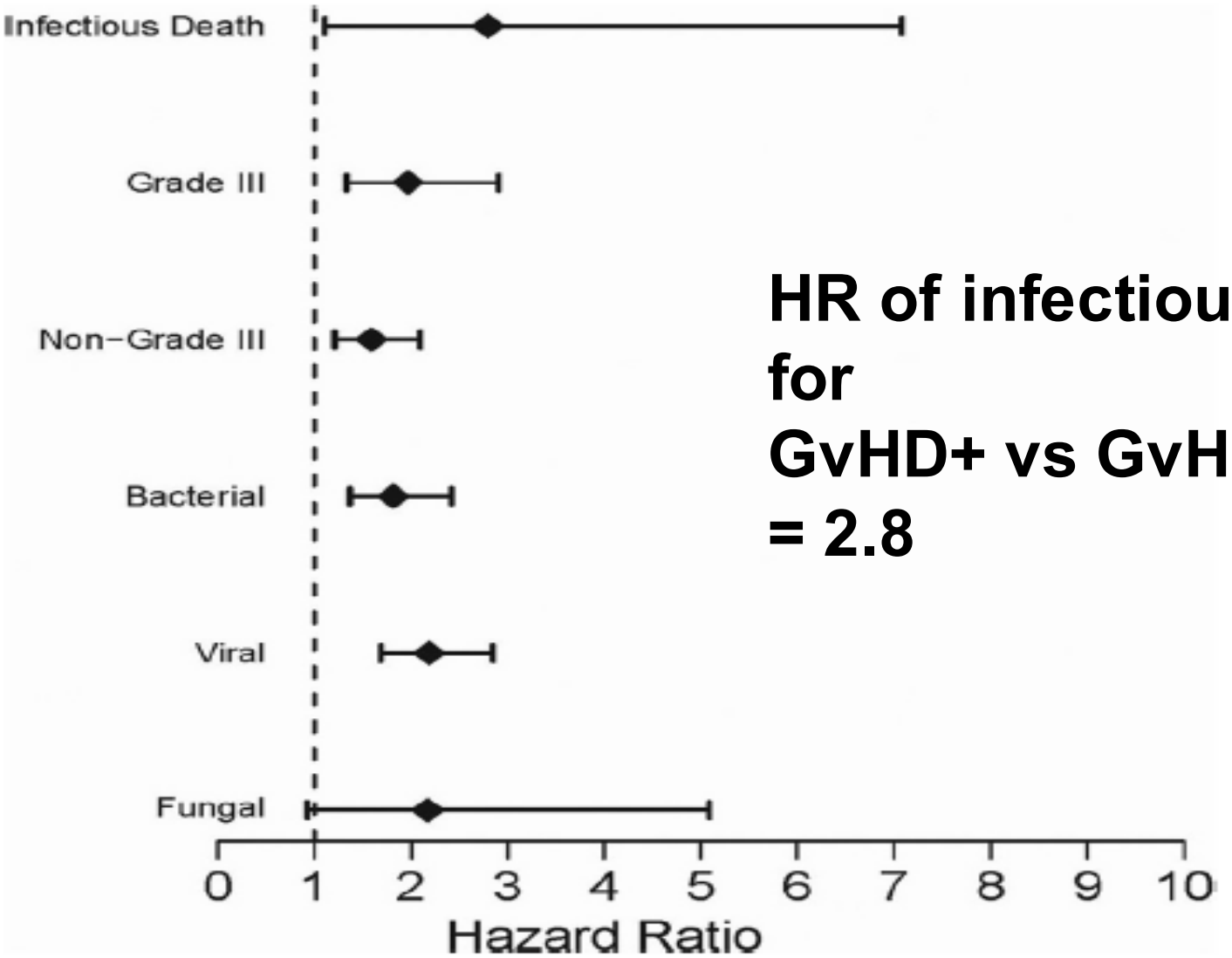



| | Pre HSCT | Post HSCT | |
|---|---|---|---|
| Inf/year | ≤2 | 2.3 | |
| Inf/year | >2 | 4.3 | 0.01 |

# GvHD increases the incidence of infections

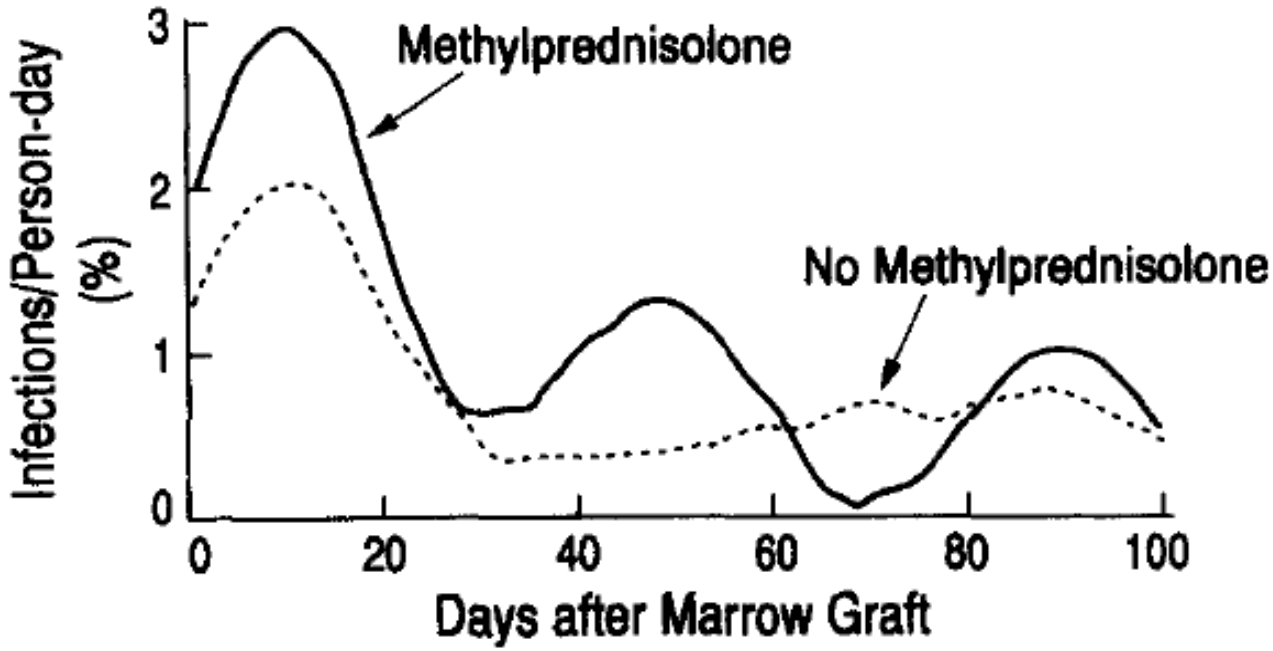


# GvHD increases the severity of infections




**HR of infectious death for GvHD+ vs GvHD- = 2.8**

# Bacterial infections and **acute** GVHD




Sayer, Blood 1994

# 4. Bacterial Infections and GvHD

## Risk factors

## Pre-Tx bacterial infections
## GvHD (increases the number and severity )

GITMO
GRUPPO ITALIANO TRAPIANTO MIDOLLO OSSEO
Commissione Infezioni

Impact of IFDs in the overall survival at 1-year from transplant **2008-2010**

# Multivariate analysis

| Parameter | Pr > ChiSq | Hazard Ratio | 95% Hazard Ratio Confidence Limits | |
|---|---|---|---|---|
| IFD, time dependent | <.0001 | 3.149 | 2.526 | 3.927 |
| aGVHD: 0-1 vs 2-4 | <.0001 | 1.432 | 1.211 | 1.694 |
| Stem cell source: BM vs PERIPH | 0.3202 | 0.910 | 0.755 | 1.096 |
| Stem cell source: CB vs PERIPH | 0.0420 | 1.300 | 1.010 | 1.674 |
| Donor: Matched rel vs unrelated | 0.0030 | 0.769 | 0.646 | 0.914 |
| Donor: Mismatched rel vs unrelated | 0.0131 | 1.475 | 1.085 | 2.004 |
| Age, continuous | <.0001 | 1.014 | 1.008 | 1.019 |
| Disease phase at transplant: CR vs no CR | <.0001 | 0.466 | 0.386 | 0.561 |
| Disease: AL vs other | <.0001 | 1.630 | 1.354 | 1.961 |

# 5. Fungal Infections and GvHD

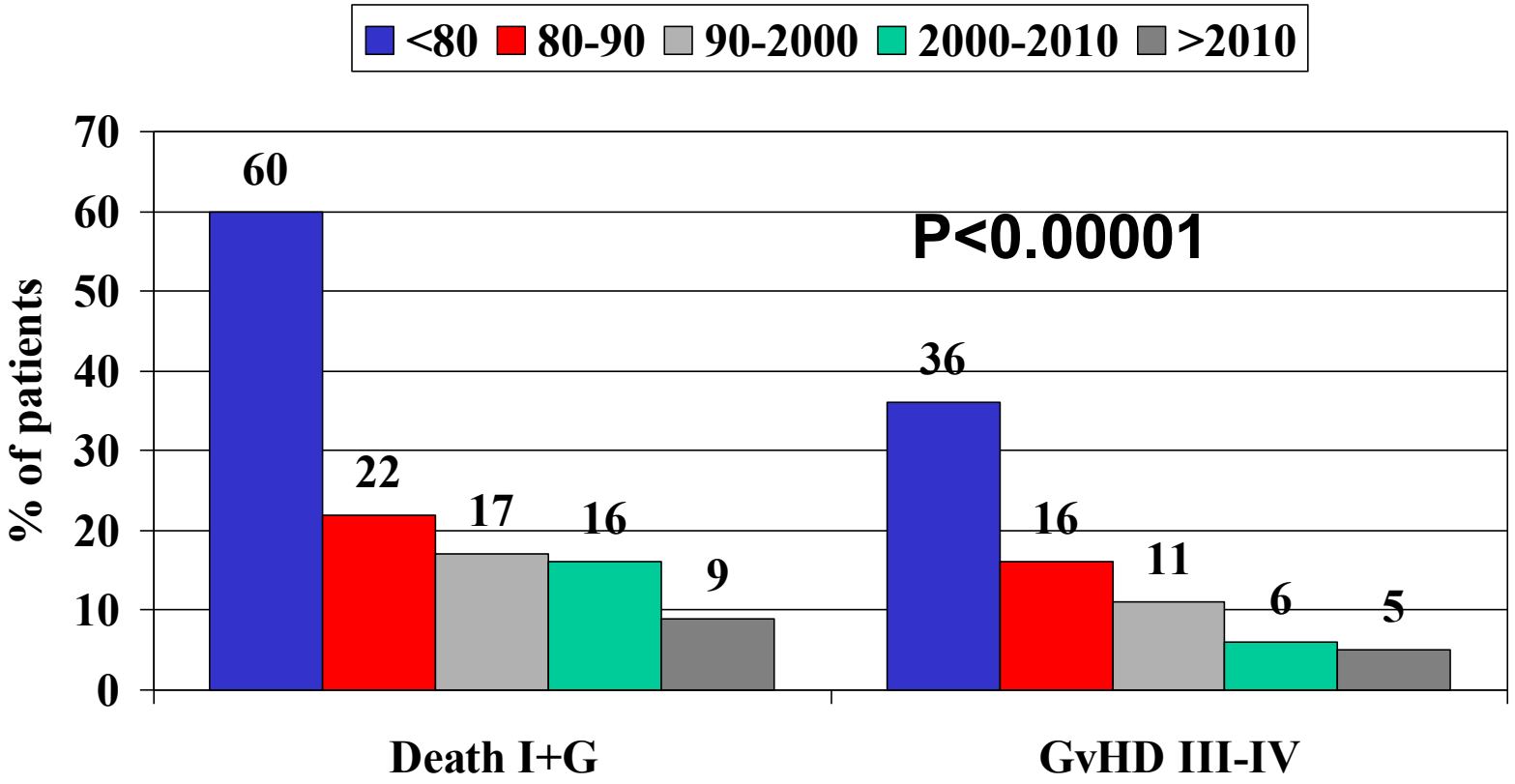
# risk factors are
GvHD, age, advanced disease,
acute leukemia

# IFI increase mortality

**If GvHD promotes infections and infectious mortality**

**Preventing severe GvHD should reduce infection related mortality**

# Reduced incidence of severe GvHD n=2455 allogeneic HSCT



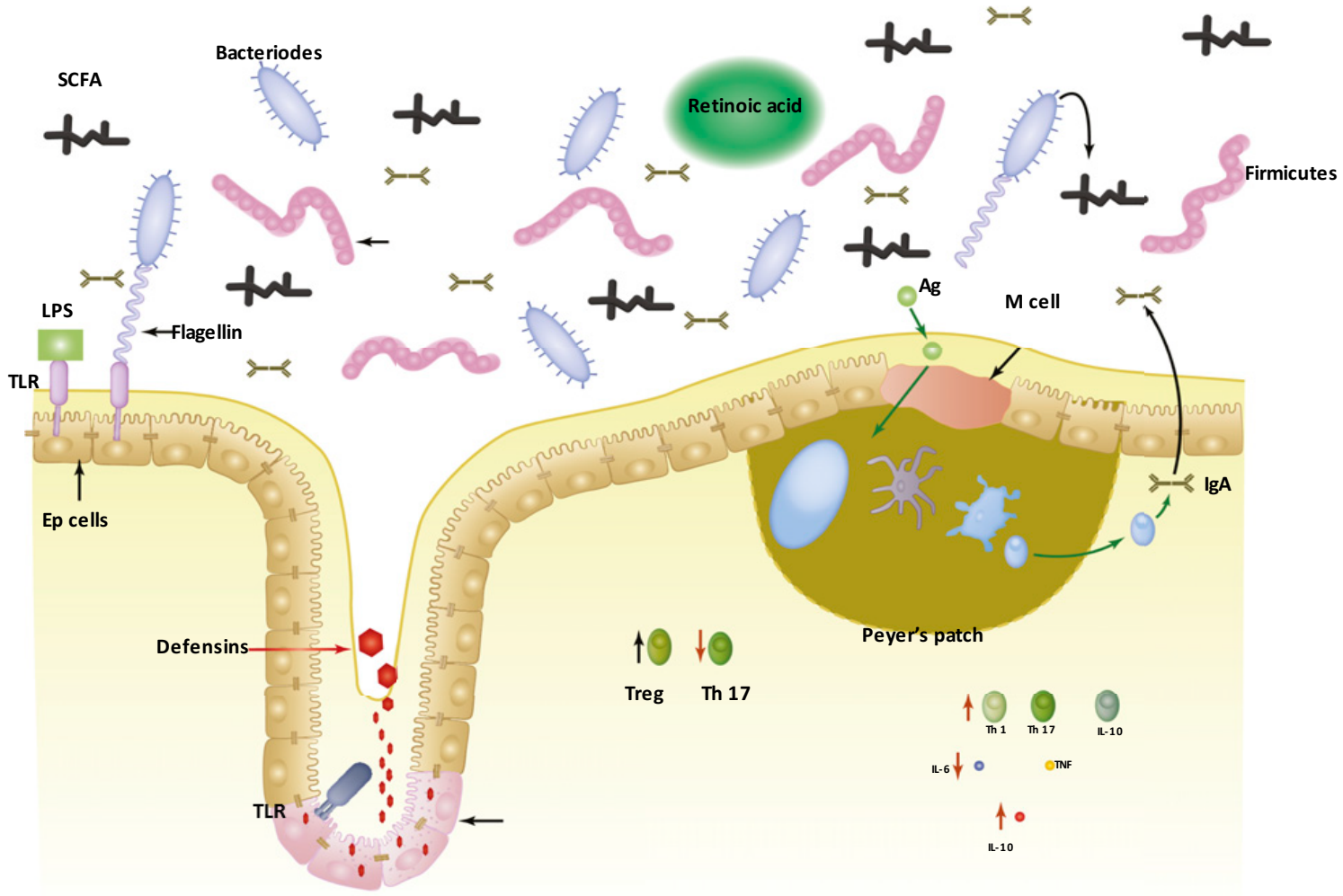
# 6. Infections and GvHD

**YES:**

**Prevention of GvHD decreases mortality due to infections (+ GvHD)**

# New trends?

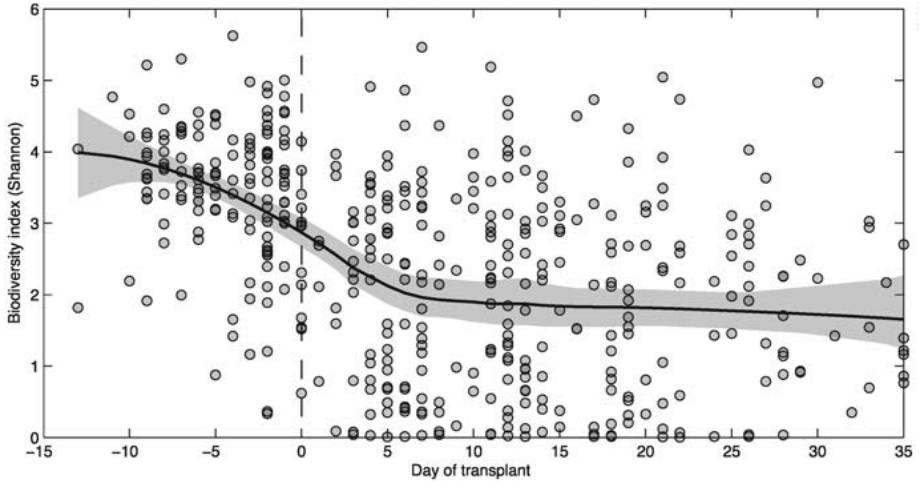
# Bacterial infections and GVHD: the microbiota

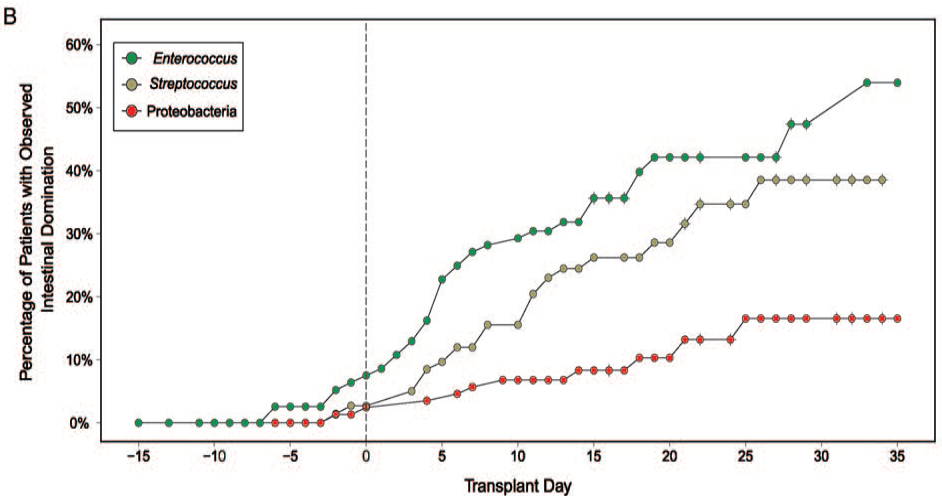



Manzo, Blood 2015

# Bacterial infections and GVHD: the microbiota

- Fecal analysis from 94 patients until day +35




Taur, CID 2012

# CONCLUSIONS

**Very strong correlation of GvHD and infections**

**Effective prevention of GvHD is the secret for successful allogeneic HSCT**

## Genova BMT Unit

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