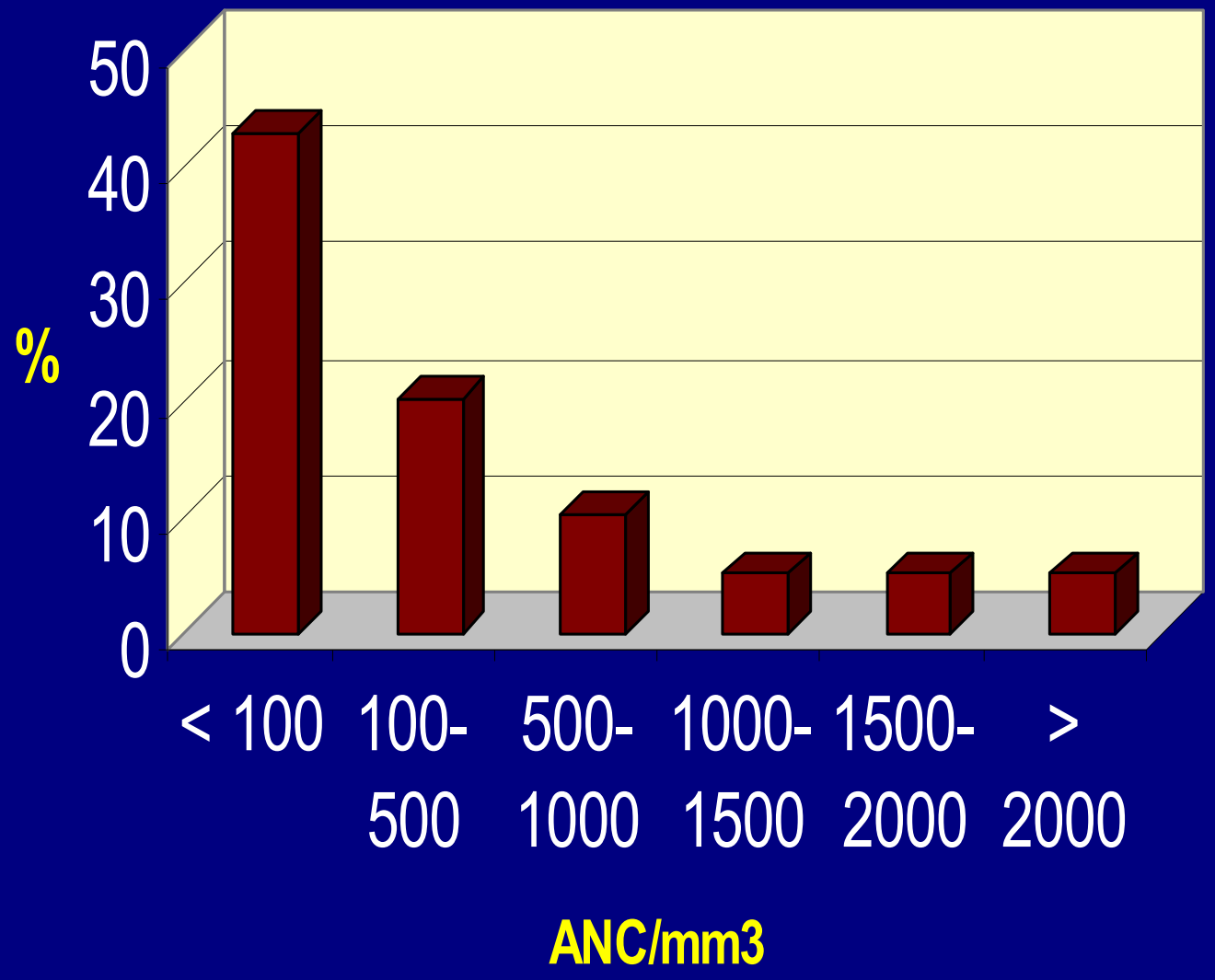
Complicanze infettive nelle malattie linfoproliferative

Alessandro Busca

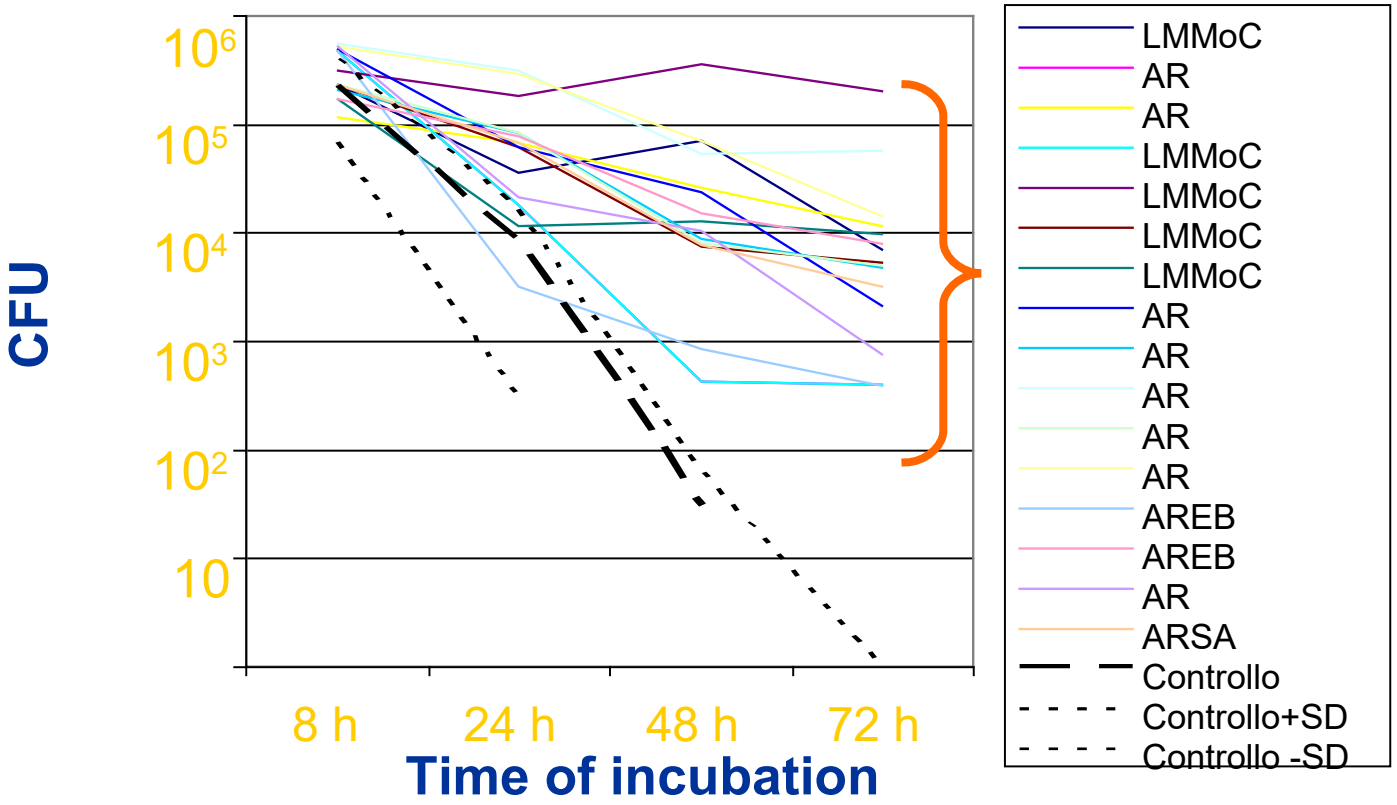
Episodes of Severe Infection



Bodey et al Ann Int Med 1966

Impaired bactericidal and fungicidal activities of neutrophils in patients with myelodysplastic syndrome

Fianchi *et al*, Leuk Res 2012

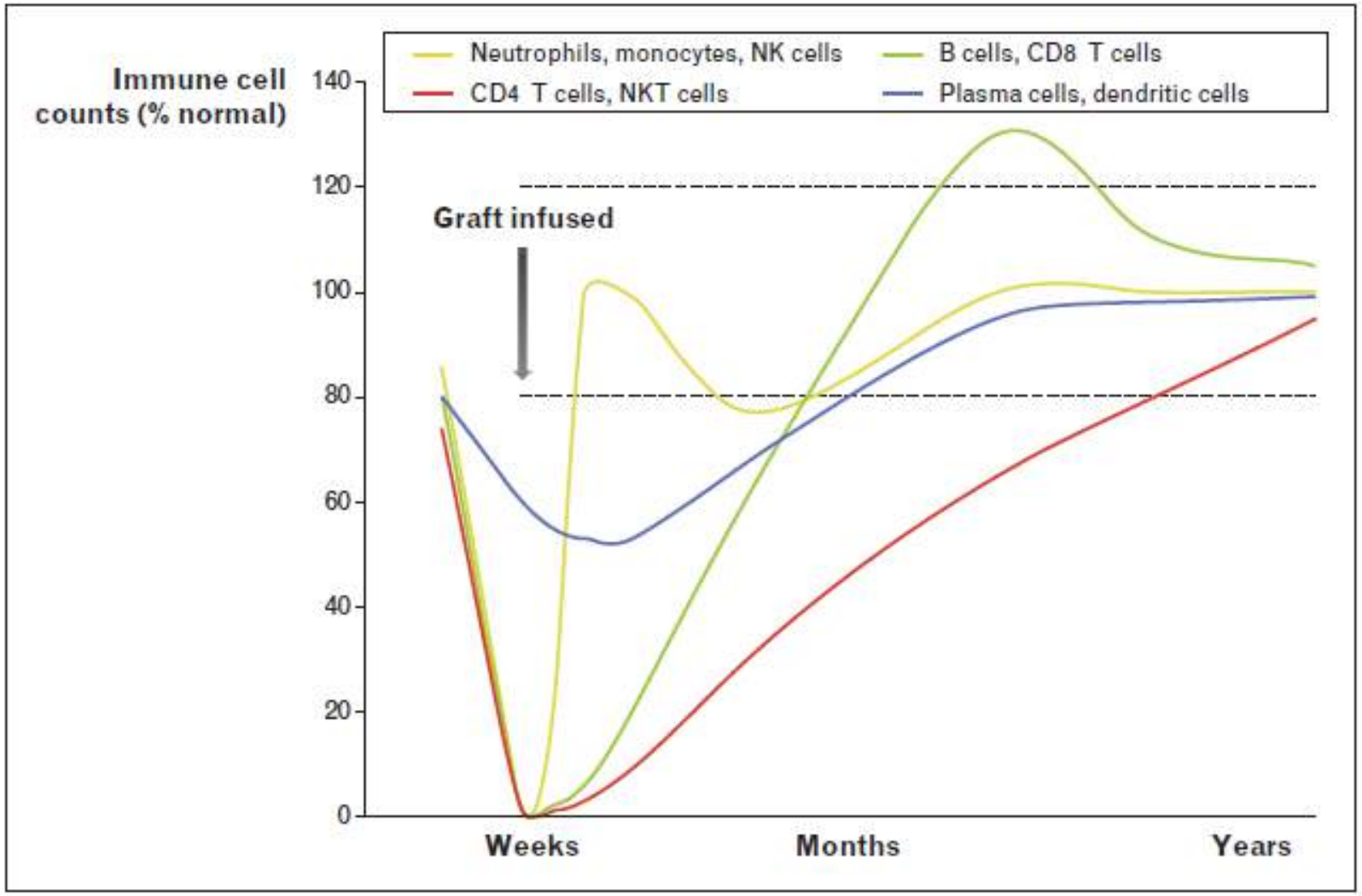


<u>Dysplastic vs normal PMN:</u>

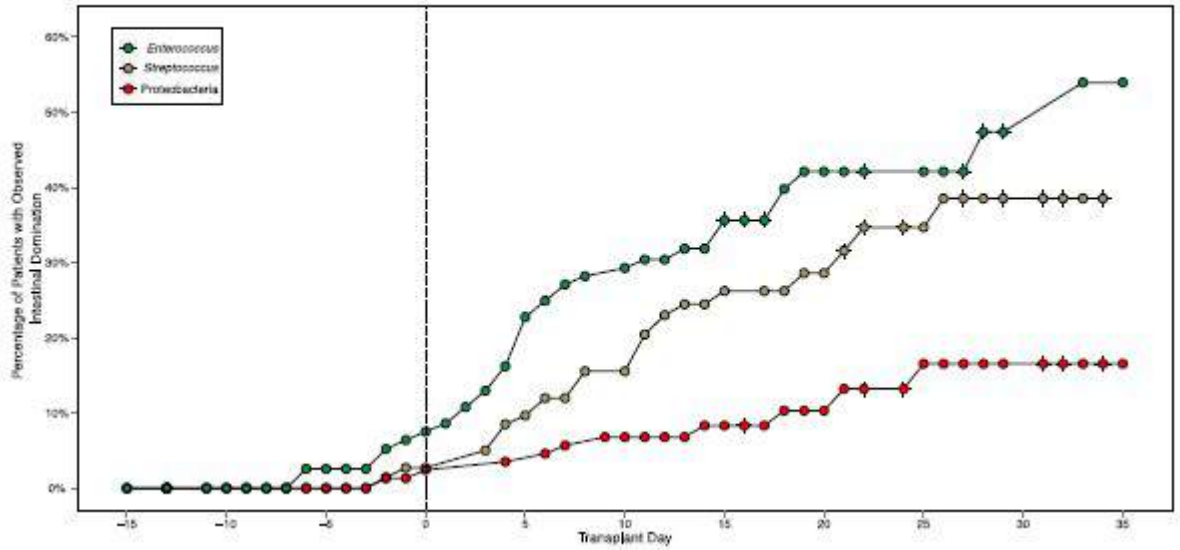
↓ fungicidal activity against yeasts

↑ susceptibility to infections in myelodysplasia

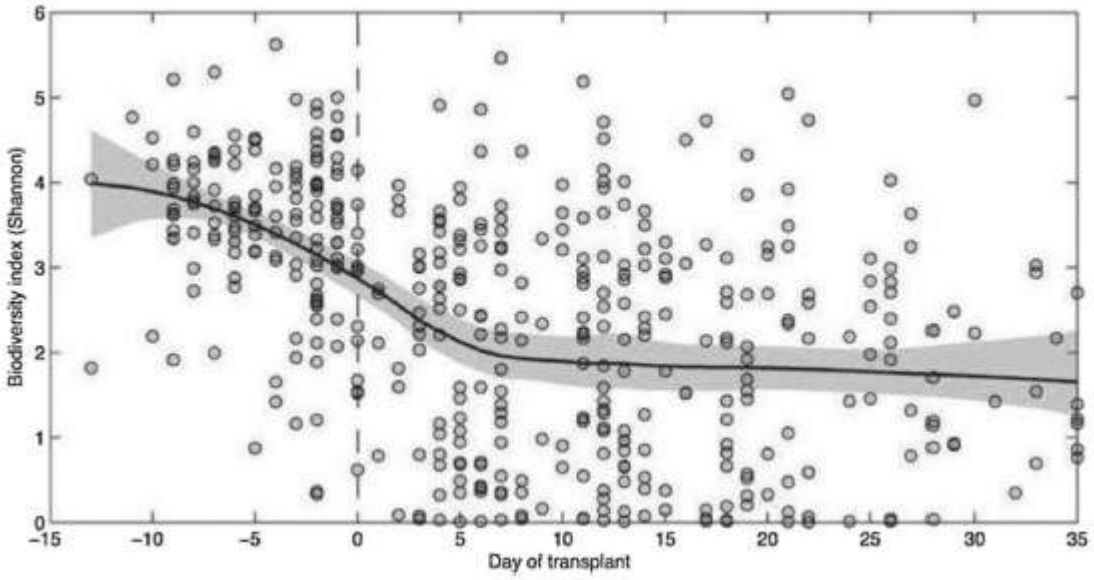
Innate immunity recovers in the first months:
monocytes > neutrophils and NK
Adaptive immunity recovery in 1-2 years: B > T lymphocytes



Bosch M et al



Intestinal domination, defined as occupation of at least 30% of the microbiota by a single predominating bacterial taxon



Intestinal Domination and the Risk of Bacteremia in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

Ying Taur,[1,2] Joao B. Xavier,[2,3] Lauren Lipuma,[2] Carles Ubeda,[5] Jenna Goldberg,[4] Asia Gobourne,[2] Yeon Joo Lee,[1] Krista A. Dubin,[2] Nicholas D. Socci,[3] Agnes Viale,[6] Miguel-Angel Perales,[4] Robert R. Jenq,[4] Marcel R. M. van den Brink,[4,5] and Eric G. Pamer[1,2,5]

Table 3. Association of Intestinal Domination With Bacteremia[a]

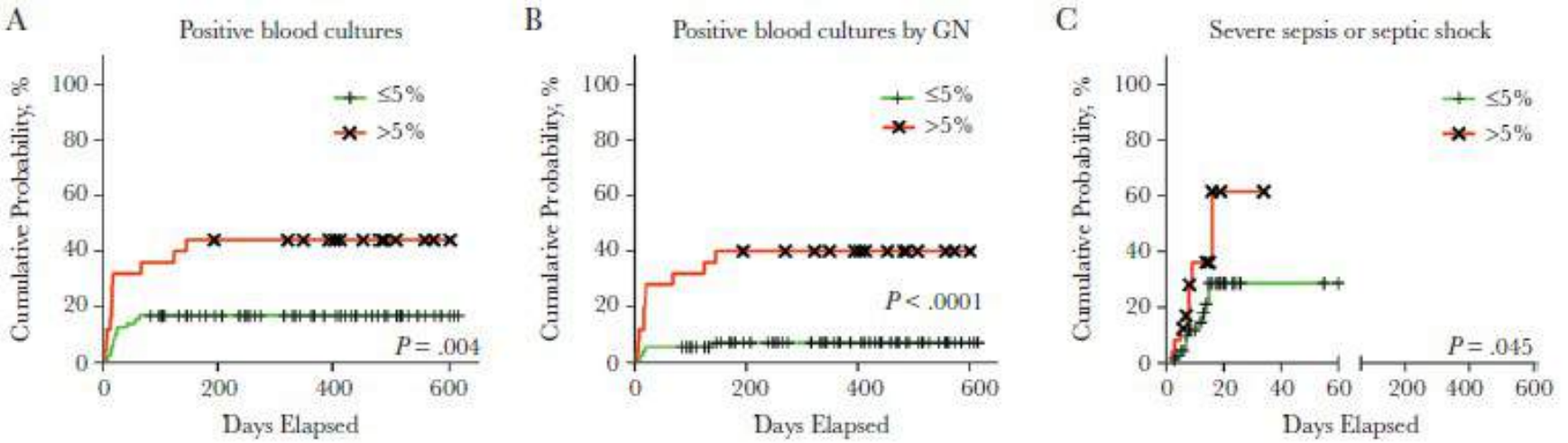
	VRE Bacteremia		Gram-negative Bacteremia	
Dominating Taxon[b]	HR (95% CI)	*P*	HR (95% CI)	*P*
Enterococcus	9.35 (2.43–45.44)	.001	1.35 (.25–5.08)	.690
Streptococcus	0.21 (.00–1.75)	.184	0.82 (.09–3.65)	.823
Proteobacteria	0.75 (.01–6.14)	.837	5.46 (1.03–19.91)	.047

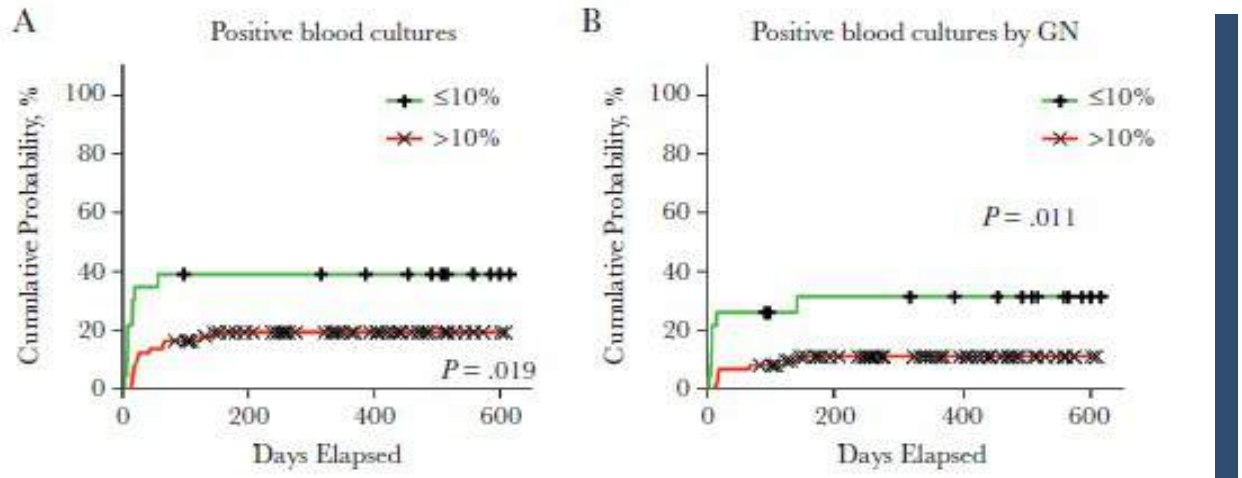
CID 2012

Enteric Microbiome Markers as Early Predictors of Clinical Outcome in Allogeneic Hematopoietic Stem Cell Transplant: Results of a Prospective Study in Adult Patients

Nicasio Mancini,[1,2,a] Raffaella Greco,[3,a] Renée Pasciuta,[1] Maria Chiara Barbanti,[3] Giacomo Pini,[1] Olivia Beatrice Morrow,[1] Mara Morelli,[3] Luca Vago,[3] Nicola Clementi,[2] Fabio Giglio,[3] Maria Teresa Lupo Stanghellini,[3] Alessandra Forcina,[3] Laura Infurnari,[1] Sarah Marktel,[3] Andrea Assanelli,[3] Matteo Carrabba,[3] Massimo Bernardi,[3] Consuelo Corti,[3] Roberto Burioni,[1,2] Jacopo Peccatori,[3] Maria Pia Sormani,[4] Giuseppe Banfi,[5] Fabio Ciceri,[3,6,b] and Massimo Clementi[1,2,b]

Enterobacteriaceae





Lachnospiraceae

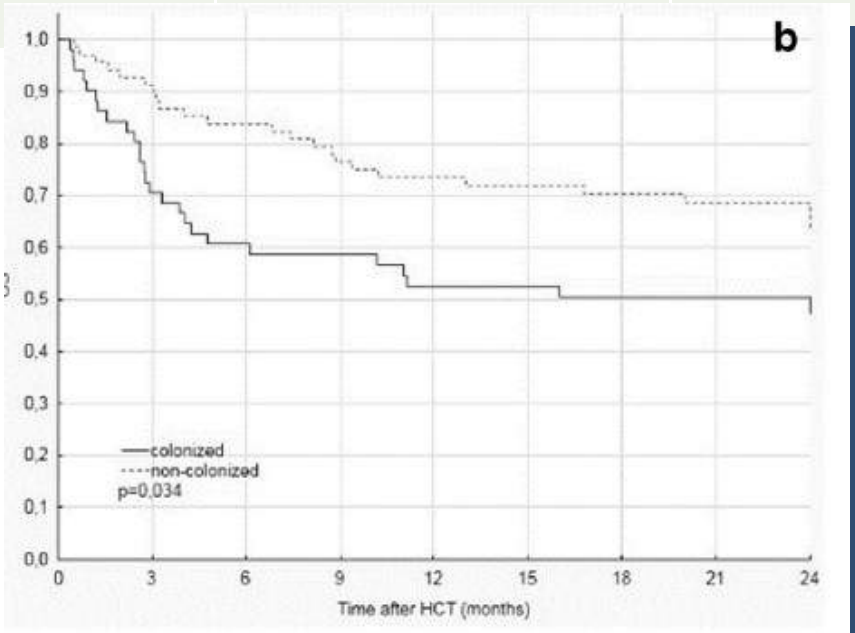
OFID 2017

Colonization with multidrug-resistant bacteria increases the risk of complications and a fatal outcome after allogeneic hematopoietic cell transplantation

Alicja Sadowska-Klasa[1] · Agnieszka Piekarska[1] · Witold Prejzner[1] · Maria Bieniaszewska[1] · Andrzej Hellmann[1]

120 patients Allo HSCT: 42.5% colonized by MDR bacteria

	Colonized	Noncolonized	p
MDR Bacteremia	16%	6%	0.038



Ann Hematol 2018

CANCER IMMUNOTHERAPY

Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors

Bertrand Routy,[1,2,3] Emmanuelle Le Chatelier,[4] Lisa Derosa,[1,2,3] Connie P. M. Duong,[1,2,5] Maryam Tidjani Alou,[1,2,3] Romain Daillère,[1,2,3] Aurélie Fluckiger,[1,2,5] Meriem Messaoudene,[1,2] Conrad Rauber,[1,2,3] Maria P. Roberti,[1,2,5] Marine Fidelle,[1,3,5] Caroline Flament,[1,2,5] Vichnou Poirier-Colame,[1,2,5] Paule Opolon,[6] Christophe Klein,[7] Kristina Iribarren,[8,9,10,11,12] Laura Mondragón,[8,9,10,11,12] Nicolas Jacquelot,[1,2,3] Bo Qu,[1,2,3] Gladys Ferrere,[1,2,3] Céline Clémenson,[1,13] Laura Mezquita,[1,14] Jordi Remon Masip,[1,14] Charles Naltet,[15] Solenn Brosseau,[15] Coureche Kaderbhai,[16] Corentin Richard,[16] Hira Rizvi,[17] Florence Levenez,[4] Nathalie Galleron,[4] Benoit Quinquis,[4] Nicolas Pons,[4] Bernhard Ryffel,[18] Véronique Minard-Colin,[1,19] Patrick Gonin,[1,20] Jean-Charles Soria,[1,14] Eric Deutsch,[1,13] Yohann Loriot,[1,3,14] François Ghiringhelli,[16] Gérard Zalcman,[15] François Goldwasser,[9,21,22] Bernard Escudier,[1,14,23] Matthew D. Hellmann,[24,25] Alexander Eggermont,[1,2,14] Didier Raoult,[26] Laurence Albiges,[1,3,14] Guido Kroemer,[8,9,10,11,12,27,28]* Laurence Zitvogel[1,2,3,5]*

Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients

V. Gopalakrishnan,[1,2]* C. N. Spencer,[2,3]* L. Nezi,[3]* A. Reuben,[1] M. C. Andrews,[1] T. V. Karpinets,[3] P. A. Prieto,[1]† D. Vicente,[1] K. Hoffman,[4] S. C. Wei,[5] A. P. Cogdill,[1,5] L. Zhao,[3] C. W. Hudgens,[6] D. S. Hutchinson,[7] T. Manzo,[3] M. Petaccia de Macedo,[6]‡ T. Cotechini,[8] T. Kumar,[3] W. S. Chen,[9] S. M. Reddy,[10] R. Szczepaniak Sloane,[1] J. Galloway-Pena,[11] H. Jiang,[1] P. L. Chen,[9]§ E. J. Shpall,[12] K. Rezvani,[12] A. M. Alousi,[12] R. F. Chemaly,[11] S. Shelburne,[3,11] L. M. Vence,[5] P. C. Okhuysen,[11] V. B. Jensen,[13] A. G. Swennes,[7] F. McAllister,[14] E. Marcelo Riquelme Sanchez,[14] Y. Zhang,[14] E. Le Chatelier,[15] L. Zitvogel,[16] N. Pons,[15] J. L. Austin-Breneman,[1]|| L. E. Haydu,[1] E. M. Burton,[1] J. M. Gardner,[1] E. Sirmans,[17] J. Hu,[18] A. J. Lazar,[6,9] T. Tsujikawa,[8] A. Diab,[17] H. Tawbi,[17] I. C. Glitza,[17] W. J. Hwu,[17] S. P. Patel,[17] S. E. Woodman,[17] R. N. Amaria,[17] M. A. Davies,[17] J. E. Gershenwald,[1] P. Hwu,[17] J. E. Lee,[1] J. Zhang,[3] L. M. Coussens,[8] Z. A. Cooper,[1,3]¶ P. A. Futreal,[3] C. R. Daniel,[4,2] N. J. Ajami,[7] J. F. Petrosino,[7] M. T. Tetzlaff,[6,9] P. Sharma,[5,19] J. P. Allison,[5] R. R. Jenq,[3]# J. A. Wargo[1,3]#**

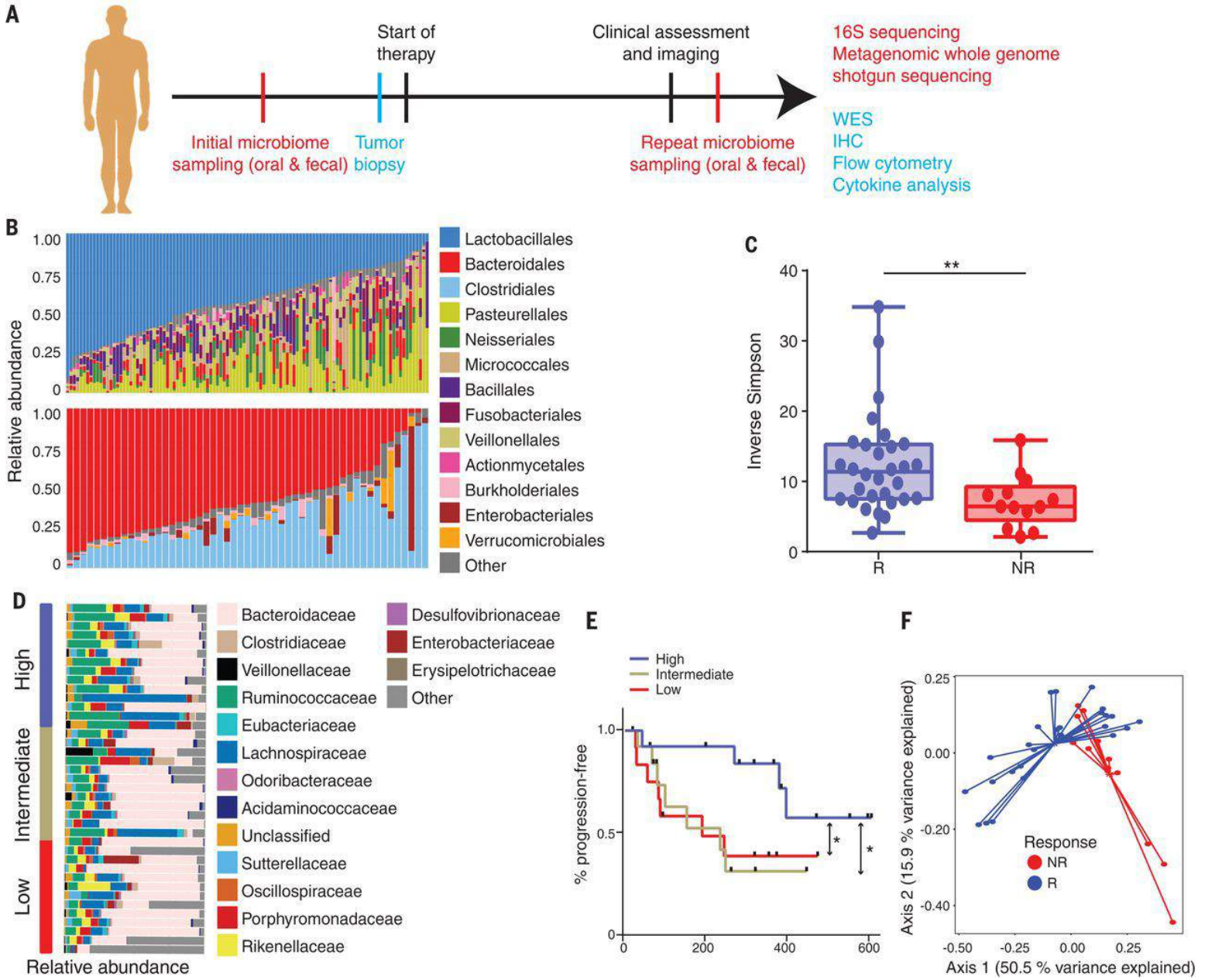
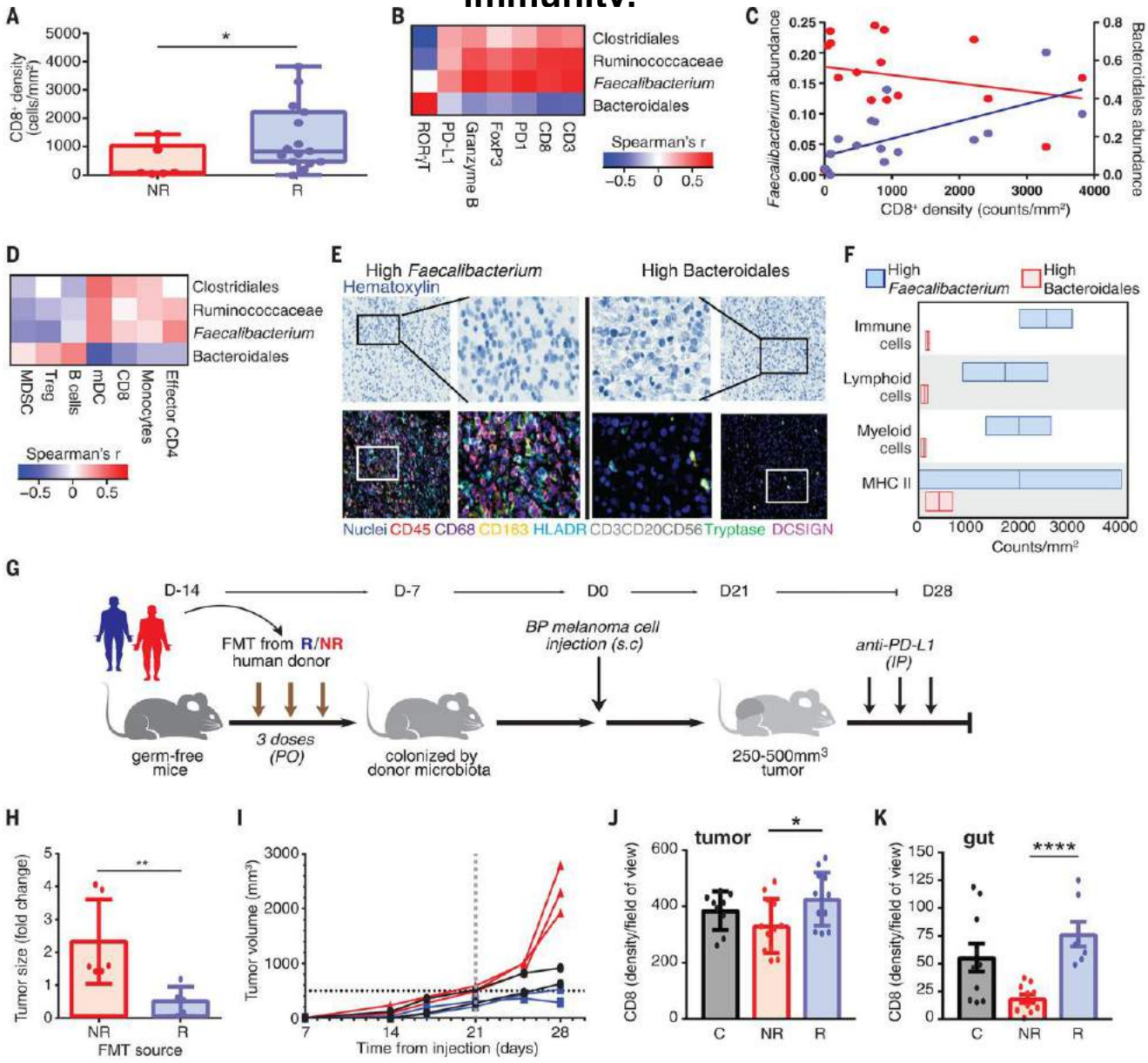

A
Start of therapy
Clinical assessment and imaging
16S sequencing
Metagenomic whole genome shotgun sequencing
Initial microbiome sampling (oral & fecal)
Tumor biopsy
Repeat microbiome sampling (oral & fecal)
WES
IHC
Flow cytometry
Cytokine analysis
B
Relative abundance
1.00
0.75
0.50
0.25
0
Lactobacillales
Bacteroidales
Clostridiales
Pasteurellales
Neisseriales
Micrococcales
Bacillales
Fusobacteriales
Veillonellales
Actionmycetales
Burkholderiales
Enterobacteriales
Verrucomicrobiales
Other
C
Inverse Simpson
40
30
20
10
0
**
R
NR
D
High
Intermediate
Low
Bacteroidaceae
Clostridiaceae
Veillonellaceae
Ruminococcaceae
Eubacteriaceae
Lachnospiraceae
Odoribacteraceae
Acidaminococcaceae
Unclassified
Sutterellaceae
Oscillospiraceae
Porphyromonadaceae
Rikenellaceae
Desulfovibrionaceae
Enterobacteriaceae
Erysipelotrichaceae
Other
Relative abundance
E
High
Intermediate
Low
% progression-free
1.0
0.5
0
0
200
400
600
*
*
F
Axis 2 (15.9 % variance explained)
0.25
0.00
-0.20
-0.40
-0.50
-0.25
0.00
0.25
Response
NR
R
Axis 1 (50.5 % variance explained)

Fig. 4 A favorable gut microbiome is associated with enhanced systemic and antitumor immunity.



V. Gopalakrishnan et al. Science 2018;359:97-103

Our results indicate that the gut microbiome may modulate responses to anti–PD-1 immunotherapy in melanoma patients. We propose that patients with a favorable gut microbiome (for example, high diversity and abundance of Ruminococcaceae and *Faecalibacterium*) have enhanced systemic and antitumor immune responses mediated by increased antigen presentation and improved effector T cell function in the periphery and the tumor microenvironment. By contrast, patients with an unfavorable gut microbiome (for example, low diversity and high relative abundance of Bacteroidales) have impaired systemic and antitumor immune responses mediated by limited intratumoral lymphoid and myeloid infiltration and weakened antigen presentation capacity. These findings highlight the therapeutic potential of modulating the gut microbiome in patients receiving checkpoint blockade immunotherapy and warrant prompt evaluation in cancer patients through clinical trials.

Fattori da considerare:

- ✓ Eta’
- ✓ Comorbidita’ (diabete, BPCO…..)
- ✓ colonizzazione
- ✓ Epidemiologia locale
- ✓ Terapia: - chemio ± intensiva,
  - immunoterapia

Complicanze batteriche

Profilassi e Terapia

Figure 4. *Escherichia coli*: percentage of invasive isolates with resistance to third-generation cephalosporins, EU/EEA, 2012 (left), 2015 (right)

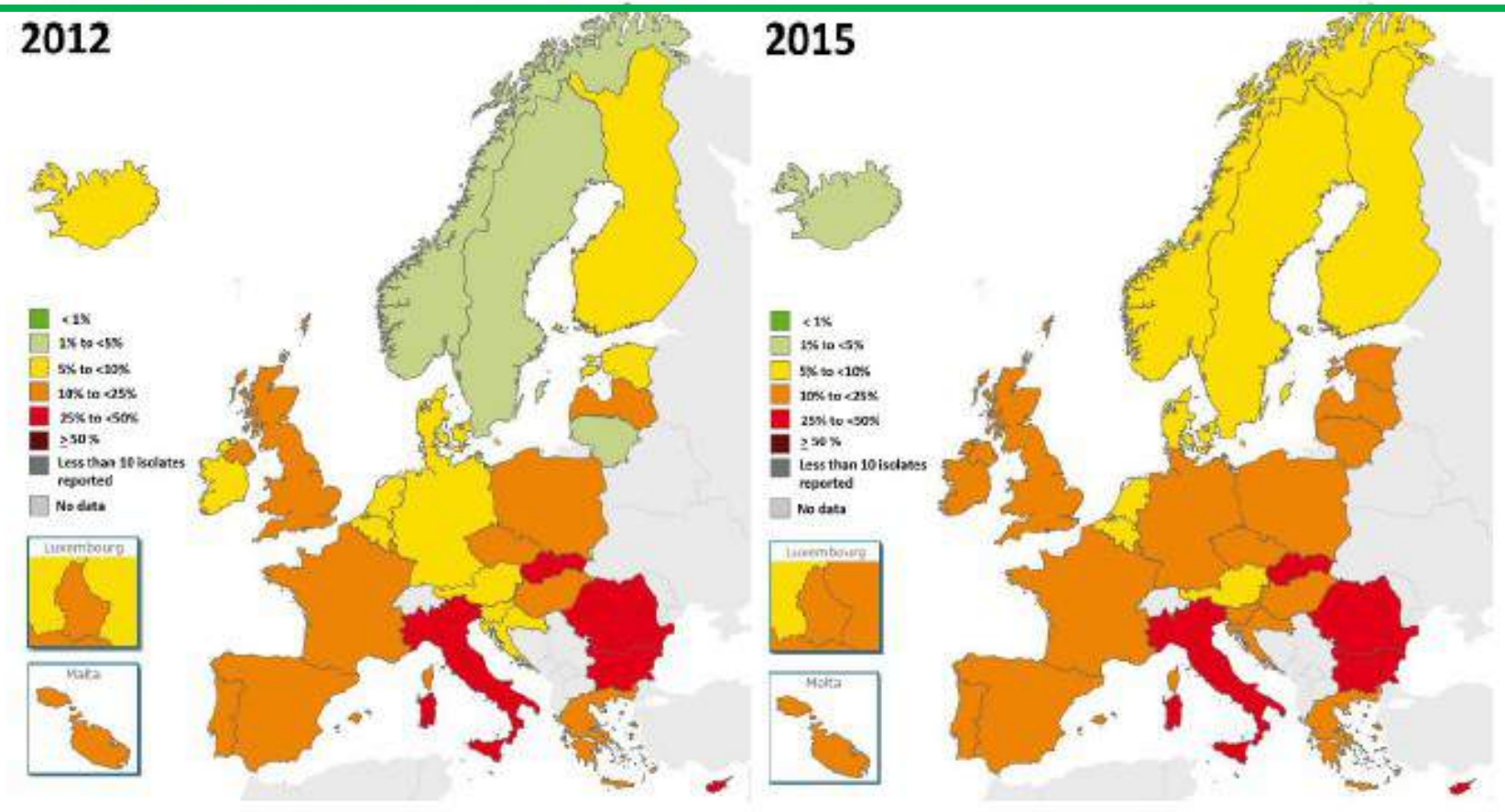


Figure 2. *Klebsiella pneumoniae*: percentage of invasive isolates with resistance to carbapenems, EU/EEA, 2012 (left), 2015 (right)

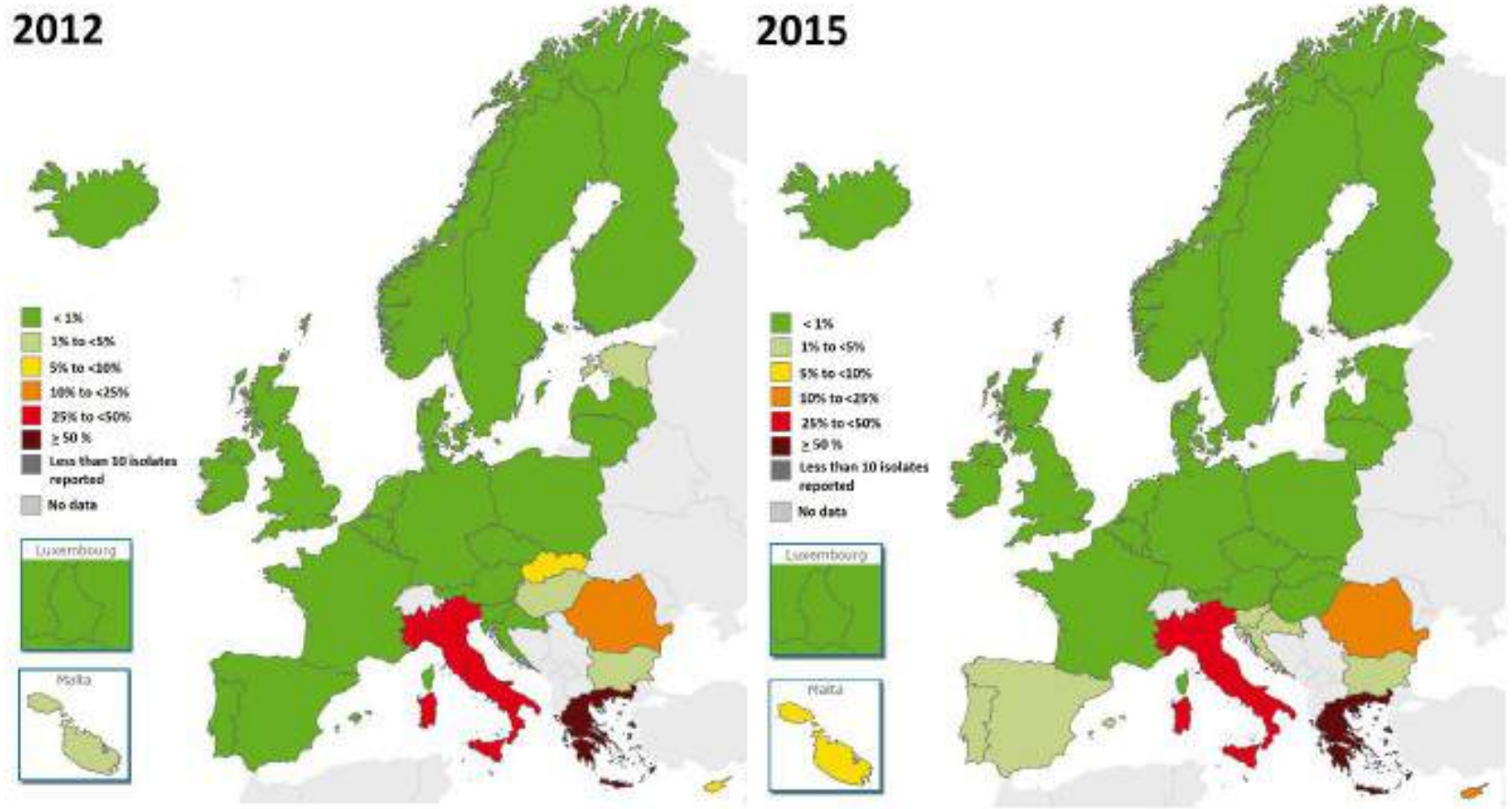
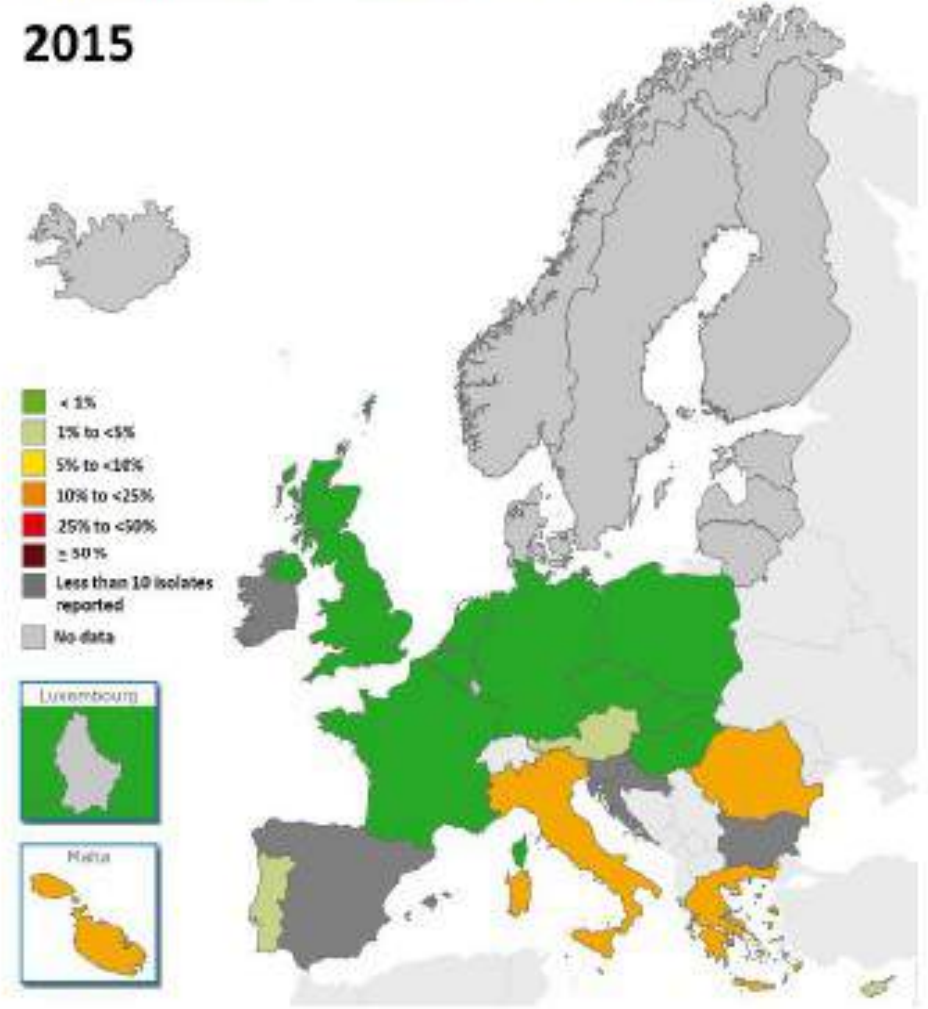
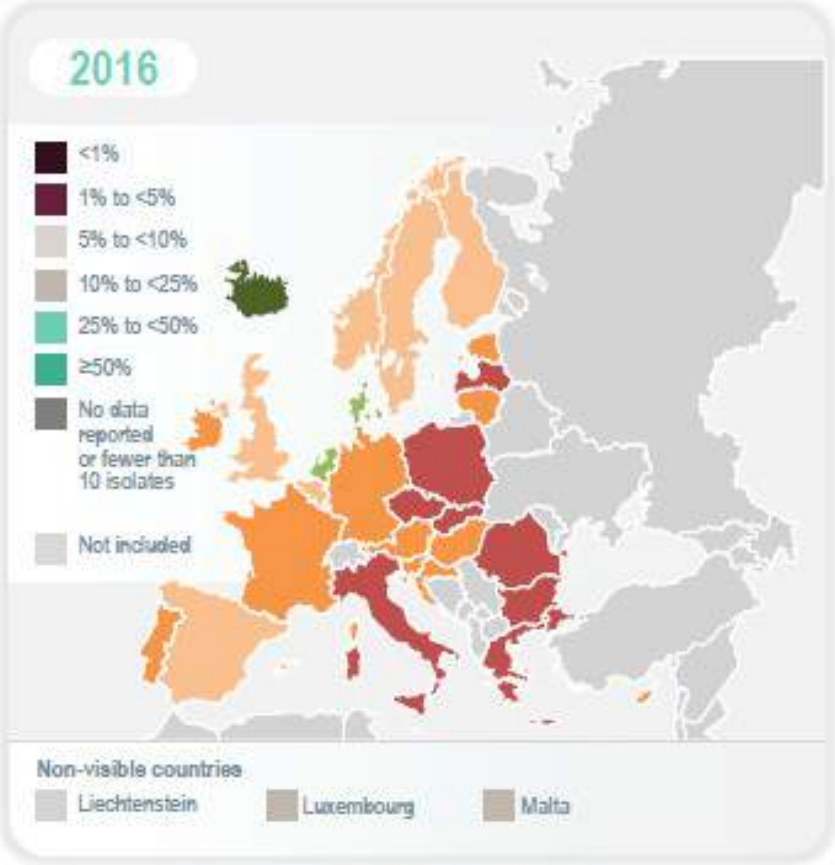


Figure 3. *Klebsiella pneumoniae*: percentage of invasive isolates with combined resistance to carbapenems and colistin*, EU/EEA, 2015

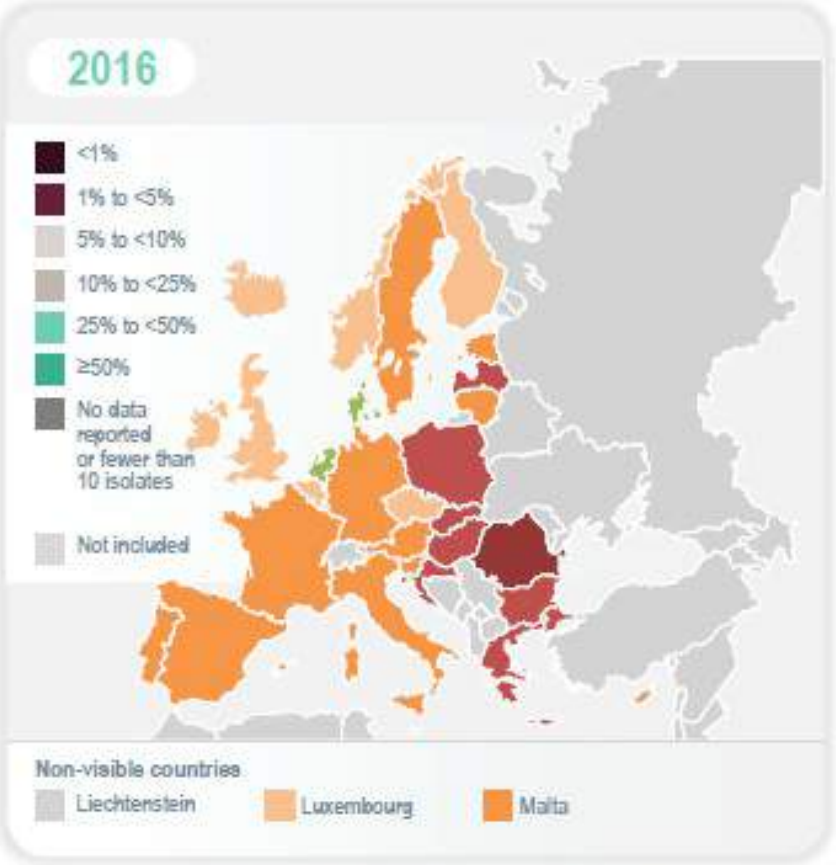


Antibiotic resistance in EU

Pseudomonas aeruginosa



percentage of invasive isolates with resistance to piperacillin±tazobactam, 2016

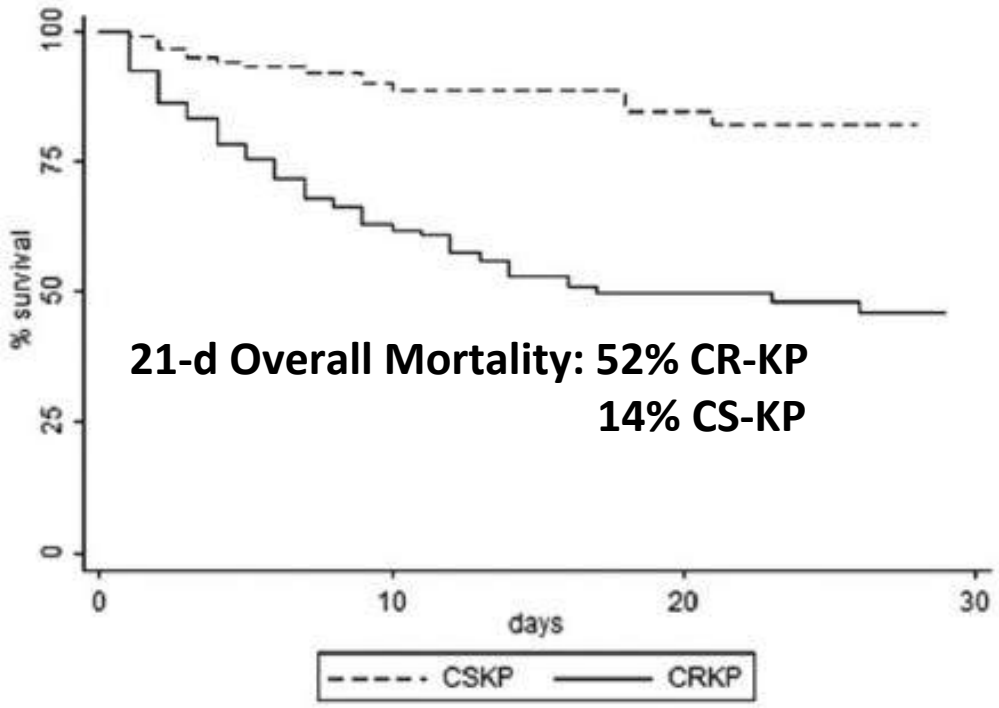


percentage of invasive isolates with resistance to carbapenems, 2016

ECDC Antimicrobial resistance surveillance in Europe 2016. Annual Report of EARS-Net, 2017

Bloodstream infections caused by *Klebsiella pneumoniae* in onco-hematological patients: clinical impact of carbapenem resistance in a multicentre prospective survey

278 KP-BSI → **58% Carbapenem-resistant**



21-d Overall Mortality: 52% CR-KP
14% CS-KP

		n-susceptible KP
No. patient		17
AML		2%
ALL		2%
CLL		8%
NHL	11%	21%
HD	1.2%	2.6%

Trecarichi Am J Hematol 2016

Antimicrobial Resistance in Gram-Negative Rods Causing Bacteremia in Hematopoietic Stem Cell Transplant Recipients: Intercontinental Prospective Study of the Infectious Diseases Working Party of the European Bone Marrow Transplantation Group

Averbuch et al. CID 2017

655 GN episodes: 414 Allo/241 Auto

73% Enterobacteriaceae

24% nonfermentative Rods

3% others

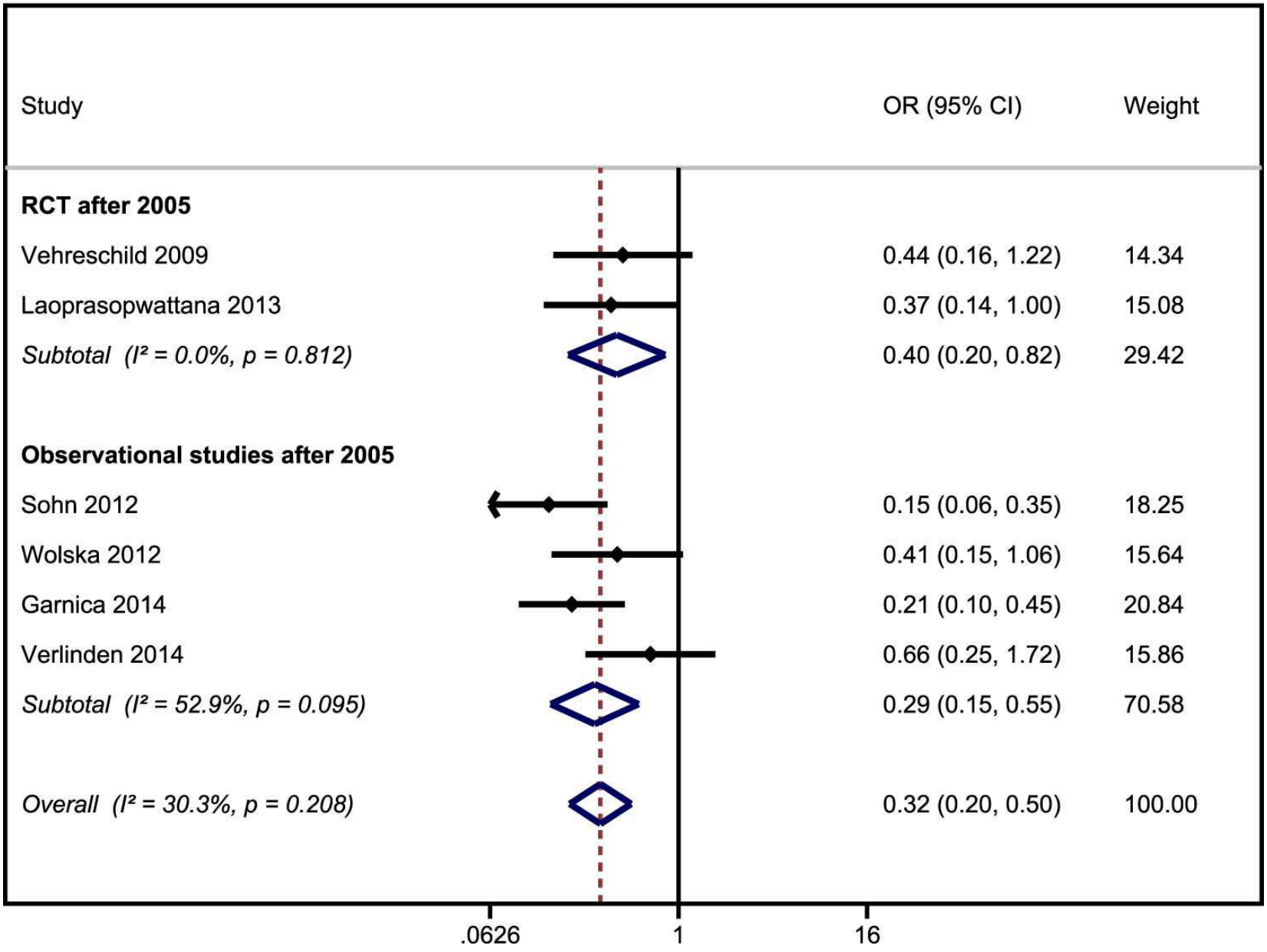
	Prophylaxis FQ	No prophylaxis FQ	p
Rate MDR	35%	8%	<0.001

Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines

Malgorzata Mikulska [a,*], Diana Averbuch [1,b], Frederic Tissot [1,c], Catherine Cordonnier [d], Murat Akova [e], Thierry Calandra [f], Marcello Ceppi [g], Paolo Bruzzi [g], Claudio Viscoli [a] on behalf of the European Conference on Infections in Leukemia (ECIL), a joint venture of the European Group for Blood and Marrow Transplantation (EBMT), the European Organization for Research and Treatment of Cancer (EORTC), the International Immunocompromised Host Society (ICHS) and the European Leukemia Net (ELN)

J Infection 2018

Fever during Neutropenia



Overall Mortality

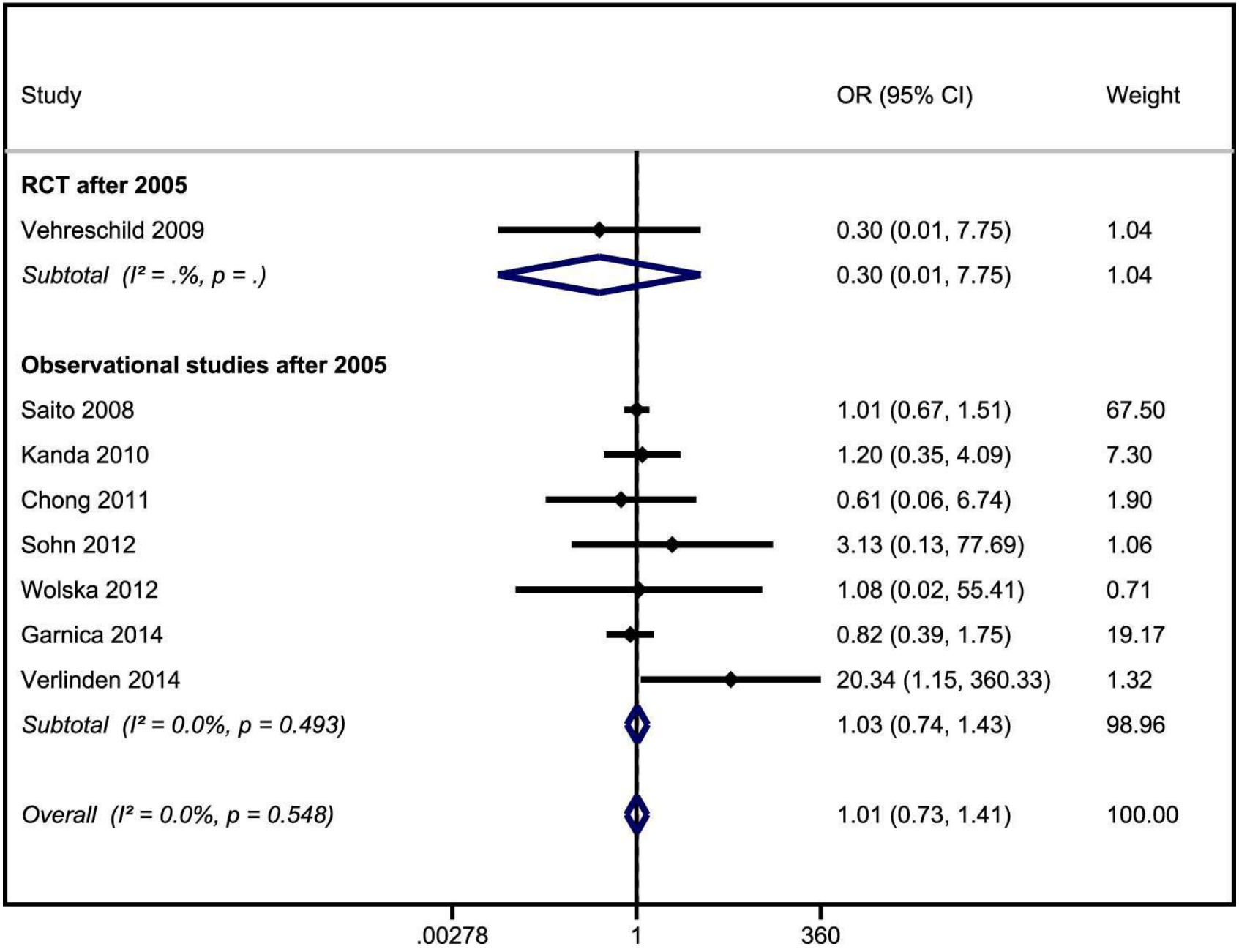


Table 2 The efficacy of FQ prophylaxis on the overall mortality, rate of BSI and episodes of fever during neutropenia in the main meta-analyses published between 2006 and 2014.

Author, year of publication	Type of studies and patients included	Number of patients, number of studies	Reported outcome, FQ prophylaxis vs. placebo		
			Overall mortality	Bloodstream infections	Episodes of fever during neutropenia
Imran 2008[21]	RCT FQ vs. placebo, double blind only	2721 patients, 8 studies	4% vs. 5.3%, p = 0.13	ND	31% vs. 39.7%, p = 0.08
Gafter-Gvili 2012[20]	RCT FQ vs. placebo	3776 patients, 19 studies	2.8% vs. 5.3%, p = 0.00012	10.4% vs. 16.9%, p < 0.00001	41% vs. 53.8%, RR 0.74, p < 0.00001
Kimura 2014[22]	RCT FQ vs. placebo, HSCT recipients	243 patients, but only 4 allo-HSCT recipients, 3 studies	0% vs. 1.8%, NS	6.9% vs. 31.5% (OR 0.18, 95%CI 0.08–0.47)	66.2% vs. 93.7% (OR 0.14, 95%CI 0.07–0.32)

Allo-HSCT: allogeneic haematopoietic stem cell transplant; 95%CI: confidence interval of 95%; FQ: fluoroquinolones; NS: not significant; OR: odds ratio; RR: risk ratio.

Author, year of publication	FQ prophylaxis recommended	Start and end of prophylaxis	Prophylaxis not recommended
Bucaneve 2007 **ECIL**	High risk: neutropenia ≥ 7 d (**AI** for levofloxacin and ciprofloxacin)	Start with chemotherapy, only FQ prophylaxis start 24–48 h after the end of high dose cyclophosphamide therapy (AIII), and continue until resolution of neutropenia or initiation of empirical antibacterial therapy for febrile neutropenia (AII)	ND
Freifeld 2011 - IDSA	High risk: neutropenia ≥ 7 d, **BI**	With the first day of cytotoxic therapy or the day following administration of the last dose of chemotherapy, stop at the end of neutropenia	**Low-risk patients who are anticipated to remain neutropenic for <7 days (A-III)**
Slavin 2011 **Australia**	Consider in outpatient HSCT and palliative patients with bone marrow failure **(grade C)**	ND	**Not be routinely used in high-risk haematology patients (grade C); Low risk of developing neutropenic fever (<7days, mostly solid tumours) (level I-II, grade C)**
Phillips 2012 - UK	Adult patients (aged ≥18 years) with acute leukaemia, HSCT, or solid tumours (duration of n/p not mentioned)	During the expected period of neutropenia	ND
Baden 2012/2013 NCCN	High risk: HSCT, acute leukaemia, lymphoma, multiple myeloma, alemtuzumab, GvHD, neutropenia ≥ 7 days	ND	**Neutropenia expected to last less than 7 days who are not receiving immunosuppressive regimens (e.g., systemic corticosteroids)**
Flowers 2013 ASCO	High risk: neutropenia for > 7 days, unless other factors which increase risks for complications or mortality	ND	If neutropenia is less severe or of shorter duration and the usual course with current chemotherapy regimens for solid tumours
Neumann 2013 Germany	High risk: neutropenia ≥ 7 days; some low risk (1st chemo, aggressive chemo with high infections rate, elderly)	Start prophylaxis with onset of neutropenia in low-risk patients, with start of cytostatic drugs in high-risk patients (both BIII)	Low risk except for those mentioned in the "recommended" group
Klastersky 2016 ESMO	Never: the use of antimicrobials, including fluoroquinolones, should be discouraged.	NA	All patients with febrile neutropenia.

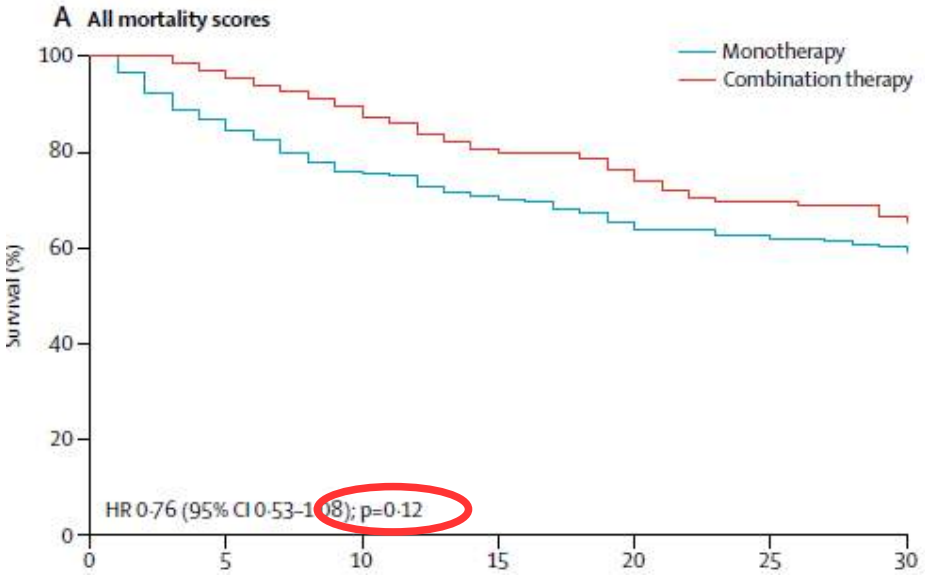
Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study

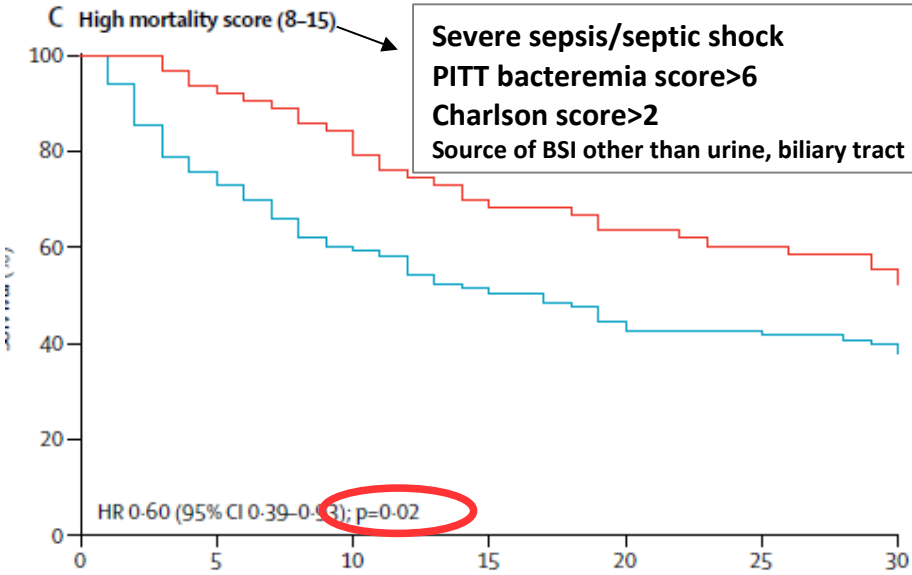
Gutierrez-Gutierrez B et al
Lancet Infect 2017

2004-2013; 26 Hospitals. 480 patients with CPE

Appropriate therapy (at least 1 active ATB < 5 days): n=343 (78%)
Inappropriate therapy: n=94 (22%)

	Appropriate Therapy	Inappropriate therapy	p
Mortality	38%	61%	0.0001





Severe sepsis/septic shock
PITT bacteremia score>6
Charlson score>2
Source of BSI other than urine, biliary tract

Matteo Bassetti
Matthew E. Falagas
Marin Kollef

Ten old antibiotics that will never disappear

Table 1 Main indication, dosage, cautions of 10 old antibiotics in critically ill patients

Drug	Main indications	Dosage	Cautions
Amikacin	MDR and XDR Gram-negative infections (*P. aeruginosa*, *K.*	15–20 mg/kg iv qd	Use only in combination Nephrotoxicity with high dose and co-administration with other nephrotoxic medications
Cefazolin	MSS pt	6–8 g daily iv in CI	Reported seizures with high dosage in patients with impaired renal function
Colistin (colistimethate)	MD *K.*	9 million IU loading dose, then 4.5 million IU bid	Nephrotoxicity Neurotoxicity Neuromuscular blockade
Co-trimoxazole	*Pneumocystis jiroveci* pneumonia, nocardiosis, *Stenotrophomonas maltophilia*, *Listeria monocytogenes*, MRSA	15 mg/kg/day iv trimethoprim bid	Stevens-Johnson syndrome, anemia
Fosfomycin	*K.* inary tract,	16 g iv qid	For MDR and XDR use in combination Hypokalemia
Gentamicin	eruginosa,	7–10 mg/kg iv qd	Use only in combination Nephrotoxicity with high dose and co-administration with other nephrotoxic medications
Oxacillin	MSSA infections (bacteremia, skin and skin structure, pneumonia, endocarditis, orthopedic)	12–16 g iv in CI	Hepatotoxicity
Penicillin G	*Streptococcus pyogenes* infections (cellulitis, septic arthritis, pelvic infections, bacteremia), *Neisseria meningitidis* and *Streptococcus pneumoniae* meningitis; anaerobic streptococci abdominal infections; syphilis	20–24 million iv in CI	Fatal hypersensitivity reactions
Rifampin	Prosthetic infections, biofilm infections; leprosy (Hansen's disease), XDR Gram-negative bacteria in combination, tuberculosis	10 mg/kg qd	Use only in combination for staphylococcal infections
Vancomycin	MRSA infections (bacteremia, endocarditis, pneumonia)	30 mg/kg iv in CI	Monitor blood levels

Iv intravenously, *qd* once daily, *bid* twice daily, *CI* continuous infusion, *IU* international unit, *qid* four times daily, *MSSA* methicillin-sensitive *Staphylococcus aureus*, *MRSA* methicillin-resistant *Staphylococcus aureus*, *ESML* extended spectrum beta-lactamase(-producing)

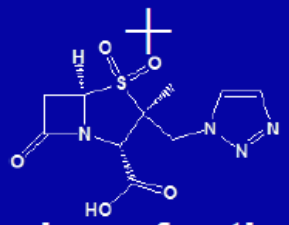
Targeted Therapy:
A. Baumannii
P. Aeruginosa
K. Pneumoniae
Other CRE

81% K. Pneumo. Sensibile
Target therapy:
ESBL-CRE-PA

Ceftolozane/Tazobactam Overview

Class

- Antipseudomonal cephalosporin + β-lactamase inhibitor
- Fixed 2:1 ratio



Mechanism of action

- Rapidly bactericidal
- Inhibits cell wall synthesis
- Active against organisms with porin deficiencies or mutations
- Inhibits β-lactamases, broadens coverage to most ESBL-producing Enterobacteriaceae

In vitro activity

Pseudomonas aeruginosa, including drug-resistant strains

Escherichia coli, including ESBL-positive strains

Klebsiella pneumoniae, including ESBL-positive strains

Minimal activity against Gram-positive bacteria

Limited activity against anaerobes

No activity against KPC, MBL

Development stage

Completed Phase 3 trials for treatment of cIAI and cUTI

Phase 3 trial underway for nosocomial pneumonia

In vivo efficacy

Activity in mouse models of sepsis, pneumonia, urinary tract infection, burn wound infection, and thigh infection

Positive outcomes and adhered to an expected safety profile in Phase 2 and 3 trials in adult patients with cUTI and cIAI

Pharmacokinetics

Linear PK

Lung penetration

Rapid tissue distribution

Minimal accumulation

Extensive renal excretion

Low protein binding

Minimal CYP450 drug-drug interactions

Zhanel et al. *Drugs*. 2014;74:31-51.

Ceftazidime - Avibactam

- Cephalosporin plus beta-lactamase inhibitor
- Spectrum of activity: Gram-negatives, including MDR *Pseudomonas aeruginosa*, ESBL-producing strains, KPCs
- FDA approval in February 2015 (based Phase 2 data)
  - Complicated Urinary Tract Infections, including Pyelonephritis
  - Complicated Intra-abdominal Infections (plus metronidazole)
  - For patients with limited or no alternative treatment options
  - IV dose: 2.5 g (2 g ceftazidime; 0.5 g avibactam) q8h (2-h infusion)
- Clinical trials: Nosocomial pneumonia - Dose of 2.5 g q8h
- Plasma-to-epithelial lining fluid penetration ~30%

Liscio JL, et al. *Int J Antimicrob Agents* 2015 Jun 14 (Epub)
Nicolau D, et al. *J Antimicrob Chemother* 2015 (Epub); clinicaltrials.gov

Complicanze fungine

Profilassi e Terapia

SEIFEM

IFI risk statification in HM

HIGH Risk	INTERMEDIATE Risk	LOW Risk
AML undergoing Induction CHT with any of the following Risk Factors: Neutropenia at baseline, low CR probability (Adverse K, secondary AML), age > 65 yrs, Significant pulmonary disfunction, high e-TRM score. AML with Prior IA AML undergoing salvage regimens for Relapsed/Refractory disease.	AML not meeting criteria for High or Low Risk groups.	AML <45 yrs; Undergoing first remission-induction or consolidation CHT and without Risk Factors for IFI APL treated with ATRA/ATO
Allogeneic Stem Cell transplantation (from donors other than a matched sibling donor, patients active HM, GVHD requiring high-dose steroids and history of previous IFI)	Allogeneic Stem Cell transplantation (from matched sibling donors, patients in complete remission with no evidence of GVHD and no previous IFI)	
MDS/LAM receiving azacitidine as salvage therapy after intensive regimens	MDS with IPSS > 1.5 treated with azacitidine 75 mg/m(2) for 7 days MDS during the first 2-3 cycles of AZA/Decitabine	
Acute Lymphoblastic Leukemia: Elderly pts; HD Desametazone + Chemotherapy ; intensive pediatric regimens (induction) ; Previously treated	Acute Lymphoblastic Leukemia: Adults <55y; Intensive consolidation treatment (CR); TKI + reduced Cht (Ph+)	Acute Lymphoblastic Leukemia: Younger adolescents; Maintainance treatment (CR); ?? TKI+steroids
	Autologous Stem Cell Transplantation: Previous IFI; >3 lines of therapy (disease burden); Prolonged neutropenia (ANC <500/mm3 for more than 14 days); corticosteroid therapy; Colonization by Candida spp; Previous Fludarabine treatment	MPN (Chronic Myeloid Leukemia, Essential Thrombocitemia, Idiopathic Thrombocytosis, Policytemia Vera)
	CLL treated with multiple lines of CTX Multiple Myeloma in 3 or more lines or during ASCT DLBCL relapsed/refractory	Low or high grade NHL, CLL, MM, HD treated with conventional frontline chemotherapy

Interactions of mold-active azoles with coadministered chemotherapic agents and target therapies

COADMINISTERED AGENT	INTERACTION MECHANISM	EFFECT	RECOMMENDATIONS AND ACTIONS
Vincristine	Inhibition CYP3A4	Increased neurotoxicity	**Avoid combo**
Cyclophosphamide (CTX)	Inhibition CYP3A4/2C9	↑ hepatotoxicity ↓ activation to hydroxy-CTX	Monitor **Avoid combo**
Ibrutinib	Inhibition CYP3A4/2C9	↑ Ibrutinib exposure	420 mg standard dose 280 mg if Fluco; 140 mg if Posa/vori
Idelalisib	Inhibition CYP3A4/Pgp	↑ AUC	Monitor for side effect
Ruxolitinib	Inhibition CYP3A4/2C9	↑ Ruxolitinib exposure	↓ **dose 50%;** monitor cytopenias
Imatinib	Inhibition CYP3A4	↑ Imatinib exposure	**Avoid combo**
Dasatinib	Inhibition CYP3A4	↑ D. exposure, **↑ QT interval**	**Avoid combo**, **monitor ECG**
Nilotinib	Inhibition CYP3A4	↑ N. exposure, **↑ QT interval**	**Avoid combo**, **monitor ECG**
ponatinib	Substrate CYP3A4	↓ TKI dosage	**Avoid combo**
sorafenib	Inhibition CYP3A4	No effect	**Monitor QTc**
Midostaurin	Inhibition CYP3A4	↑ adverse reaction	**Avoid combo, monitor QTc**
Quirzatinib	Inhibition CYP3A4	↑ Quirzatinib exposure	↓ **dose (induc 40 mg ->20 mg)**
Lestaurtinib	?	↑ efficacy ???	?

ECIL-6 recommendations for first-line treatment of invasive aspergillosis.

(Tissot et al, Haematologica 2017)

	Grade	Comments
Voriconazole	A I	Daily dose: 2x6 mg/kg on day 1 then 2x4 mg/kg (Initiation with oral therapy: C III)
Isavuconazole	A I	As effective as voriconazole and better tolerated
Liposomal amphotericin B	B I	Daily dose: 3 mg/kg
Amphotericin B lipid complex	B II	Daily dose: 5 mg/kg
Amphotericin B colloidal dispersion	C I	Not more effective than d-AmB but less nephrotoxic
Caspofungin	C II	
Itraconazole	C III	
Combination voriconazole + anidulafungin	C I	
Other combinations	C III	
d-AmB	A I – against	Less effective and more toxic

Infezioni Virali

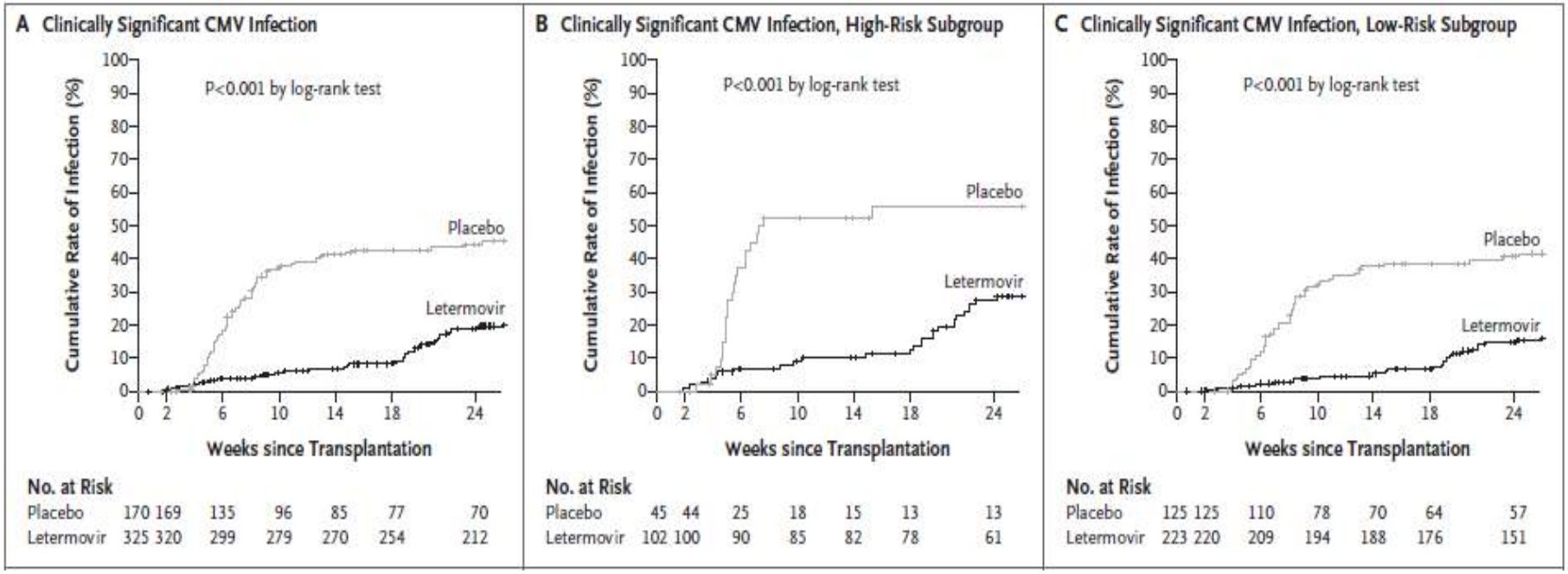
Infezione da CMV

Farmaci per l'infezione da CMV	
VECCHI	**NUOVI**
Ganciclovir	Maribavir
Valganciclovir	Brincidofovir
Foscarnet	Letermovir
Cidofovir	

Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation

F.M. Marty, P. Ljungman, R.F. Chemaly, J. Maertens, S.S. Dadwal, R.F. Duarte, S. Haider, A.J. Ullmann, Y. Katayama, J. Brown, K.M. Mullane, M. Boeckh, E.A. Blumberg, H. Einsele, D.R. Snydman, Y. Kanda, M.J. DiNubile, V.L. Teal, H. Wan, Y. Murata, N.A. Kartsonis, R.Y. Leavitt, and C. Badshah

Phase 3 double-blind trial: CMV-seropositive patients
Letermovir vs placebo through w14 after HSCT
Primary end-point: CMV infection through w24



Complicanze infettive in corso di targeted therapies

Agents targeting lymphoid cells surface antigens

Agent	Mechanism of action	Type of immunity impairment
Rituximab	Anti CD20 MoAb	T and B cells
Obinutuzumab	Anti CD20 MoAb	T and B cells
Ofatumumab	Anti CD20 MoAb	T and B cells
Y-Ibritumomab	Anti CD20 MoAb delivery radioactive isotope	T and B cella, GN
Alemtuzumab	Anti CD52 MoAb	Lympho, mono,macrophages

- **CD20 e’ espresso sui linfo B normali e maligni.**

non e’ espresso sui precursori B e plasmacellule, per cui AcMo antiCD20 non alterano la produzione di IG, sebbene ipoɣ si verifica con l’aumentare del numero di cicli di antiCD20

- **Ipoɣ e’ descritta per lo piu’ nei paz con M autoimmuni, ma l’impatto clinico non e’ chiaro**

Nei paz con M autoimmuni ⬆ il rischio di infezioni non severe

- **AntiCD20 modula le interazioni B/T cells piu' che influire direttamente sull'immunita' umorale**

I linfo B svolgono un ruolo fondamentale nell'attivazione T cell attraverso la presentazione Ag e nel rilascio di citok.

- **Vi sono diverse segnalazioni di paz trattati con antiCD20 con severa alterazione della risposta T cell:**

PJP, PML, riattivazione HCV, VZV

- **La deplezione B linfo altera la produzione di citok durante un'infezione virale primaria e riduce la produzione di CD4+ memory favorendo una virosi disseminata**

- **Il 3-5% dei linfo T esprime CD20 e quindi vi e' una concomitante T deplezione**

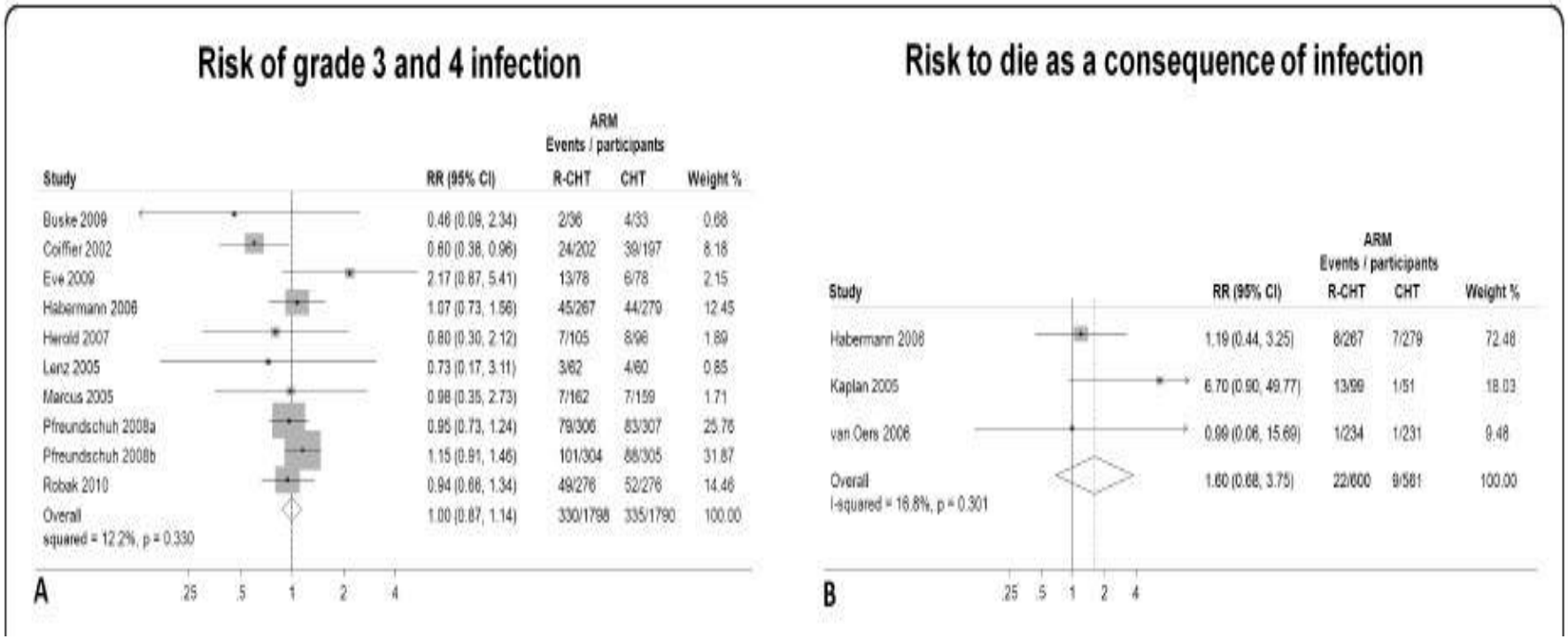
- **AntiCD20 si associa ad una neutropenia nel 10-33% dei casi anche per effetto della chemio concomitante**

- **AntiCD20 si associa ad un documentato rischio di riattivazioni HBV e HCV**

- **AntiCD20 si associa ad un aumentato rischio di infezioni da ENTEROVIRUS e PML**

Risk of infection in patients with lymphoma receiving rituximab: systematic review and meta-analysis

Simone Lanini[1*], Aoife C Molloy[2], Paul E Fine[3], Archibald G Prentice[4], Giuseppe Ippolito[1] and Christopher C Kibbler[2]



Anti CD20: INTERVENTI

- **Nei paz HBsAg+ e HBc+ e' indicata una profilassi per 12-18 mesi dall'ultima somministrazione di antiCD20 con LAM/ENTEC/TENOF**
- **Vi e' un aumentato rischio di PJP.** Il rischio e' differente per R-CHOP 21 e 14 per cui alcune LG raccomandano la profilassi solo per 21, opzionale x 14. Indicata anche la profilassi se concomitante uso di steroidi (PDN 20 mg/d x >4 w)
- **Un'alterata risposta alle vaccinazioni e' descritta soprattutto per anti-influenzale, -pneumo, -haemoph. Per cui la vaccinazione x influenza deve essere eseguita >6 mesi dall'ultima dose di antiCD20**

- **CD52 e’ espresso sui linfo maturi, monoc, macrofagi.**
- **Deplezione dei linfo T e B**
- **Aumentato rischio di CMV, HSV, HZV**
- **Aumentato rischio di PJP**
- **Aumentato rischio di riattivazioni HBV, HCV e papillomavirus (2%)**

Campath: INTERVENTI

- **Monitoraggio CMV-DNA – preemptive therapy**
- **Screening x HBV e HCV prima del trattamento**
- **Profilassi per HBV fino a 2 mesi da ultima somministr. Nei paz HBsAg+/HBc+ con LAMIVUDINA**
- **Screening per TBC e papillomavirus nelle donne**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 13, 2014 VOL. 370 NO. 11

Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia

Richard R. Furman, M.D., Jeff P. Sharman, M.D., Steven E. Coutre, M.D., Bruce D. Cheson, M.D., John M. Pagel, M.D., Ph.D., Peter Hillmen, M.B., Ch.B., Ph.D., Jacqueline C. Barrientos, M.D., Andrew D. Zelenetz, M.D., Ph.D., Thomas J. Kipps, M.D., Ph.D., Ian Flinn, M.D., Ph.D., Paolo Ghia, M.D., Ph.D., Herbert Eradat, M.D., Thomas Ervin, M.D., Nicole Lamanna, M.D., Bertrand Coiffier, M.D., Ph.D., Andrew R. Pettitt, Ph.D., F.R.C.Path., Shuo Ma, M.D., Ph.D., Stephan Stilgenbauer, M.D., Paula Cramer, M.D., Maria Aiello, M.A., Dave M. Johnson, B.S., Langdon L. Miller, M.D., Daniel Li, Ph.D., Thomas M. Jahn, M.D., Ph.D., Roger D. Dansey, M.D., Michael Hallek, M.D., and Susan M. O'Brien, M.D.

Table 5: Number of cases of PJP and CMV in studies GS-US-312-0123, GS-US-313-0124 and -0125

CMV: Any Grade AEs

Study	Idelalisib	Placebo
123 I+R+Benda	6	2
124 I+R	1	0
125 I+R+Benda	14	0
Deaths	4	0

PJP: Any Grade AEs

Study	Idelalisib	Placebo
123	1	0
124	1	0
125	9	0
Deaths	2	0

In these studies, PJP prophylaxis was recommended but was administered in only 15-30% of patients.

GS-US-312-0123: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of **Idelalisib in Combination with Bendamustine and Rituximab for Previously Untreated CLL**
GS-US-313-0124: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety **of Idelalisib in Combination with Rituximab for Previously Treated iNHL**
GS-US-313-0125: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety **of Idelalisib in Combination with Bendamustine and Rituximab for Previously Treated iNHL**

PJP: relative risk 12.5% (no correlation with CD4+ count
prophylaxis with TMP-SMZ now recommended

CMV: CMV-PCR at least every month

IBRUTINIB

Grade >3 infections occurred in 10-13% of 60 treatment-naive patients and 24-52% of 407 relapsed/refractory patients on ibrutinib monotherapy

- **Viral**

  HZV, CMV, HBV: occasional

- **Mycobacterial**

  TB: occasional

- **Anti mould prophylaxis recommended when Ibrutinib is Associated to steroids – TDM required with azoles due to drug-drug interactions**

- **Fungal**

  cryptococcus: occasional cases

  Aspergillus: risk seems to be significantly increased if co-administered with steroids

  Non-Aspergillus moulds: occasional

  Yeasts: no reported cases

Checkpoint Inhibitors

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective—immune checkpoint inhibitors, cell adhesion inhibitors, sphingosine 1–phosphate receptor modulators and proteasome inhibitors

G. Redelman-Sidi [1,*], O. Michielin [2], C. Cervera [5], C. Ribi [3], J.M. Aguado [6,7], M. Fernández-Ruiz [6,7], O. Manuel [4]

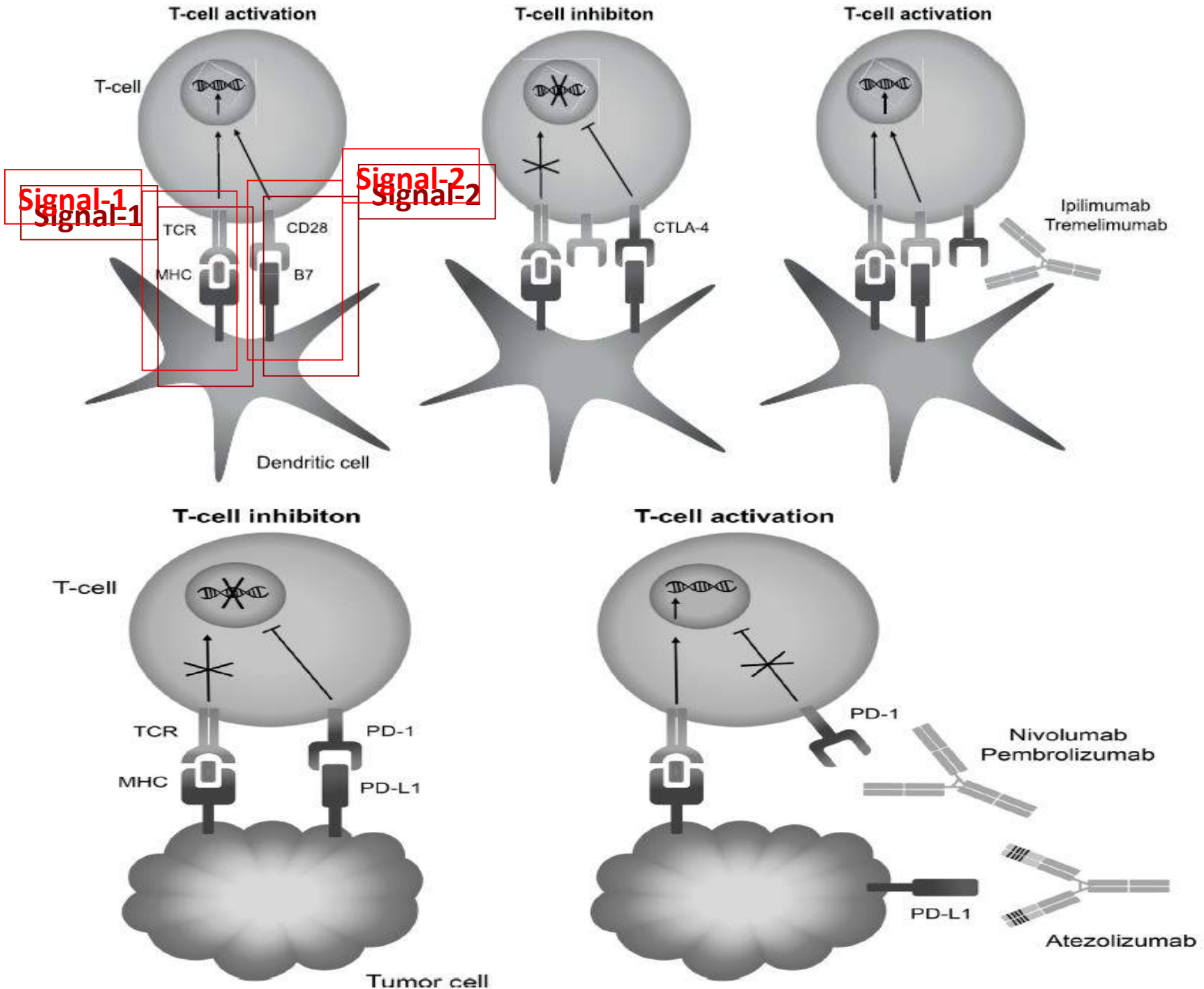

T-cell activation
T-cell
Signal-1
Signal-1
TCR
CD28
MHC
B7
Signal-2
Signal-2
Dendritic cell
T-cell inhibiton
CTLA-4
T-cell activation
Ipilimumab
Tremelimumab
T-cell inhibiton
T-cell
TCR
PD-1
MHC
PD-L1
Tumor cell
T-cell activation
PD-1
Nivolumab
Pembrolizumab
PD-L1
Atezolizumab

Table 1
Summary of infection risks associated with use of reviewed targeted agents

Agent	Pathway affected	Current indications	Increased risk of infection	Observations
Ipilimumab, tremelimumab	CTLA-4	Melanoma	Variable	• No intrinsic increase in risk of infection. • Increased risk of infection in patients developing irAEs and treated with additional immunosuppressive (i.e. corticosteroids and/or TNF-α–targeted agents).
Nivolumab, pembrolizumab, atezolizumab	PD-1 or PD-L1	Melanoma, NSCLC, HNSCC, Hodgkin lymphoma, urothelial carcinoma, bladder carcinoma, metastatic RCC, tumour with microsatellite instability	Variable	• No intrinsic increase in risk of infection. • Increased risk of infection in patients developing irAEs and treated with additional immunosuppressive (i.e. corticosteroids and/or TNF-α–targeted agents).
Alefacept	LFA-3/CD2 interaction	Plaque psoriasis (currently withdrawn)	Minor	• No apparent increase in risk of infection (currently halted for economic reasons, not safety issues). • Transient peripheral blood $CD4^+$ T-cell lymphopenia.

Checkpoint Inhibitors: INTERVENTI

- **Profilassi PJP se insorgenza di irAEs che richiedono steroidi**

- **Screening x TBC, HBV e HCV prima del trattamento**

Checkpoint inhibitors and aspergillosis in AML: the double hit hypothesis

*Naval Daver, *Dimitrios P Kontoyiannis*
Department of Leukemia, Division of Medical Oncology (ND) and Department of Infectious Diseases, Infection Control and Employee Health (DPK), The University of Texas, MD Anderson Cancer Center, Houston, Texas 77030, USA
dkontoyi@mdanderson.org

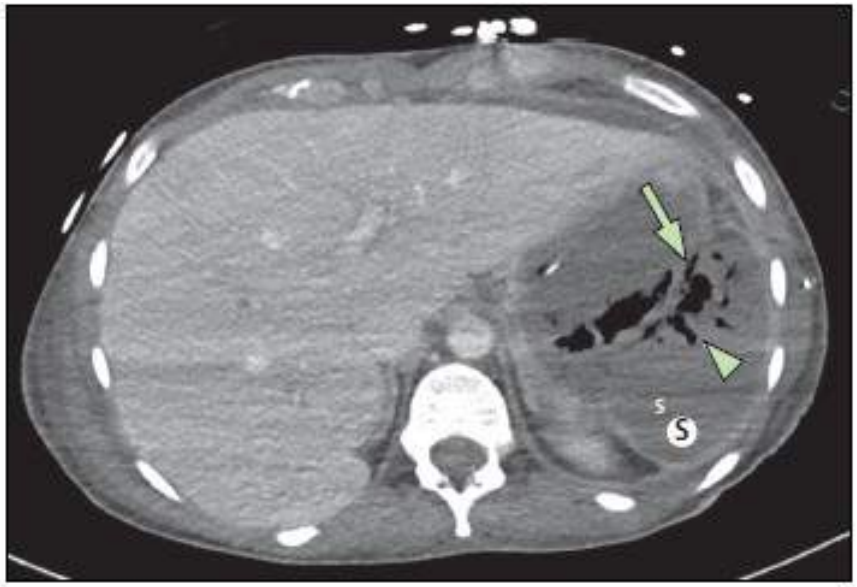
Lancet Oncol 2017

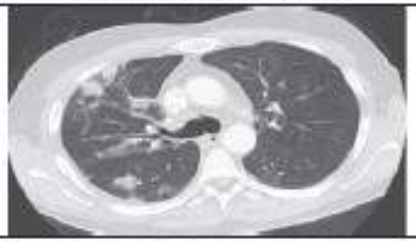
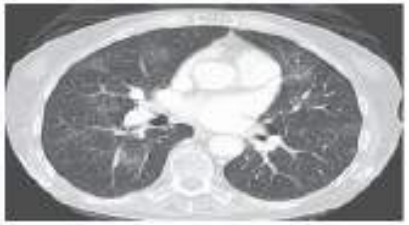
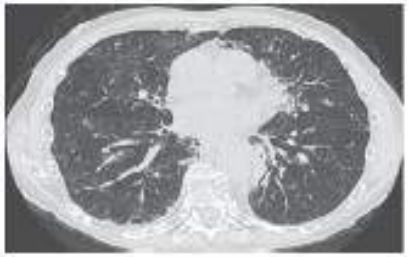
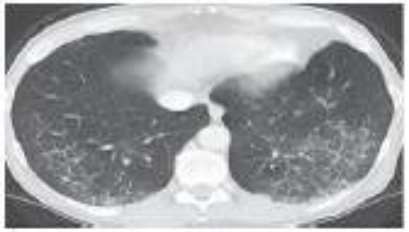
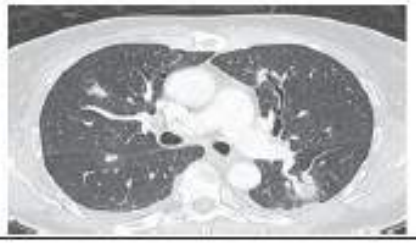
Nivolumab plus interferon-γ in the treatment of intractable mucormycosis

David Grimaldi, Olivier Pradier, Richard S Hotchkiss, *Jean-Louis Vincent

Lancet Infect 2017

L-AmB + posaconazolo
Linfocitopenia e aumentata espressione di PD-1
IFN-gamma + Nivolumab: risoluzione della linfocitopenia
RC mucormicosi



Radiologic Subtypes	Representative Image	Description
Cryptogenic organizing pneumonia-like (n = 5, 19%)		Discrete patchy or confluent consolidation with or without air bronchograms Predominantly peripheral or subpleural distribution
Ground glass opacities (n = 10, 37%)		Discrete focal areas of increased attenuation Preserved bronchovascular markings
Interstitial (n = 6, 22%)		Increased interstitial markings, interlobular septal thickening Peribronchovascular infiltration, subpleural reticulation Honeycomb pattern in severe patient cases
Hypersensitivity (n = 2, 7%)		Centrilobular nodules Bronchiolitis-like appearance Tree-in-bud micronodularity
Pneumonitis not otherwise specified (n = 4, 15%)		Mixture of nodular and other subtypes Not clearly fitting into other subtype classifications

Anti CD30, Brentuximab

- CD30 espresso sulle cellule di RS ma anche T-, B-cells, monociti
- MoAb anti-CD30 puo' inibire ADCC e immunita' umorale

Anti CD30, Brentuximab: INTERVENTI

- Non evidenza di aumentato rischio infettivo, ma aumentato rischio di neutropenia
- Profilassi PJP, herpes
- PML potenzialmente associato all'uso di Brentuximab
- Monitoraggio CMV (particolare attenzione a retinite)