XII°Corso Avanzato di Terapia Antibiotica
Pisa, 15-16 novembre 2017

La neutropenia febbrile

Alessandra Micozzi
Dipartimento di Biotecnologie Cellulari ed Ematologia
Sapienza Università di Roma

SAPIENZA
UNIVERSITÀ DI ROMA

- Fever developing during neutropenia is frequent in neutropenic cancer patients:
  - 80% of HM patients
  - 50% of ST patients
  - 13–21% in solid metastatic cancers (mostly during the first chemotherapy cycle)

in neutropenic hematological patients
bacteremias are responsible of 25-50% of febrile neutropenia episodes

High risk AL patients

GIMEMA trial	N°of febrile neutropenia episodes	% of BSI
1988-90	183	52%
1997-99	733	34%
2001-2003	221	28%
2008-2010	364	49%

Higher rate in HSCT recipients

in the setting of febrile neutropenia
occurrences of severe sepsis: 20–30%
occurrences of septic shock: 5–10%

Improvement in management strategies

- **appropriate empirical antibacterial treatment is critical for a successful outcome**
  - Particuarly in HM patients with febrile neutropenia
- **the aim of the empiric antibiotic treatment is to protect patients from early death**

➢ **broad-spectrum antibacterial drugs targeting Gram-negative bacteria** has reduced the mortality in neutropenic patients developing BSI: **<10%**

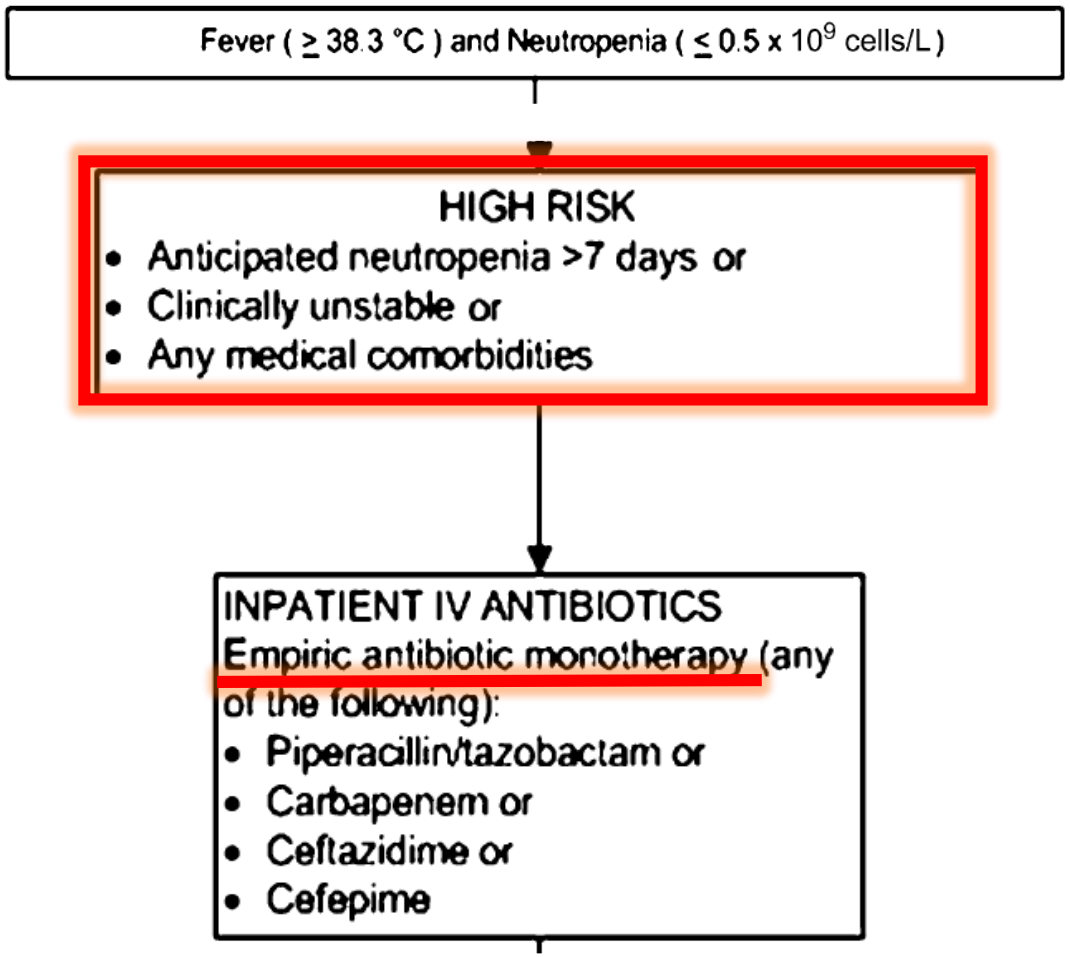
recommended empirical antibacterial regimens for the treatment of FN

have continued to focus on targeting GNB
including Enterobacteriaceae and P.aeruginosa,

anti-pseudomonal beta-lactam agent
with or without an aminoglycoside

IDSA GUIDELINES

Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America



Clinical Infectious Diseases 2011;52(4):e56–e93

Two major changes in the epidemiology of BSI during the last decade

1. the increasing proportion of GNB
2. the rapid increase in antimicrobial resistance among both Gram-negative and Gram-positive isolates
3. increasing detection of extended spectrum beta-lactamase (ESBL)-production in Enterobacteriaceae (including carbapenemase-production), increasing multidrug-resistance in P. aeruginosa and Acinetobacter spp., methillicin-resistant Staphylococcus aureus (MRSA), and isolation of vancomycinresistant enterococci (VRE).

Aetiology and resistance in bacteraemias among adult and paediatric haematology and cancer patients

(ECIL-4), a joint venture of EBMT, EORTC, ICHS, ELN and ESGICH/ESCMID

Journal of Infection (2014) **68**, 321–331

- *literature review on bacteraemias in cancer patients (papers published between 2005 2011)*
- *questionnaire on the aetiology and resistance in bacteraemias, and empirical treatment participants of ECIL meetings 2011*

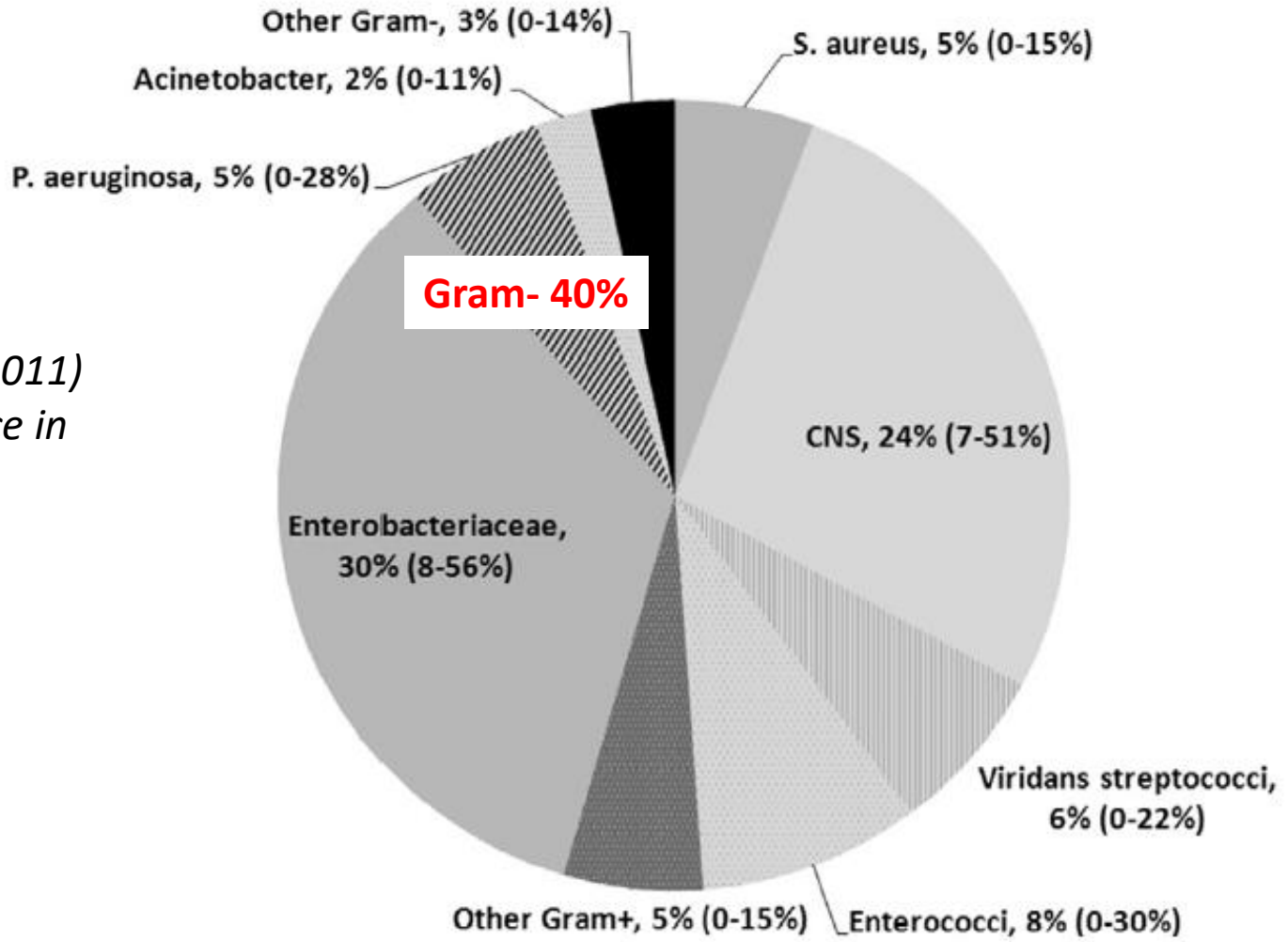


Figure 1 Aetiology of bacteraemias (median prevalence with range) reported in the ECIL-4 questionnaire survey. Notes: CNS, coagulase negative staphylococci.

increasing proportion of GNB

Ola Blennow[1,2] and Per Ljungman[2,3]

Table I. Epidemiology of BSI in haemato-oncology patients in studies with the majority of the observational time occurring after 2006.

Study	Country	Period	Setting	Age	Total isolates (n)	Gram-neg %	E. coli %	K. pneumoniae %	P. aeruginosa %
Ke *et al* (2010)	China	2005–2009	H/C	Children	74	69	18	20	16
Prabash *et al* (2010)	India	2007	H/C	All	484	68	11	7	30
Jin *et al* (2010)	Singapore	2008–2009	H/C	Adults	49	51	22	20	6
Chong *et al* (2010)	Japan	2006–2008	H	All	135	50	19	10	16
Aydemir *et al* (2013)	Turkey	2005–2011	H/C	>60 years	108	49	32	7	6
Aslan *et al* (2012)	Turkey	2007–2010	H/C	Children	171	43	8	5	2
Sood *et al* (2012)	India	2009–2010	H	All	105	73	17	16	9
Poon *et al* (2012)	Singapore	2008–2010	H	Adults	159	52	24	17	7
Samonis *et al* (2013)	Greece	2007–2011	H/C	Adults	110	65	17	16	17
Gudiol *et al* (2013)	Spain	2006–2010	H	Adults	283	49	25	11	11
Lv and Ning (2013)	Chin	2010	H	Children	78	44	15	15	6
Bucaneve *et al* (2014)	Italy	2008–2010	H	Adults	180	35	21	4	5
Cattaneo *et al* (2014)	Italy	2004–2011	H	NS	250	NR	46	NR	13
Bousquet *et al* (2014)	France	2003–2010	H	Adults	723	71	19	NR	15
Rosa and Goldani (2014)	Brazil	2009–2011	H	Adults	115	66	42	11	10
Moghnieh *et al* (2015)	Lebanon	2009–2012	H/C	All	75	57	23	13	3
Trecarichi *et al* (2015)	Italy	2009–2012	H	Adults	668	53	28	6	10

Gram-neg, Gram-negative bacteria; CNS, coagulase-negative staphylococci; H, haematology patients; C, cancer patients; NR, not report
All percentages are calculated from the total number of blood stream isolates in the studies, and only major pathogens are included.

Two major changes in the epidemiology of BSI during the last decade

1. the increasing proportion of GNB
2. the rapid increase in antimicrobial resistance among both Gram-negative and Gram-positive isolates
   - Enterobacteriaceae: increasing detection of ESBL-production and carbapenemase-production
   - *P. aeruginosa* and Acinetobacter spp.: increasing MDR
   - MRSA
   - VRE

Aetiology and resistance in bacteraemias among adult and paediatric haematology and cancer patients

(ECIL-4), a joint venture of EBMT, EORTC, ICHS, ELN and ESGICH/ESCMID

literature review 2005 2011
questionnaire 2011

Table 3 Median rates of resistance to different antibiotics in pathogens causing bacteraemias in h and children, based upon literature reports.

Pathogen and studies	Type of resistance	Adults median rate of resistance (range)
S. aureus	MRSA	56% (18–100%)[a]
CNS	MR-CNS	80% (33–100%)[c]
Enterococci	VRE	23% (0–50%)[e]
Gram-negatives	Fluoroquinolone-resistant	41% (18–74%)[g]
Gram-negatives	Carbapenem-resistant	20% (11–72%)[i]
Gram-negatives	Aminoglycoside-resistant	28% (6–41%)[j]
Gram-negatives	Ceftazidime-resistant	43% (17–45%)[l]
Enterobacteriaceae	ESBL-producing	34% (16–44%)[m] + 42% of *E. coli*[n]
Enterobacteriaceae	Fluoroquinolone-resistant	56% (28–87%)[p] + 63% of *E. coli*[n]
P. aeruginosa	Fluoroquinolone-resistant	53% (7–72%)[q]
P. aeruginosa	Carbapenem-resistant	44% (3–66%)[s]

Abbreviations: CNS, coagulase-negative staphylococci; ESBL, extended-spectrum beta-lactamase; MRSA, MR-CNS, meticillin-resistant CNS; VRE, vancomycin-resistant enterococci.

Generally, the reported patterns of resistance in BSI isolates reflect the rates in the reporting country
(exception of local outbreaks).

higher median rate of ESBL-GNB and CR *P.aeruginosa* in the South-East versus North-West Europe

Journal of Infection (2014) 68, 321–331

Factors influencing mortality in neutropenic patients with haematologic malignancies or solid tumours with bloodstream infection

M. Marín[1], C. Gudiol[2,5], C. Ardanuy[3], C. Garcia-Vidal[2,5], L. Jimenez[1], E. Domingo-Domenech[4], F. J. Pérez[6] and J. Carratalà[2,5]

TABLE 3. Risk factors for the overall case-fatality rate of 510 episodes of BSI in neutropenic patients with haematologic malignancies according to univariate and multivariate analysis

		Dead	Alive[a]	Univariate analysis		Multivariate analysis[b]	
Risk factor	*n*	(*n* = 61)	(*n* = 445)	OR (95% CI)	p	OR (95% CI)	p
Age, y, median (range)		61 (21–84)	57 (19–89)	1 (1.0–1.04)	0.035	—	
Male sex	311	31 (10)	280 (90)	0.6 (0.4–1)	0.069		
Advanced neoplasm	39	13 (33.3)	26 (66.7)	4.46 (2.2–9.3)	<0.001	8.7 (2.9–25.7)	<0.001
Haematopoietic stem cell transplant	129	12 (9.3)	117 (90.7)	0.7 (0.7–1.4)	0.29		
MASCC score <21	150	37 (24.7)	113 (75.3)	6.7 (3.5–12.7)	<0.001	3.1 (1.3–7.4)	0.01
Corticosteroid therapy	128	32 (25)	96 (75)	4.0 (2.3–6.9)	<0.001	7.00 (3–16.4)	<0.001
Gram negative	250	33 (13.2)	217 (86.8)	1.2 (0.7–2.1)	0.43		
Escherichia coli	128	13 (10.2)	115 (89.8)	0.8 (0.4–1.5)	0.44		
Klebsiella pneumoniae	55	9 (16.4)	46 (83.6)	1.5 (0.7–3.2)	0.30		
Pseudomonas aeruginosa	54	9 (16.7)	45 (83.3)	1.5 (0.7–3.3)	0.27		
Enterobacter spp.	23	3 (13.04)	20 (86.96)	1.1 (0.3–3.8)	0.75		
MDR GNB	38	12 (31.6)	26 (68.4)	3.9 (1.9–8.2)	<0.001	3.8 (1.2–11.8)	0.019
Inadequate empirical antibiotic therapy	378	46 (12.2)	332 (87.8)	1.02 (0.5–1.9)	0.93		
Empirical antibiotic combination therapy	366	31 (8.5)	335 (91.5)	0.3 (0.2–0.6)	<0.001	0.1 (0.05–0.3)	<0.001
Days before adequate antibiotic therapy		0 (0–4)	0 (0–7)	1.1 (0.8–1.4)	0.56		
Growth factors	129	21 (16.3)	108 (83.7)	1.6 (0.9–2.9)	0.09		
ICU admission	53	29 (54.7)	24 (45.3)	16 (8.3–30.4)	<0.001	15.2 (5.4–42.7)	<0.001

Clin Microbiol Infect 2015; **21:** 583–590

important question when facing a patient with febrile neutropenia

- should the empiric treatment cover resistant pathogens such as ESBL-and CR Enterobacteriaceae, MDR *P. aeruginosa*, and MRSA?

NO:

Risk of inadequate therapy, probably an increased risk of poor outcome

YES

Risk of unnecessary broad-spectrum ATB and increased rates of infection with resistant bacteria, both for the patient at hand and for future patients

Risk of toxicity if combining antimicrobial agents.

2013 ECIL guidelines for empirical antibacterial therapy for febrile neutropenia :

- the choice of antimicrobial coverage should be based on an <u>estimation of</u>

- **the risk that the patient has an infection with resistant bacteria**

  +

- **the risk for a complicated clinical course**

ECIL: European Conference on Infection in Leukemia

de-escalation strategy

risk of infection caused by resistant pathogens

- *prior infection/coloniz with a resistant path*
- *high local resistance rates*

complicated clinical course *hypotension or shock*

very broad empiric treatment

- Carbapenem monotherapy
- anti-pseudomonal β-lactams + AG or FQ
  Colistin + β-lactam or rifampicin
- Early coverage of resistant gram-positives

non-resistant pathogen isolated or favourable clinical response

de-escalation to simpler or targeted therapy

escalation to to broad-spectrum coverage

the patient deteriorates or a resistant pathogen is isolated

empiric monotherapy

e.g. piperacillin/tazob , ceftazidime or cefepime

escalation strategy:

- ***No risk for infection caused by resistant pathogen***
  - *Low local GNB resistance*
  - *no prior infection with a resistant pathogen*

. ***No complicated clinical course***

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

Clinical Infectious Diseases® 2017;XX(00):1–10

D. Averbuch et al

704 GNRs causing BSI in HSCT patients, *25 countries from Europe, Asia, and Australia*.
antimicrobial susceptibility patterns and *geographical distribution of resistance*

call for reassessment of local empiric antibiotic protocols.

The emerging resistance complicates empiric and targeted treatment choices.

- **Universal recommendations** for empiric therapy are difficult (significant geographical variations)
- Practical decisions based on **continuously updated data on local resistance patterns** and BSI rate
- to recommend the **specific resistance rate threshold** that indicates change in the empiric therapy protocol

Questionnaire sent to participants of the ECIL meetings

(80 haematology centres)

Mikulska, Journal of Infection 2014

the question about which resistant pathogens were causing most clinical problems in their unit:

- **➢76% highlighted ESBL producing Enterobacteriaceae**
- 46% fluoroquinolone-resistant Gram-negatives

ECIL:European Conference on Infection in Leukemia

Reported resistance rates in GNB in BSI in haematology-oncology patients in studies with the majority of the observational time occurring after 2006.

Study	Country	Years	Setting	Age	Number of isolates (% of isolates)	ESBL %
E. coli						
Prabash *et al* (2010)	India	2007	H/C	Adult	53 (11)	51
Aslan *et al* (2012)	Turkey	2007-2010	H/C		13 (8)	23
Lv and Ning (2013)	China	2010	H	Children	12 (15)	
Metan *et al* (2013)	Turkey	2006-2011	H	>16 years	86 (56% of all Gram-)	
Cattaneo *et al* (2014)	Italy	2004-2011	H	NS	115 (46)	19
Moghnieh *et al* (2015)	Lebanon	2009-2012	H/C	All	17 (23)	
Trecarichi *et al* (2015)	Italy	2009-2012	H	Adults	187 (28)	
Ke *et al* (2010)	China	2005-2009	H/C	Children	13 (17)	69
Gudiol *et al* (2011)	Spain	2006-2009	H/C	>14 years	184 (44% of all Gram-)	14
Aydemir *et al* (2013)	Turkey	2005–2011	H	>60 years	34 (31)	50
Gudiol *et al* (2013)	Spain	2006–2010	H	Adult	71 (25)	11
Kim *et al* (2013)	South Korea	2007–2008	H	>16 years	87 (NS)	17
Rosa and Goldani (2014)	Brazil	2009–2011	H	Adult	48 (41)	15
K. pneumonia						
Prabash *et al* (2010)	India	2007	H/C	All	35 (7)	63
Lv and Ning (2013)	China	2010	H	Children	12 (15)	
Metan *et al* (2013)	Turkey	2006–2011	H	>16 years	28 (18% of all Gram-)	
Pagano *et al* (2014)	Italy	2009–2012	H	NS	38 (2% of all Gram-)	
Moghnieh *et al* (2015)	Lebanon	2009–2012	H/C	All	11 (13)	
Trecarichi *et al* (2015)	Italy	2009–2012	H	Adults	43 (6)	
Ke *et al* (2010)	China	2005–2009	H/C	Children	15 (19)	53
Kim *et al* (2013)	South Korea	2007–2008	H	>16 years	14 (NS)	79

the burden of ESBL-E in patients with cancer and neutropenia, SCT recipients

high incidence

bacteria of the GI flora are more likely to penetrate the disrupted mucosa and cause BSI

variability in the prevalence of ESBL-E colonization and infection with respect to country and patient population

British Journal of Haematology, 2016, **172**, 497–511

Figure 3.2. *Escherichia coli*. Percentage (%) of invasive isolates with resistance to third-gene
country, EU/EEA countries, 2015

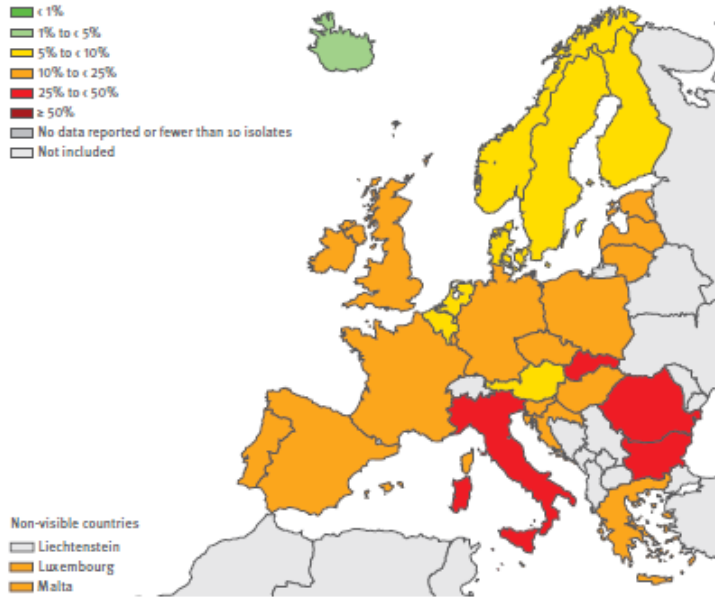


Figure 3.10. *Klebsiella pneumoniae*. Percentage (%) of invasive isolates with combined resis
third-generation cephalosporins and aminoglycosides, by country, EU/EEA countries, 2015

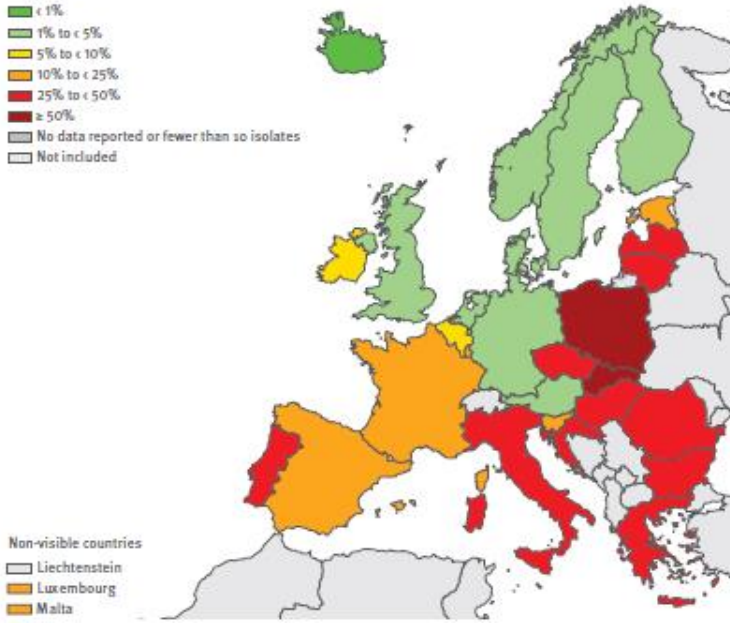


Table 3.3. *Escherichia coli*. Total number of invasive isolates tested (N) and percentage with resistance to third-generation cephalosporins (%R), including 95% confidence intervals (95% CI), EU/EEA countries, 2012–2015

Country	2012			2013			2014			2015			Trend 2012–2015		
	N	%R	(95% CI)	N	%R	(95% CI)	N	%R	(95% CI)	N	%R	(95% CI)			Comment*
Romania	191	25.1	(19–32)	258	22.8	(18–28)	306	29.4	(24–35)	369	26.8	(22–32)			
Cyprus	176	31.8	(25–39)	162	38.9	(31–47)	153	28.8	(22–37)	123	28.5	(21–37)			
Slovakia	693	30.7	(27–34)	807	29.7	(27–33)	889	31.8	(29–35)	893	30.0	(27–33)			
Italy	2997	26.3	(25–28)	3990	26.2	(25–28)	3694	28.7	(27–30)	5592	30.1	(29–31)			)
Bulgaria	223	38.1	(32–45)	187	39.6	(33–47)	218	40.4	(34–47)	205	38.5	(32–46)			

Current epidemiology and antimicrobial resistance data for bacterial bloodstream infections in patients with hematologic malignancies: an Italian multicentre prospective survey

Clin Microbiol Infect 2015; 21: 337–343

E. M. Trecarichi[1], L. Pagano[2], A. Candoni[4], D. Pastore[5], C. Cattaneo[6], R. Fanci[7], A. Nosari[8], M. Caira[2], A. Spadea[3], A. Busca[9], N. Vianelli[10] and M. Tumbarello[1] for the HeMABIS Registry—SEIFEM Group, Italy

January 2009 to December 2012.

TABLE 3. Antimicrobial susceptibility profiles of all Gram-negative bacteria and of most frequently isolated bacterial species

		Susceptible, *n* (%)					
Gram negative microorganism	Total	Ceftazidime	Ciprofloxacin	Meropenem	Amikacin	Gentamicin	Piperacillin/tazobactam
Total[a]	344	203 (59.1)	[illegible])	272 (79.1)	293 (85.2)	238 (69.2)	240 (69.8)
Escherichia coli	187	131 (70.0)	[illegible]	184 (98.4)	183 (97.9)	155 (82.9)	156 (83.4)
Klebsiella pneumoniae	43	18 (41.9)	[illegible])	28 (65.1)	25 (58.1)	29 (67.4)	19 (44.2)
Enterobacter cloacae	26	12 (46.1)	[illegible])	24 (92.3)	23 (88.5)	23 (88.5)	12 (46.1)
Pseudomonas aeruginosa	66	30 (45.4)	13 (19.7)	19 (28.8)	43 (65.1)	15 (22.7)	38 (57.6)

30%
40%

[a]Total of Gram-negative bacteria was 344; nine *Stenotrophomonas maltophilia* isolates were excluded.

E.coli bacteremias in patients with HM

Ematologia, Sapienza Università di Roma

periodo 2009-2014

	N° of *E.coli* blood isolates	ESBL	no-ESBL	acute myeloid leukemia pts	ESBL	other HM pts	ESBL
2009-2014	**250**	**42%**	**58%**	**98**	**46%**	**152**	**38%**
Related death	**19%**	**25%**	**14%**	**19%**	**26%**	**20%**	**25%**
		p=0.06					

Problems with ESBL producer in neutropenic febrile patients

- often not covered by empirical regimens
  - resistance to most beta-lactams and frequent co-resistance to quinolones and aminoglycosides
- delayed initiation of adequate treatment is associated with increased morbidity and mortality
- scarce evidence for treatment of ESBL-E infections in high-risk patients.
- **Carbapenems are currently considered the standard of care, but….**

✓Restriction

✓empirical therapy should not unconditionally cover ESBL-E (selection of further resistance including carbapenems)

treatment options other than carbapenems

- some studies support the use of quinolones and BLBLI as an alternative to carbapenems, these results cannot be transferred to high-risk patients due to the differences in co-resistance rates

- Tygecicline?
- Ceftolozane-tazobactam?

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Results of a Multicenter, Controlled, Randomized Clinical Trial Evaluating the Combination of Piperacillin/Tazobactam and Tigecycline in High-Risk Hematologic Patients With Cancer With Febrile Neutropenia

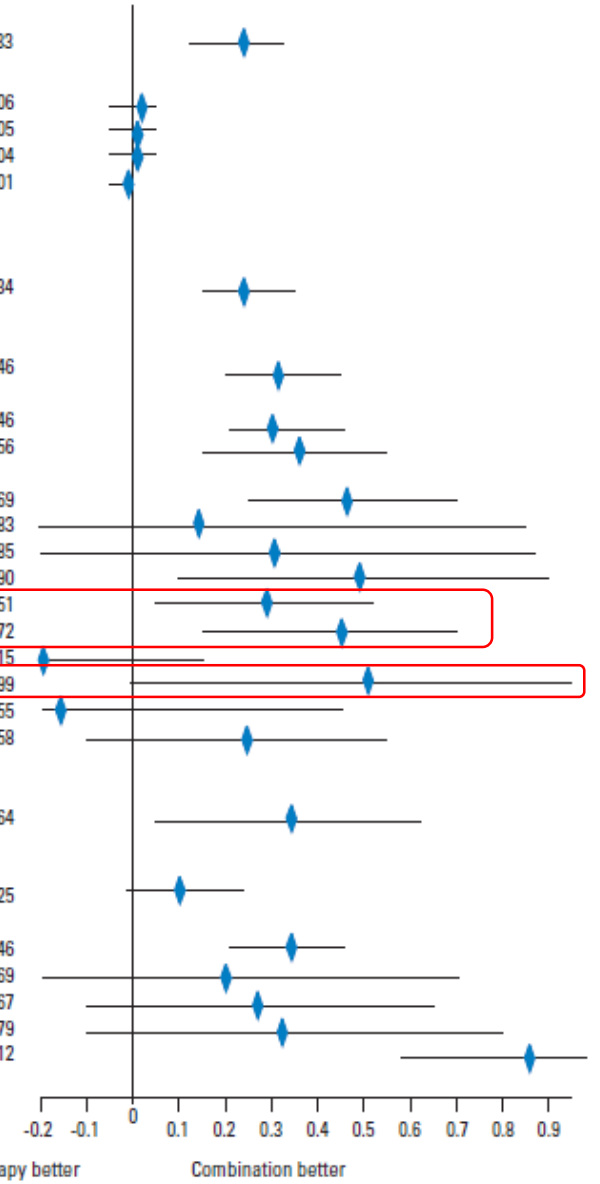
Giampaolo Bucaneve, Alessandra Micozzi, Marco Picardi, Stelvio Ballanti, Nicola Cascavilla, Prassede Salutari, Giorgina Specchia, Rosa Fanci, Mario Luppi, Laura Cudillo, Renato Cantaffa, Giuseppe Milone, Monica Bocchia, Giovanni Martinelli, Massimo Offidani, Anna Chierichini, Francesco Fabbiano, Giovanni Quarta, Valeria Primon, Bruno Martino, Annunziata Manna, Eliana Zuffa, Antonella Ferrari, Giuseppe Gentile, Robin Foà, and Albano Del Favero

Pipera-tazo + tigecycline combination improve the likelihood that **the empiric treatment may initially address the possible involved MDR pathogens**

390 pts (acute leukemia: 69%)

Success rate of pip-tazo+tyge combination: 68%

Group and Event	Combination No.	Combination %	Monotherapy No.	Monotherapy %	Absolute Difference in Risk	95% CI
All treated patients						
Febrile episode resolution	127 of 187	67.9	90 of 203	44.3	0.23	0.14 to 0.33
Death	16 of 187	8.5	15 of 203	7.3	0.01	-0.04 to 0.06
Death resulting from infective cause	11 of 187	5.8	11 of 203	5.4	0.004	-0.04 to 0.05
AEs	12 of 187	6.4	13 of 203	6.4	0.0001	-0.04 to 0.04
Withdrawal due to AEs	3 of 187	1.6	5 of 203	2.4	-0.008	-0.03 to 0.01
All assessable patients						
Febrile episode resolution	126 of 174	72.4	90 of 190	47.4	0.25	0.15 to 0.34
Microbiologically documented infections	54 of 88	61.4	27 of 96	28.1	0.33	0.19 to 0.46
Bacteremia	52 of 86	60.5	26 of 94	27.7	0.32	0.19 to 0.46
Gram positive	30 of 42	71.4	16 of 46	34.8	0.36	0.17 to 0.56
Staphylococcus aureus			2 of 4	50.0		
*Coagulase-negative Staph**	20 of 26	76.9	9 of 29	31.0	0.45	0.22 to 0.69
Enterococci	2 of 3	66.7	3 of 6	50.0	0.16	-0.50 to 0.83
Streptococci	5 of 7	71.4	2 of 5	40.0	0.31	-0.23 to 0.85
Other gram positive	3 of 6	50.0	0 of 2	0.0	0.50	0.09 to 0.90
Gram negative	18 of 34	52.9	7 of 29	24.1	0.28	0.05 to 0.51
Escherichia coli	15 of 22	68.2	4 of 17	23.5	0.44	0.16 to 0.72
Pseudomonas spp	0 of 5	0.0	1 of 5	20.0	-0.20	-0.55 to 0.15
Klebsiella spp	2 of 4	50.0	0 of 3	0.0	0.50	0.01 to 0.99
Other gram negative	1 of 3	33.3	2 of 4	50.0	-0.16	-0.89 to 0.55
Polymicrobial	4 of 10	40.0	3 of 19	15.8	0.24	-0.10 to 0.58
Clinically documented infection	16 of 19	84.2	9 of 19	47.4	0.36	0.09 to 0.64
Fever of unknown origin	56 of 67	83.6	54 of 75	72.0	0.11	-0.01 to 0.25
Documented infections	70 of 107	65.4	36 of 115	31.3	0.34	0.21 to 0.46
Pneumonia	5 of 7	71.4	4 of 8	50.0	0.21	-0.26 to 0.69
Central venous catheter	5 of 8	62.5	6 of 17	35.3	0.27	-0.13 to 0.67
Abdominal	4 of 8	50.0	1 of 6	16.7	0.33	-0.12 to 0.79
SSTI†	6 of 6	100	1 of 7	14.3	0.85	0.59 to 1.12



piperacillin/tazobactam plus tigecycline combination **superior** to piperacillin/tazobactam monotherapy also in the **subset of HM patients with persistent profound neutropenia**

Table 1. Response to Assigned Antibiotic Regimen (success/failure)

Characteristic	Piperacillin/ Tazobactam + Tigecycline		Piperacillin/ Tazobactam		
	Success/Failure	%	Success/Failure	%	*P**
All assessable patients	126/174	72	90/190	47	< .01
All patients with persistent profound neutropenia†	21/55	38	10/80	12	< .01
Microbiologically documented infection	9/37	24	3/55	5	.02
With bacteremia	9/36	25	3/54	5	.01
Clinically documented infection	3/6	50	2/5	40	.6
Fever of unknown origin	9/13	69	5/20	25	.03

Alessandra Micozzi *Journal of Clinical Oncology*, Vol 32, 2014

	PIPERA/TAZO + TYGE	PIPERA/TAZO
Total deaths	16/187(8%)	15/203 (7%)
Bacterial infection related death	8 (4%)	10 (5%)
Early death (within 72 h)	**1/8 (12 %)**	**4/10 (40%)**

Identification of neutropenic cancer patients at risk of ESBL- E BSI

- **association between ESBL-E colonization and subsequent infection is confirmed in several studies**.

Colonisation with extended-spectrum β-lactamase-producing Enterobacteriaceae and risk for infection among patients with solid or haematological malignancy: a systematic review and meta-analysis

Michail Alevizakos, Styliani Karanika, Marios Detsis, Eleftherios Mylonakis *

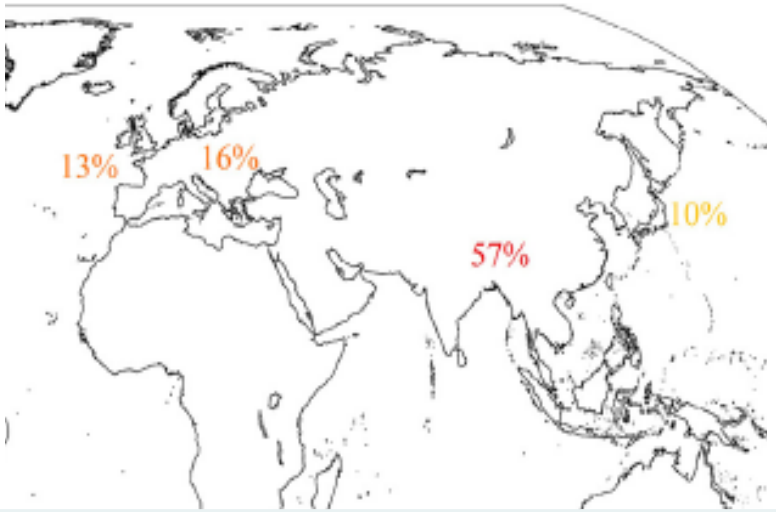
1991 - 2016 (25 years)

- to estimate the prevalence of ESBL-E colonisation in cancer populations
- to determine the risk for subsequent BSI

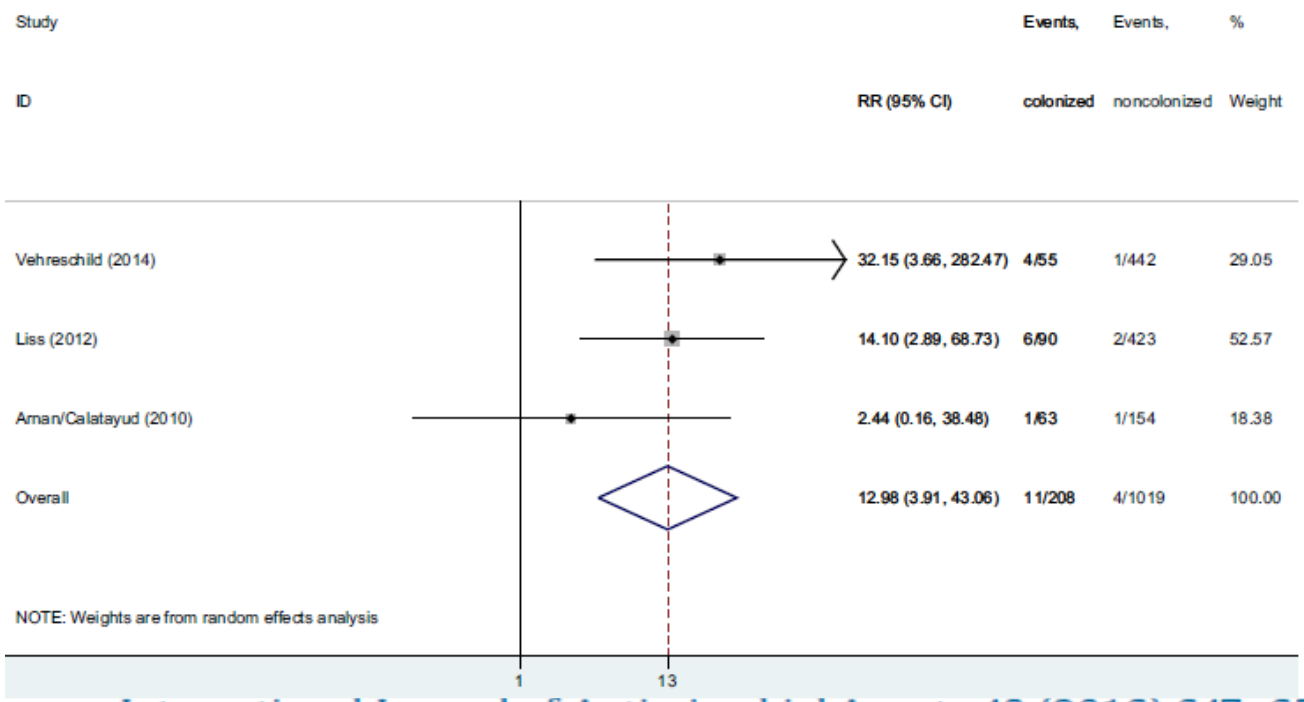
- **Pooled prevalence of ESBL-E colonization: 19%** [95% CI 8–32%]
  - **Europe : 15%** (95% CI 10–21%)

patients with malignancy represent a high-risk population for colonisation with ESBL-E

ESBL- E colonisation was associated with an almost 13 times higher risk for developing ESBL-PE BSI



Prior colonization as Risk Factor for Infection



International Journal of Antimicrobial Agents 48 (2016) 647–654

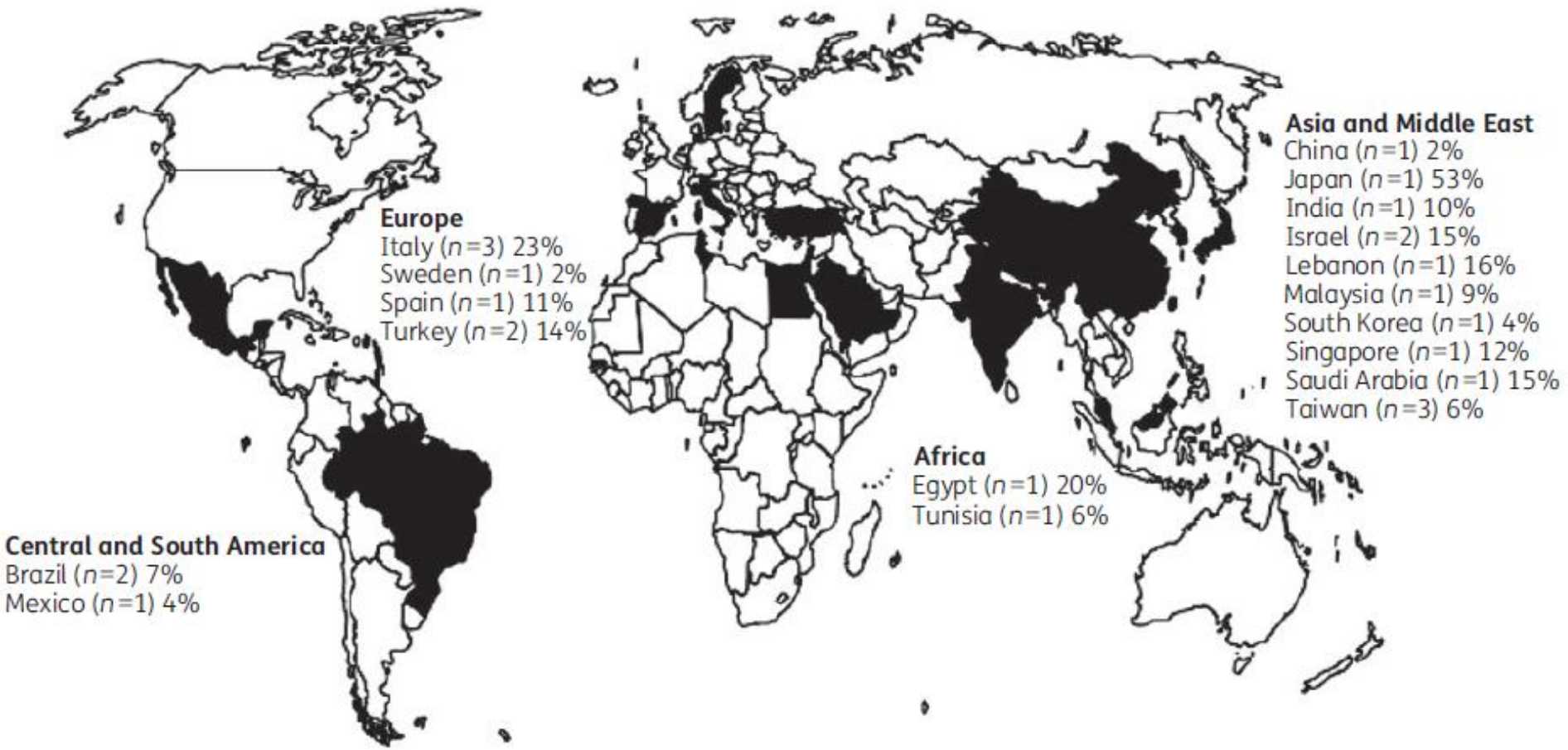
association between colonization and subsequent infection with ESBL-E

- screening for ESBL colonization in neutropenic cancer patients with the aim of adjusting empirical treatment may be effective in improving patient outcome
  - However, the approach of systematic screening and a consecutive adaption of empirical treatment has not been evaluated in a systematic fashion.

Global prevalence of carbapenem resistance in neutropenic patients and association with mortality and carbapenem use: systematic review and meta-analysis

Elda Righi[1,2]*, Anna Maria Peri[2,3], Patrick N. A. Harris[2], Alexander M. Wailan[2], Mariana Liborio[4], Steven W. Lane[5-7] and David L. Paterson[2]

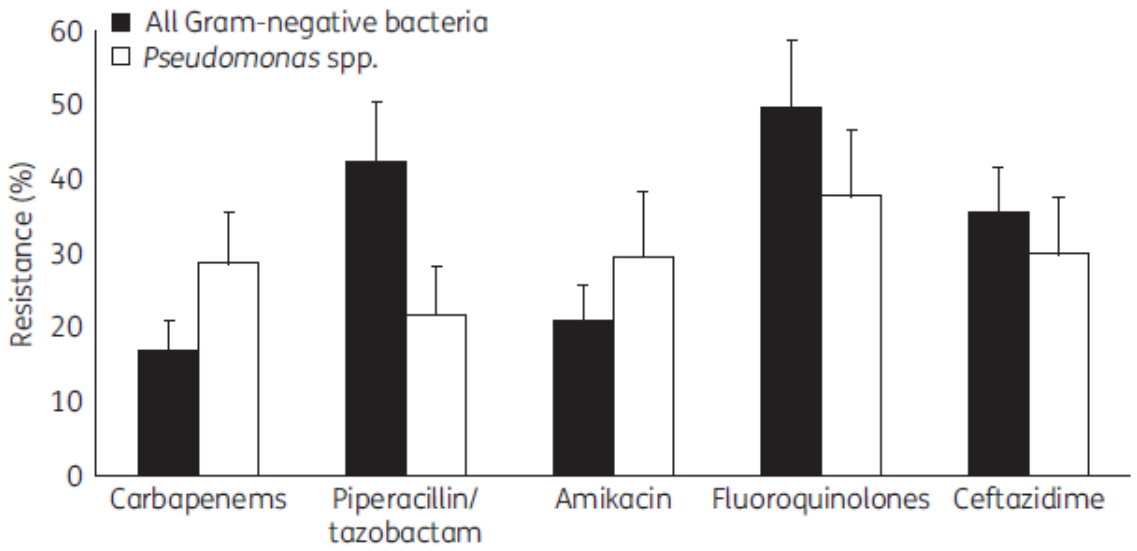
Figure 2. Geographical distribution of carbapenem resistance prevalence (%) in GNB isolated from BSIs in neutropenic patients, with number of included studies per country in parentheses.



J Antimicrob Chemother 2017; **72**: 668–677

BSIs in neutropenic patients:

Percentages of resistance to carba, pipera/tazo, amikacin, fluoroquinolones and ceftazidime among GNB and *Pseudomonas* spp.



Carbapenem resistance rates ranged from 2% to 53% (median 9%)

Carba-R Pseudomonas spp:

- high median resistance rates
- 44% of all Carba R Gram-negatives
- 19% of Pseudomonas isolates

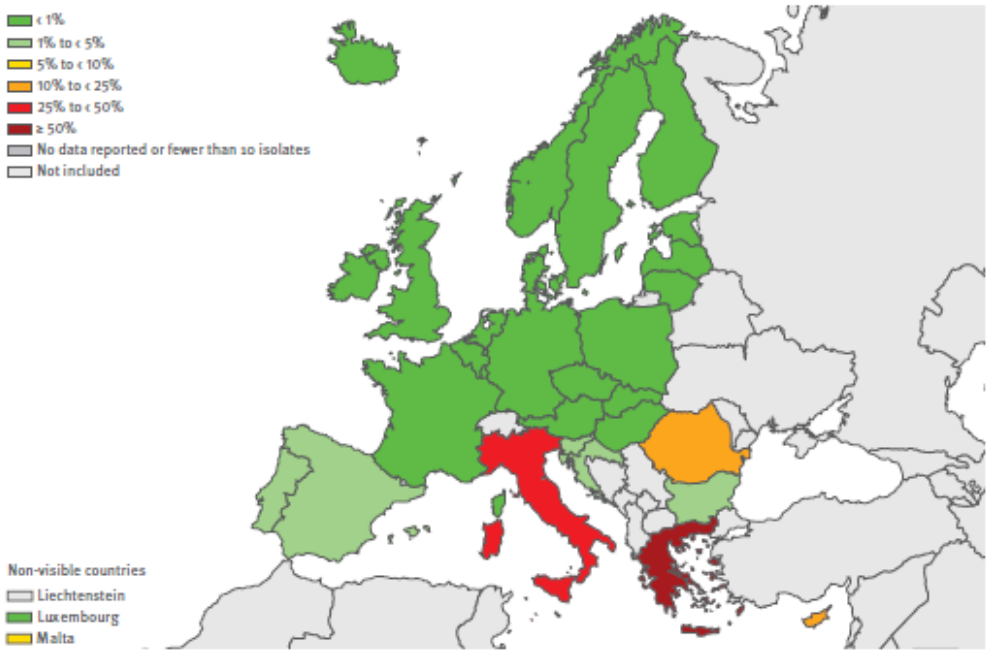
Carba-R Enterobacteriaceae

- less commonly reported
- mainly from endemic areas (Greece, Italy, Israel).

Mortality rates ranged from 33% to 71% (median 50%)

J Antimicrob Chemother 2017; **72**: 668–677

Figure 3.9. *Klebsiella pneumoniae*. Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2015



Endemicity of KPC-KP in Italian healthcare facilities predominant role among CPE.

Infections with KPC-KP affect mostly older patients hospitalised in medical or surgical wards with a known history of previous hospital admission in the country.

Country	2012			2013			2014			2015				Trend 2012–2015	
	N	%R	(95% CI)	N	%R	(95% CI)	N	%R	(95% CI)	N	%R	(95% CI)			Comment*
Italy	845	29.1	(26–32)	1453	34.3	(32–37)	1315	32.9	(30–36)	1999	33.5	(31–36)		34.0 31.5 29.0	

Reports on carbapenemase-producing *K. pneumoniae* in haematological patients have come mostly from Italy

KPC-KP: 68% delle KP

, Rome, Italy, 2009–2012*

Year	Non-KPC–producing *K. pneumoniae* BSI, no.	Non-KPC–producing *K. pneumoniae* Deaths, no. (%)	KPC-producing *K. pneumoniae* BSI, no.	KPC-producing *K. pneumoniae* Deaths, no. (%)
2009	1	0	0	0
2010	2	0	1	1 (100)
2011	5	1 (20)	13	7 (53.8)
2012	4	1 (25)	12	7 (58.3)
Total	12	2 (16.6)	26	15 (57.6)

L.Pagano et al Emerg Infect Dis 2014

TABLE 3. Antimicrobial susceptibility profiles of all Gram-negative bacteria and of most frequently isolated bacterial species

Gram negative microorganism	Total	Susceptible, *n* (%) Ceftazidime	Ciprofloxacin	Meropenem	Amikacin	Gentamicin	Piperacillin/tazobactam
Total[a]	344	203 (59.1)	69 (20.1)	272 (79.1)	293 (85.2)	238 (69.2)	240 (69.8)
Escherichia coli	187	131 (70.0)	18 (9.6)	184 (98.4)	[illegible]	155 (82.9)	156 (83.4)
Klebsiella pneumoniae	43	18 (41.9)	13 (30.2)	28 (65.1)	[illegible]	29 (67.4)	19 (44.2)
Enterobacter cloacae	26	12 (46.1)	13 (50.0)	24 (92.3)	[illegible]	23 (88.5)	12 (46.1)
Pseudomonas aeruginosa	66	30 (45.4)	13 (19.7)	19 (28.8)	43 (65.1)	15 (22.7)	38 (57.6)

35% CR Kp

[a]Total of Gram-negative bacteria was 344; nine *Stenotrophomonas maltophilia* isolates were excluded.

E. M. Trecarichi *Clin Microbiol Infect* 2015;

Risk factors for carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection among rectal carriers: a prospective observational multicentre study

Clin Microbiol Infect 2014

M. Giannella[1], E. M. Trecarichi[2], F. G. De Rosa[3], V. Del Bono[4], M. Bassetti[5], R. E. Lewis[1], A. R. Losito[2], S. Corcione[3], C. Saffioti[4], M. Bartoletti[1], G. Maiuro[2], C. S. Cardellino[3], S. Tedeschi[1], R. Cauda[2], C. Viscoli[4], P. Viale[1] and M. Tumbarello[2]

multicentre prospective matched case–control study of all adult CR-KP rectal carriers hospitalized in five tertiary teaching hospitals in Italy

- **Colonization at multiple sites with CR-KP was the strongest predictor of BSI development in our large cohort of CR-KP rectal carriers.**

TABLE 2. Logistic regression analysis of risk factors for CR-KP BSI development in rectal carriers

	OR (95% CI)	P-value	Risk score point
Admission to ICU	1.65 (1.05–2.59)	0.03	2
Invasive abdominal procedures	1.87 (1.16–3.04)	0.01	3
Chemotherapy/radiation therapy	3.07 (1.78–5.29)	<0.0001	4
Colonization at site besides stool (risk per each additional site)	3.37 (2.56–4.43)	<0.0001	5 per site

ICU, intensive care unit; OR, odds ratio.

ORIGINAL ARTICLE

Bone Marrow Transplantation (2015) **50,** 282–288

Infections by carbapenem-resistant *Klebsiella pneumoniae* in SCT recipients: a nationwide retrospective survey from Italy

C Girmenia[1], GM Rossolini[2,3,4], A Piciocchi[5], A Bertaina[6], G Pisapia[7], D Pastore[8], S Sica[9], A Severino[10], L Cudillo[11], F Ciceri[12], R Scimè[13], L Lombardini[14], C Viscoli[15], A Rambaldi[16] and the Gruppo Italiano Trapianto Midollo Osseo (GITMO)[17]

(January 2010 to July 2013) involving 52 Italian centers

Cases of CRKp infection were reported in 53.4% of centers.

	auto-SCT (n.25)	allo-SCT (n.87)
Incidence of CRKp infection	0.4%	2%
CRKp colonization followed by infection:	26%	39%
Infection-related mortality:	16%	64%

The detection of carriers and the definition of early therapeutic strategies represent critical aspects of the management of CRKp infections after SCT.

Carbapenem-resistant *Klebsiella pneumoniae* in high-risk haematological patients: factors favouring spread, risk factors and outcome of carbapenem-resistant *Klebsiella pneumoniae* bacteremias

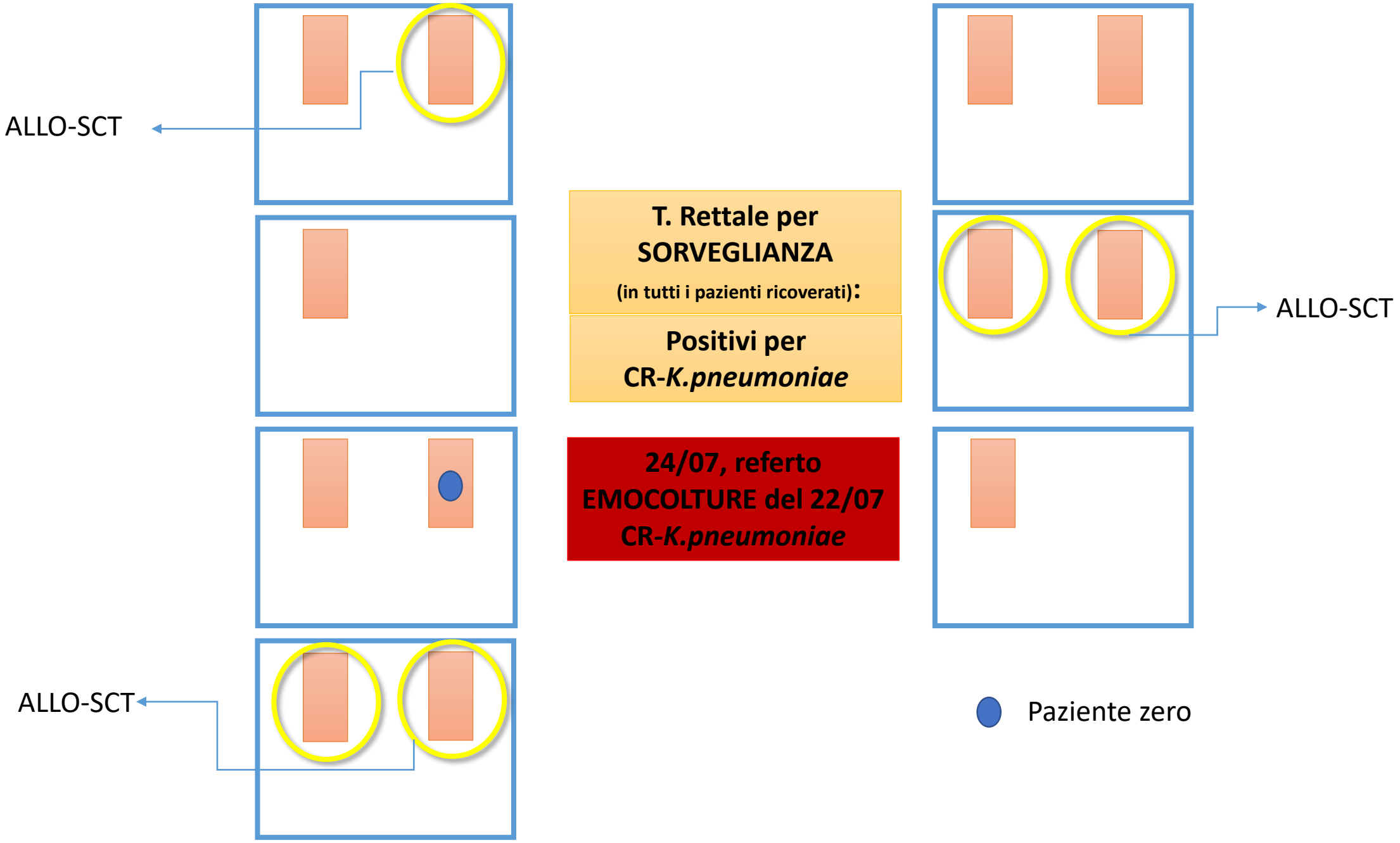
Micozzi *et al. BMC Infectious Diseases* (2017) 17:203

CHARACTERISTICS OF PATIENTS AT CRKP ACQUISITION (n° of patients)	19
First hospitalization (n° of patients)	14
Mean, median (range) days of previous hospitalization	28, 17 (7–60)
n°of patients hospitalized together with other CRKP-positive patients	17/19
n°of patients hospitalized together with 4 or more CRKP carriers	11/19
n°of patients hospitalized together with 9 or more CRKP carriers	6/19
n°of patients hospitalized when clinical emergencies occurred in other CRKP-positive patients [a]	14/19
CRKP bacteremia occurrence	14/19
death for any cause in at least 1 CRKP-positive patients	10/19

The high colonization pressure favors CR-KP diffusion.

The workload due to the concomitant hospitalization of a high number of CRKP carriers may increase the risk of isolation precaution transgressions.

clinical emergencies in CR-KP pos pst seems to have further facilitated and accelerated the spread
in the majority of pts we documented the CR-KP acquisition after the occurrence of CR-KP BSI or deaths in the Unit where they were hospitalized
(within the following 3 days in 42% of cases)


ALLO-SCT
T. Rettale per SORVEGLIANZA (in tutti i pazienti ricoverati):
Positivi per CR-K.pneumoniae
24/07, referto EMOCOLTURE del 22/07 CR-K.pneumoniae
ALLO-SCT
ALLO-SCT
Paziente zero

Carbapenem-resistant *Klebsiella pneumoniae* in high-risk haematological patients: factors favouring spread, risk factors and outcome of carbapenem-resistant *Klebsiella pneumoniae* bacteremias

17 month-study: **14 CR-K.pneumoniae BSI**

12,5% of all Gram-neg BSI

30% (9/30) of Gram-neg BSI in AML pts

5% (5/96) of Gram-neg BSI in other HM (p=0.0007)

Variables	Category	OR	95%CI	P
Underlying disease	AML	18.66	(1.56 to 222.93)	0.02
	Other hematologic Malignancies	1		
Gender	Female	Factors considered but excluded by the model.		
	Male			
Intensive Chemotherapy	Yes			
	No			
>/=7 days colonized by CRKP with <100 neuthrophils/mmc	Yes			
	No			

Forward stepwise logistic regression model of risk factors for BSI in CR-KP colonized patients

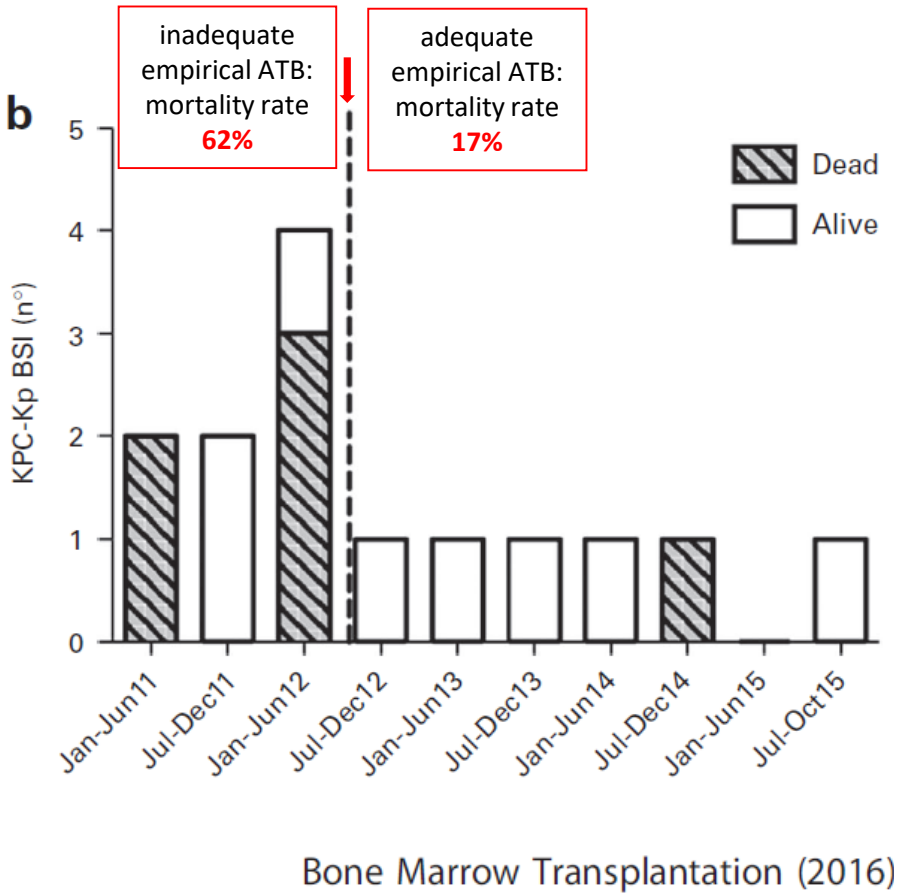
Table 3 Risk factors for bacteremia in the 19 patients colonized with carbapenem-resistant *K. pneumoniae* (CRKP) at univariate analysis

	Bacteremia	No bacteremia	*p*
N° of CRKP colonized patients	11	8	
Male	5 (45%)	8 (100%)	
Female	6 (54%)	0	0.01
Underlying disease			
Acute leukemia	10 (91%)	3 (37.5%)	0.0075
Acute myeloid leukemia	9 (82%)	0	0.0007
Other haematological malignancy	1 (9%)	5 (62.5%)	ns
Chemotherapy	7 (64%)	5 (62.5%)	ns
- Intensive induction chemotherapy	6 (54%)	0	0.01
n° of patients with <1000 neutrophils/mm3 at CRKP acquisition	5 (45%)	4 (50%)	ns
n° of patients with <100 neutrophils/mm3 at CRKP acquisition	4 (36%)	3 (37%)	ns
Days spent colonized by CRKP with:			
< 1000 neutrophils/mm3, mean, median (range)	14.8, 10 (0–78)	10.7, 5.5 (0–30)	<0.01
< 100 neutrophils/mm3, mean, median (range)	9.1, 8 (0–30)	5.6, 3 (0–15)	<0.01

Micozzi *et al. BMC Infectious Diseases* (2017) 17:203

Control of infectious mortality due to carbapenemase-producing *Klebsiella pneumoniae* in hematopoietic stem cell transplantation

A Forcina[1,2], R Baldan[3], V Marasco[2], P Cichero[4], A Bondanza[5], M Noviello[6], S Piemontese[1], C Soliman[1], R Greco[1], F Lorentino[1,2], F Giglio[1], C Messina[1], M Carrabba[1], M Bernardi[1], J Peccatori[1], M Moro[7], A Biancardi[7], P Nizzero[7], P Scarpellini[8], DM Cirillo[3], N Mancini[4], C Corti[1], M Clementi[2,4] and F Ciceri[1,2]



Bone Marrow Transplantation (2016)

Carbapenem-resistant *Klebsiella pneumoniae* in high-risk haematological patients: factors favouring spread, risk factors and outcome of carbapenem-resistant *Klebsiella pneumoniae* bacteremias

Micozzi *et al.*

Mortality rate: 71%

Table 7 Multivariate models of risk factors for 30-day crude mortality in patients with carbapenem-resistant *K.pneumoniae* bacteremia

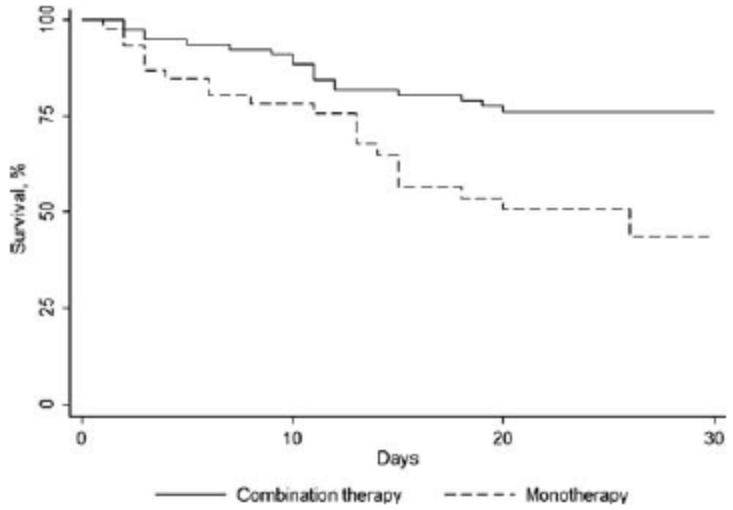
	HR (95% CI)	*p*
Model1		
• Initial adequate therapy	0.08 (0.01 to 0.72)	0.02
• Pt not identified as CRKP carrier at onset	*Not included in the model*	
• Neutrophil recovery (>1000/mmc) within 72 h from the onset of bacteremia	*Not included in the model*	
Model2		
• Initial adequate therapy	0.08 (0.01 to 0.72)	0.02
• Breakthrough bacteremia occurrence within 48 h of ongoing antibiotics	0.17 (0.01 to 2.58)	0.20
• Intensive Chemotherapy	10.9 (0.73 to 162.8)	0.08
• AML	*Not included in the model*	
Model3		
• Initial adequate therapy	0.05 (0.002 to 0.86)	0.04
• Breakthrough bacteremia occurrence within 48 h of ongoing antibiotics	0.17 (0.01 to 2.58)	0.20
• Intensive Chemotherapy	10.9 (0.73 to 162.8)	0.08
• Pt not identified as CRKP carrier at onset	*Not included in the model*	
• Neutrophil recovery (>1000/mmc) within 72 h from the onset of bacteremia	*Not included in the model*	
• AML	*Not included in the model*	

BMC Infectious Diseases (2017)

- To reduce the delay in adequate treatment of CR-KP infection and the mortality rate, **antibiotic combinations active against CR-KP could be appropriate as empiric treatment of febrile neutropenia in CR-KP colonized HM patients.**
  - In high-risk HM pts (AML, SCT recipients)
  - In the setting of high CRKP pressure
  - only in CRKP colonized pts?

Predictors of Mortality in Bloodstream Infections Caused by *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*: Importance of Combination Therapy

Mario Tumbarello,[1] Pierluigi Viale,[2] Claudio Viscoli,[3] Enrico Maria Trecarichi,[1] Fabio Tumietto,[2] Anna Marchese,[4] Teresa Spanu,[5] Simone Ambretti,[6] Francesca Ginocchio,[3] Francesco Cristini,[2] Angela Raffaella Losito,[1] Sara Tedeschi,[2] Roberto Cauda,[1] and Matteo Bassetti[3,7]



Multicenter retrospective cohort study
3 large Italian hospitals
125 pts with KPC-Kp BSIs

Table 4. Outcomes of the 36 Bloodstream Infections Treated With Combination Therapy Including Meropenem Stratified by Meropenem Minimum Inhibitory Concentration

		No. (%)	
Meropenem MIC (mg/L)	Total	Nonsurvivors	Survivors
1	1	0	1 (100)
2	4	0	4 (100)
4	10	2 (20)	8 (80)
8	4	1 (25)	3 (75)
≥16	17	6 (35.2)	11 (64.7)
Total	36	9 (25)	27 (75)

Abbreviation: MIC, minimum inhibitory concentration.

To improve survival, combined therapy with 2 or more drugs with *in vitro* activity against the isolate, expecially those also including carbapenem, may be more effective than active monotherapy

Clinical Infectious Diseases 2012;55(7):943–50

Colistin resistance superimposed to endemic carbapenem-resistant *Klebsiella pneumoniae*: a rapidly evolving problem in Italy, November 2013 to April 2014

M. Monaco[1,2], T Giani[2,3], M Raffone[1,4], F Arena[3], A Garcia-Fernandez[1], S Pollini[3], Network EuSCAPE-Italy[5], H Grundmann[6], A Pantosti (annalisa.pantosti@iss.it)[1], G M Rossolini[3,7,8]

Consecutive non-replicate clinical isolates (n=191) of carbapenem non-susceptible Enterobacteriaceae were collected from 21 hospital laboratories across Italy from November 2013 to April 2014 as part of the European Survey on Carbapenemase-producing Enterobacteriaceae (EuSCAPE) project. *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* (KPC-KP) represented 178 (93%) isolates with 76 (43%) respectively resistant to colistin, a key drug for treating carbapenamase-producing Enterobacteriaceae. KPC-KP colistin-resistant isolates were detected in all participating laboratories. This underscores a concerning evolution of colistin resistance in a setting of high KPC-KP endemicity.

- Ceftazidime-avibactam?

prophylaxis with fluoroquinolones

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 8, 2005 VOL. 353 NO. 10

Levofloxacin to Prevent Bacterial Infection in Patients with Cancer and Neutropenia

G.Bucaneve, A.Micozzi, F.Menichetti et al

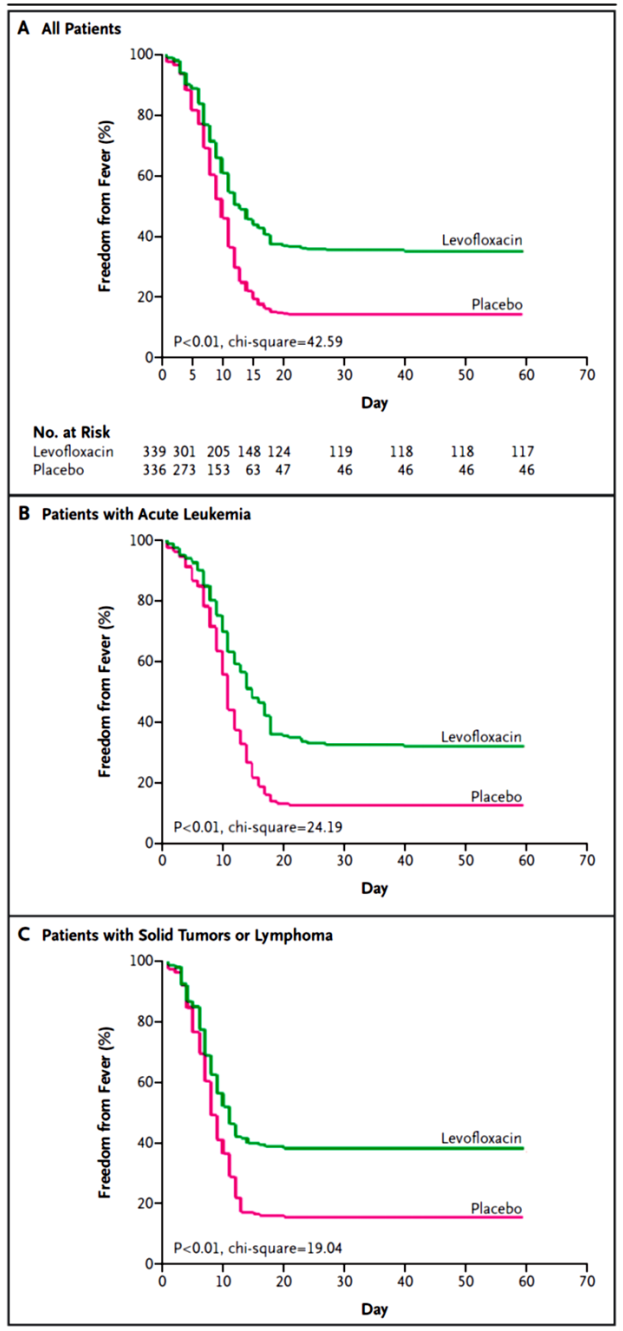
levofloxacin prophylaxis in high-risk neutropenic pts is effective, well tolerated, and cost-effective.

Reduction of febrile episodes, MDI and BSI

No effect on the risk of death

the prevalence of gram-neg FQ–R BSI did not differ significantly between the two groups

FQ resistance did not seem to affect clinical outcomes (infection-related morbidity or mortality)



Group and Event	Levofloxacin no./total no. (%)	Placebo no./total no. (%)	Absolute Difference in Risk (95% CI)
All treated patients			
Febrile episode	243/375 (65)	308/363 (85)	−0.20 (−0.26 to −0.14)
Death	10/373 (3)	18/363 (5)	−0.02 (−0.05 to 0.005)
All assessable patients			
Febrile episode	221/339 (65)	290/336 (86)	−0.21 (−0.27 to −0.14)
Microbiologically documented infection	74/339 (22)	131/336 (39)	−0.17 (−0.24 to −0.10)
Gram-positive	42/339 (12)	61/336 (18)	−0.06 (−0.11 to −0.003)
Gram-negative	21/339 (6)	47/336 (14)	−0.08 (−0.12 to −0.03)
Polymicrobial	11/339 (3)	23/336 (7)	−0.04 (−0.06 to −0.003)
Bacteremia	62/339 (18)	115/336 (34)	−0.16 (−0.22 to −0.09)
Gram-positive	37/339 (11)	54/336 (16)	−0.05 (−0.10 to 0.00)
Gram-negative	15/339 (4)	38/336 (11)	−0.07 (−0.10 to −0.02)
Polymicrobial	10/339 (3)	23/336 (7)	−0.04 (−0.07 to −0.01)
Clinically documented infection	30/339 (9)	33/336 (10)	−0.01 (−0.05 to 0.03)
Fever of unknown origin	117/339 (34)	126/336 (37)	−0.03 (−0.10 to 0.04)
Assessable patients with neutropenia ≥7 days			
Febrile episode	200/300 (67)	252/280 (90)	−0.23 (−0.29 to −0.16)
Acute leukemia			
Treated patients			
Febrile episode	123/183 (67)	154/179 (86)	−0.19 (−0.27 to −0.10)
Death	9/182 (5)	13/179 (7)	−0.02 (−0.07 to 0.02)
Assessable patients			
Febrile episode	113/165 (68)	145/165 (88)	−0.20 (−0.28 to −0.10)
Microbiologically documented infection	39/165 (24)	74/165 (45)	−0.21 (−0.31 to −0.11)
Bacteremia	34/165 (21)	64/165 (39)	−0.18 (−0.27 to −0.08)
Assessable patients with neutropenia for ≥7 days			
Febrile episode	110/159 (69)	138/151 (91)	−0.22 (−0.30 to −0.13)
Solid tumors or lymphoma			
Treated patients			
Febrile episode	120/192 (62)	154/184 (84)	−0.22 (−0.29 to −0.12)
Death	1/191 (1)	5/184 (3)	−0.02 (−0.05 to 0.004)
Assessable patients			
Febrile episode	108/174 (62)	145/171 (85)	−0.23 (−0.31 to −0.13)
Microbiologically documented infection	35/174 (20)	57/171 (33)	−0.13 (−0.22 to −0.03)
Bacteremia	28/174 (16)	51/171 (30)	−0.14 (−0.22 to −0.04)
Assessable patients with neutropenia for ≥7 days			
Febrile episode	90/141 (64)	114/129 (88)	−0.24 (−0.34 to −0.15)

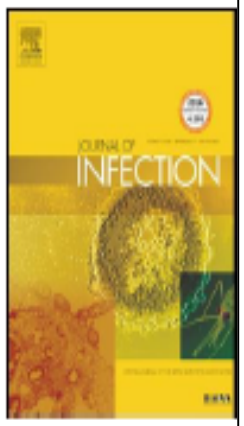
the benefit of prophylaxis with fluoroquinolones has been questioned

- growing concerns about a worldwide increase in resistance to FQs
- FQs efficacy in settings with high FQs-resistance rates
- FQs were linked to the proliferation of MRSA, *C. difficile*, VRE, ESBLs and MDR
- data on FQs resistance have led some centers to discontinue prophylaxis
  - most of the cohorts reported no increase in the mortality, despite an increase in BSIs in some studies

Accepted Manuscript

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

Author: Malgorzata Mikulska, Diana Averbuch, Frederic Tissot, Catherine Cordonnier, Murat Akova, Thierry Calandra, Marcello Ceppi, Paolo Bruzzi, Claudio Viscoli, European Conference on Infections in Leukemia (ECIL)



Highlights

- The role of fluoroquinolone prophylaxis (FQ-P) during neutropenia in the times of increasing antibiotic resistance has to be established.
- In observational and randomized studies published after 2005, FQ-P had no effect on mortality, but it reduced the rate of bloodstream infections and episodes of fever.
- No effect of background rate of resistance of *E. coli* to FQs was shown for the setting with FQ resistance rate below 27%
- Use of FQ prophylaxis should depend on local epidemiology and policy on antimicrobial use

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, 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.

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

Clinical Infectious Diseases® 2017;XX(00):1–10

D. Averbuch et al

Conclusions:

- ✓ **Our data question the recommendation for FQs prophylaxis**
  However no correlation between the rates of bacteremia and FQ resistance
- ✓ **The benefits and potential risks of FQs prophylaxis must be carefully assessed**
  especially in centers with high FQ resistance rates among GNRs
- ✓ **concern about increased rates of resistance to other antibiotics following exposure to FQ**

FQ prophylaxis and mortality

- **patients with induction chemotherapy for acute leukemia**
  - ✓**lower incidence of BSI and fewer gram-negative BSI** (3.7% vs. 9.2 %)
  - ✓**marked reduction of all-cause mortality during neutropenia** (2.3% vs. 7.3%)

- less clear positive effects in HSCT patients
  - ✓**auto HSCT**: **lower incidence of BSI and fewer gram-negative BSI** (4.0% vs. 9.0%)
  - ✓no impact was detected in allo HSCT (5.3% vs. 5.6%,)

Levofloxacin Prophylaxis During Induction Therapy for Pediatric Acute Lymphoblastic Leukemia

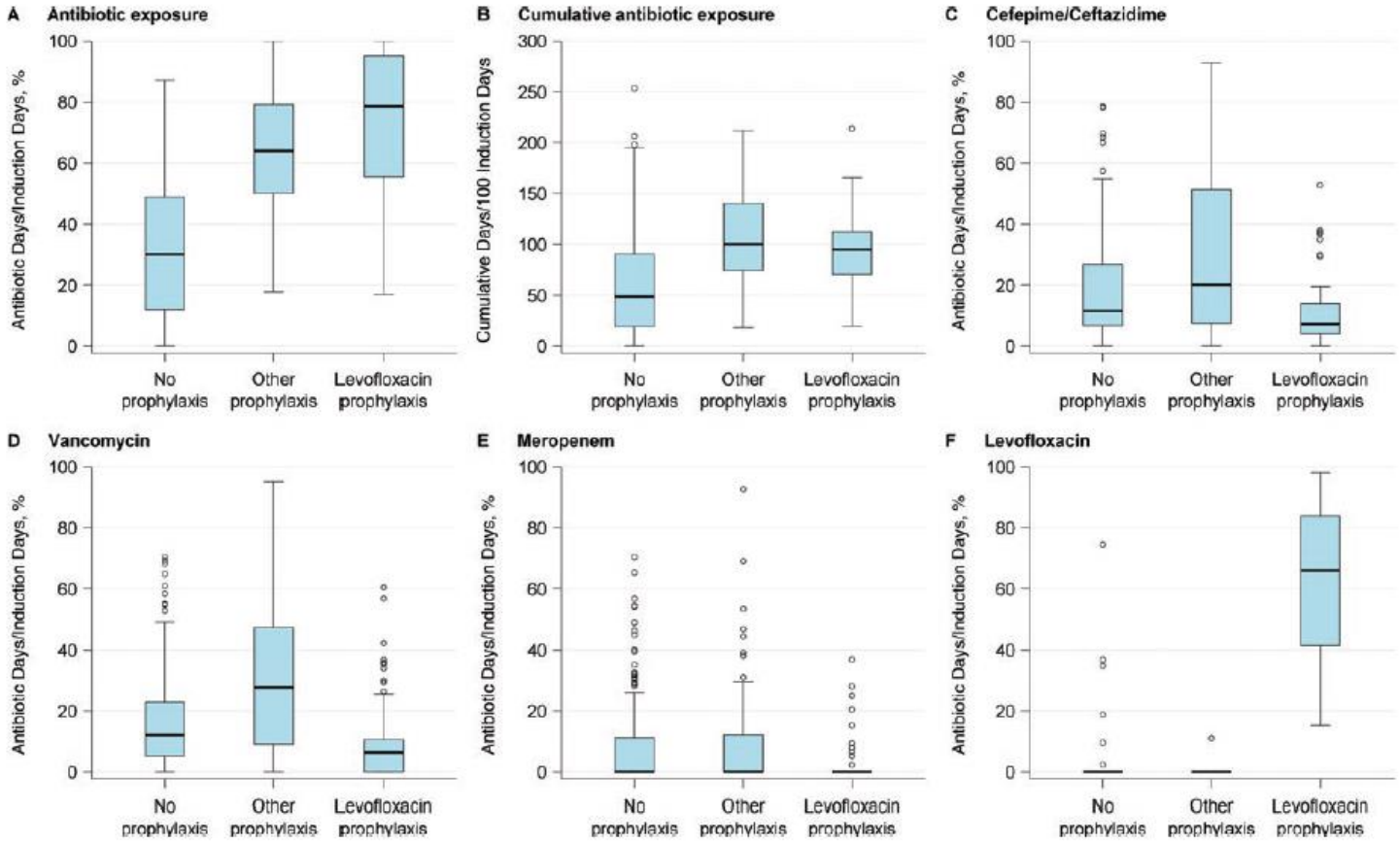
Clinical Infectious Diseases® 2017;XX(00):1–9

Joshua Wolf,[1]

344 pts: 173 no proph, 69 levo proph. 102 other proph

Prophylaxis prevented febrile neutropenia and systemic infection

Levofloxacin prophylaxis minimized the use of treatment antibiotics and drastically reduced *C. difficile* infection



conclusions

- the problem of antibiotic resistance is worrying
- It is associated with inappropriate empiric therapy and increased mortality, and high risk of infection recurrence in febrile neutropenic cancer patients
- The approach to empiric therapy should be reassessed and grounded in continuous monitoring of the local bacteremia rates and susceptibility data of infecting pathogens.
- Knowledge of pathogen-specific resistances enables early appropriate empiric therapy
- Treatment options remain limited
- Revival of old antimicrobials (colistin, fosfomycin) and developmentvof new ones (ceftolozane, plazomicin, and class A carbapenemase inhibitors such as avibactam)