Sistema Socio Sanitario

Ospedale San Gerardo

Regione Lombardia

ASST Monza

UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

QUALE TERAPIA ANTI-INFETTIVA NEL PAZIENTE EMATOLOGICO ?

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Como, 12/09/2019

Temi trattati - Outline

- **Quali infezioni nel paziente onco-ematologico ?**
- **Epidemiologia delle sepsi in Ematologia**
- **Quali farmaci in terapia empirica: Merrem, Linezolid e Caspofungina a tutti ?**
- **Quale il ruolo delle colonizzazioni rettali da MDR ?**
- **Ruolo dei biomarkers infiammatori: quale uso della PCT?**

I pazienti ematologici non sono una categoria uniforme…

- **Neutropenici con supposta ANC< 500 > 7gg (AML, ALL):** alto rischio di multipli episodi di sepsi
- **Neutropenici di breve durata < 7 gg (Linfoma):** basso rischio di sepsi
- **Portatori di CVC tunnellizzati (AML, ALL):** alto rischio di sepsi (spr CoNS) o soggetti con GvHD
- **Deficit immunità cellulare T:** ad alto rischio per infezioni fungine (siero anti-linfociti T)
- **Asplenici o iposplenici**: alto rischio di sepsi da capsulati

Infezioni batteriche: foci sepsigeni

Table 1. The main risk factors associated with BSI due to single bacterial species

Risk factor	Bacterial species
Oral mucositis	Viridans streptococci Coagulase-negative staphylococci
Enteric mucositis	Enterobacteriaceae Enterococci *Pseudomonas aeruginosa*
Extensive and prolonged use of central venous catheters	Staphylococci
Lower performance status/comorbidities	Enterococci
Graft-versus-Host Disease	Gram/negative bacteria, including MDR *P. aeruginosa*
Graft-versus-Host Disease Hypogammaglobulinemia	Pneumococci
Fluoroquinolone prophylaxis	Staphylococci Enterococci Viridans streptococci
Use of cephalosporins	Enterococci, viridans streptococci (ceftazidime)
Treatment with beta-lactams	Beta-lactam resistant viridans streptococci
Nasal colonisation due to MRSA	MRSA
Colonisation with VRE	VRE

MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.

In generale quali infezioni?

- **Trapianto autologo → Sepsi (5-10%)**
- **Trapianto Allogenico → Sepsi (20-30%)**
- **Polmoniti (15-25%)**
- **Infezioni gastro intestinali (30-35%)**
- Molto meno frequenti invece le infezioni delle vie **urinarie (IVU)**

Balletto E, 2015

Epidemiologia delle sepsi (BSI)

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*

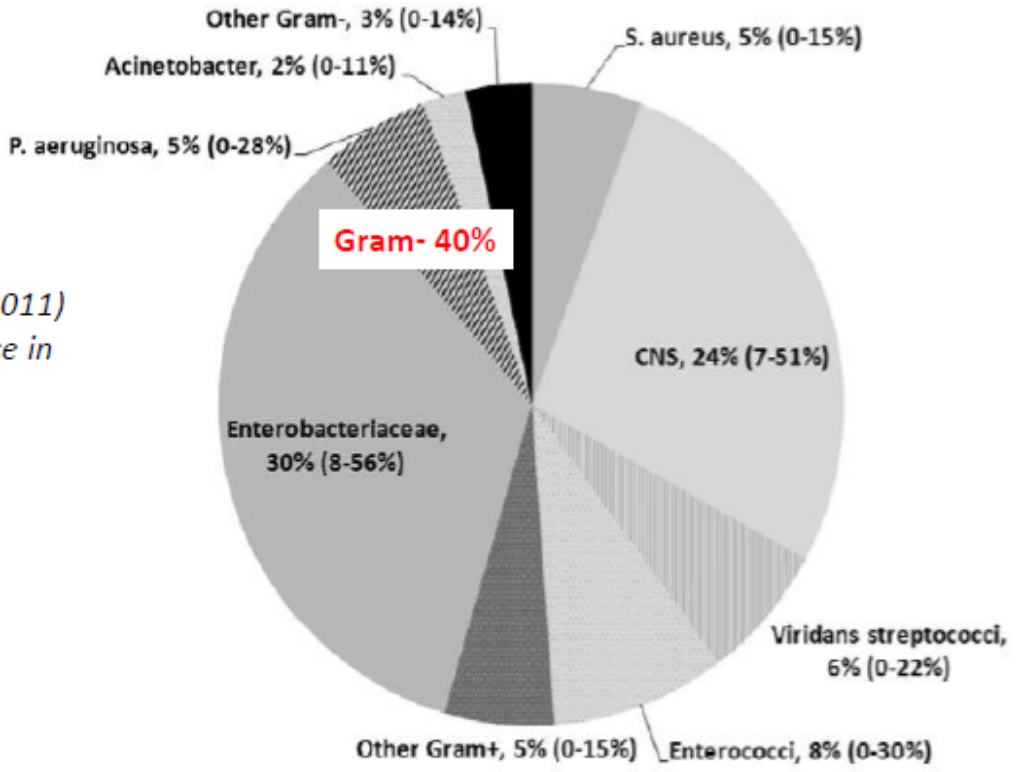


Figure 1 Aetiology of bacteraemias (median prevalence with range) reported in the ECIL-4 questionnaire survey. Notes: CNS, coagulase negative staphylococci.

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

increasing proportion of GNB

bjh review

The challenge of antibiotic resistance in haematology patients

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.

35-71%

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

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 (0.2–3.8)	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

Emato Adulti: Emocolture 2015-2018

TOTALE = 515
Gram POS= 42 %
Gram NEG= 58%

Microrganismo	2015 - Anno Totale		2016 - Anno Totale		2017 - Anno Totale		2018 - Anno Totale	
Escherichia coli	18	15.79%	28	21.71%	34	25.56%	33	23.74%
Staphylococcus epidermidis	21	18.42%	29	22.48%	29	21.80%	33	23.74%
Klebsiella pneumoniae	8	7.02%	10	7.75%	10	7.52%	8	5.76%
Pseudomonas aeruginosa	9	7.89%	7	5.43%	12	9.02%	2	1.44%
Staphylococcus haemolyticus	5	4.39%	9	6.98%	8	6.02%	8	5.76%
Staphylococcus hominis	4	3.51%	6	4.65%	6	4.51%	9	6.47%
Enterococcus faecium	3	2.63%	3	2.33%	10	7.52%	2	1.44%
Staphylococcus aureus	4	3.51%	3	2.33%	4	3.01%	6	4.32%
Enterobacter cloacae	3	2.63%	3	2.33%	4	3.01%	5	3.60%
Enterococcus faecalis	6	5.26%	3	2.33%	1	0.75%	5	3.60%
Streptococcus mitis/oralis	6	5.26%	2	1.55%				
Klebsiella oxytoca	1	0.88%	3	2.33%				
Capnocytophaga sputigena	1	0.88%	1	0.78%				
Candida parapsilosis			1	0.78%				
TOTALE GLOBALE	**114**		**129**		**133**		**139**	

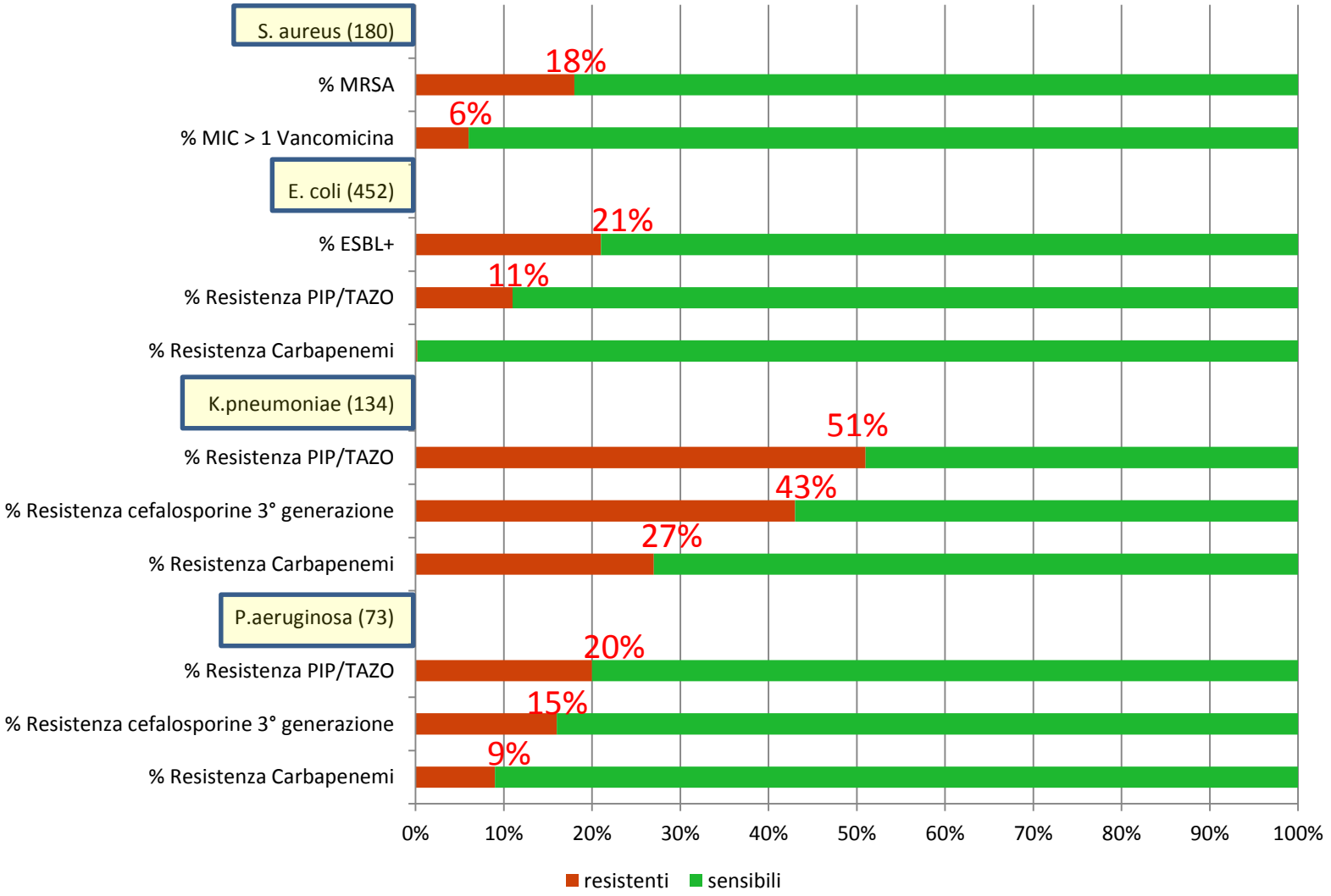
CoNS tot: 166 (32%)

Epidermidis= 21,8% (112)
Haemoliticus= 5,8% (30)
Hominis= 4,6% (24)

MDR Emato Adulti: Emocolture 2015-2018

Totale= 344 (SENSIBILITA')	K.P 36	P.A 29	E.Coli 113	Ent 48	CoNs 166	S.A. 17
	7%↓↓	6%↓↓	22%↑↑	9%↓↓	32%↑↑	3,3%↓↓
COLISTINA	89	100	97			
GENTAMICINA	65/22	100	83			
CEFTAZIDIME	25 ↓↓	89	72/8			
PIP/TZ	25 ↓↓	82	82/2			
CIPROFLOXACINA	24/4	96	72/1			
MEROPENEM	61	93	100			
AMIKACINA	35/10	93	87/13			
TIGECICLINA	84/13	-	100		100	
FOSFOMICINA	45	-	97			
KPC /MBL	41 / -	- / 7	-			
ESBL+	39		29			
OXACILLINA					16	82
VANCOMICINA					99	
DAPTOMICINA					99	
LINEZOLID					91	

Emocolture HSG: R/S % degli isolati più frequenti



Carbapenems use in cancer patients

- Large diffusion of carbapenems in clinical practice:
  - ✓initial empiric monotherapy in febrile neutropenia (IDSA, ECIL guidelines, risk of ESBLs)
  - ✓salvage treatment in case of failure
    - empiric (high rate of ESBL)
    - Targeted treatment MDR (ESBLs infections) (IDSA, ECIL guidelines)
- Carbapenems are the treatment of choice for serious infections caused by ESBL producers
- *The emergence of carbapenem-resistant Enterobacteriaceae, carbapenem sparing strategies*
- There are strategies for
  - reasonable carbapenem-sparing option to treat infections caused by ESBL producers
  - decrease delay on appropriate therapy and mortality
- but also unnecessary empiric use of carbapenems ?

Approccio terapeutico: ECIL-4 (2013)

bilancio tra rischio infezione da MDR e rischio di andamento clinico severo

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

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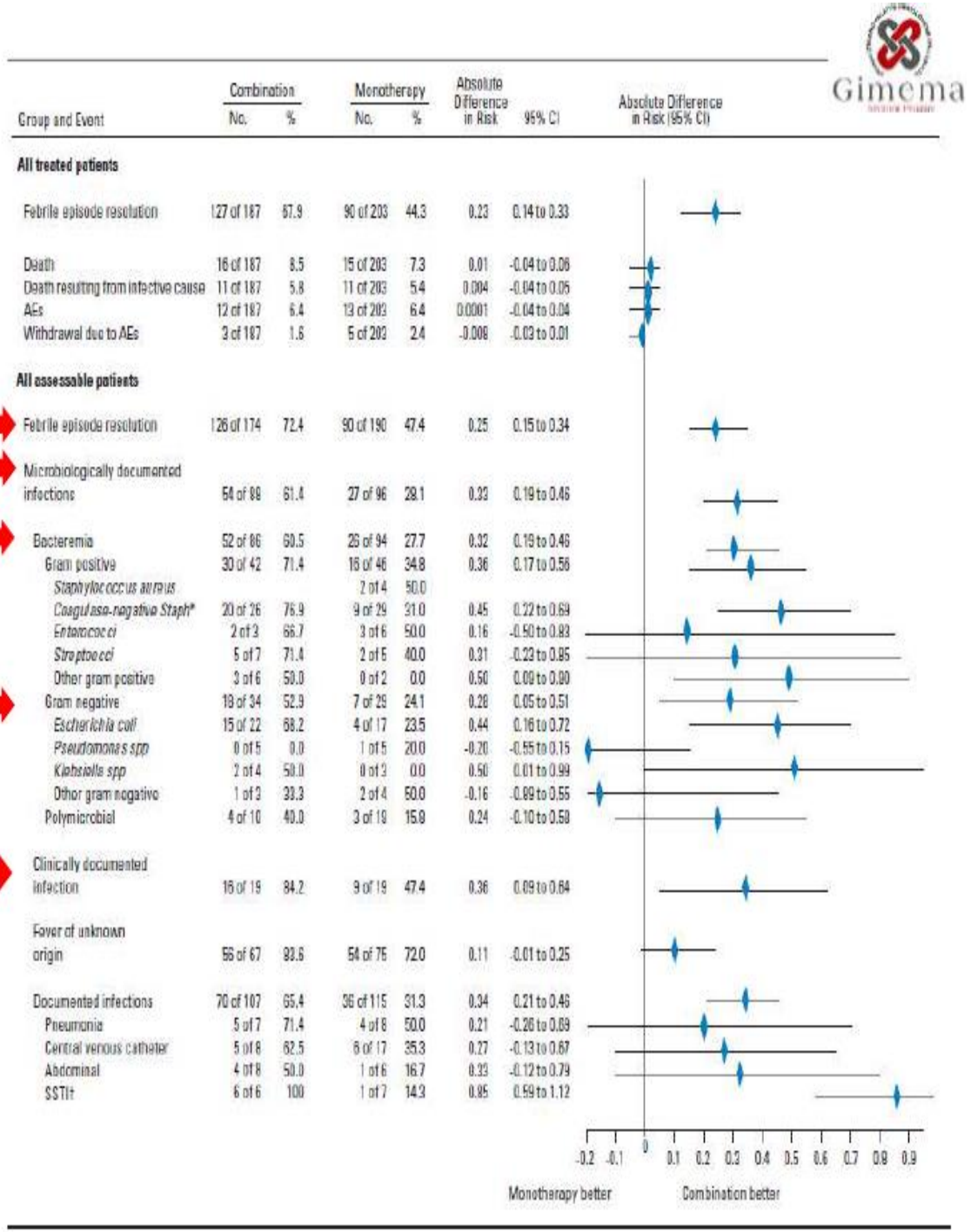
Results of a Multicenter, Controlled, Randomized Clinical Trial Evaluating the Combination of Piperacillin/Tazobactam and Tigecycline in High-Risk Hematologic Patients With Cancer With Febrile Neutropenia

Giampaolo Bucaneve, Alessandra Micozzi, Marco Picardi, Stelvio Ballanti, Nicola Casanvilla, 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

the tigecycline combination,
is able to improve the likelihood that
the empiric treatment may initially address the possible involved multidrug resistant pathogens,
which is the main aim of an empiric antibiotic strategy.

390 pts (acute leukemia: 69%)

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



Bucaneve-Micozzi: May 2014

MORTALITY AT THE END OF FEBRILE EPISODE

	PIPERA/TAZO + TYGECICLINE	PIPERA/TAZO	p
	Febrile Episodes: 187	*Febrile Episodes: 203*	
Death due to infection	**11 (6%)**	**11 (5%)**	**0.5**
Bacteremias	8 (4%)	8 (4%)	0.4
- single gram-negative	5	3	
- single gram-pos	2	2	
- polymicrobial	1	3	
Clinically documented infection	1	1	
FUO	-	1	
Fungal infection	2	1	
Death from noninfectious causes	5	4	
DEATH	**16 (8%)**	**15 (7%)**	**0.4**

Bucaneve, Micozzi et al. JCO 2014

Systematic review

Comparison of antipseudomonal β-lactams for febrile neutropenia empiric therapy: systematic review and network meta-analysis

N. Horita [1,*,3], Y. Shibata [1,3], H. Watanabe [1], H. Namkoong [2], T. Kaneko [1]

50 studi revisionati → 10 872 pazienti neutropenici

La maggior parte delle linee guida raccomandano l'uso di empirico di cefepime, meropenem, imipenem/cilastatin, piperacillina/taz o ceftazidime nell'approccio della neutropenia febbrile

<u>Imipenem/cilastatin</u> nella review mostra il migliore tasso di successo senza modifiche.

<u>Ceftazidime mostra un più basso tasso di successo microbiologico se comparato a imipenem/cilastatin [OR 0.71 (95% CI 0.57e0.89, p 0.006)] che ha il più basso tasso di mortalità</u>
Cefepime mostra una maggiore tasso di mortalità vs imipenem/cilastatin (OR 2.05, 95% CI 1.11e3.78, p 0.029)

Imipenem/cilastatin, piperacillina/tazobactam e meropenem sono da considerarsi ragionevoli farmaci di prima linea per il trattamento empirico della neutropenia febbrile.
Sconsigliato in questo setting cefepime e ceftazidime

N. Horita et al. / Clinical Microbiology and Infection 23 (2017) 723–729

Clinical Infectious Diseases
MAJOR ARTICLE
IDSA Infectious Diseases Society of America

Extended vs Bolus Infusion of Broad-Spectrum β-Lactams for Febrile Neutropenia: An Unblinded, Randomized Trial

Ron Ram,[1,2] Yael Halavy,[2] Odelia Amit,[1,2] Yael Paran,[2,3] Eugene Katchman,[2,3] Bruria Yachini,[1] Svetlana Kor,[1] Irit Avivi,[1,2] and Ronen Ben-Ami[2,3]

Studio monocentrico (Israele) randomizzato per comparare "extended infusion" (4 ore) vs il bolo (30 minuti) di PIP/TZ o CAZ in pz ad alto rischio con FN.

Endpoint combinato in 4 giornata: definito dalla risoluzione della febbre, emocolture sterili, risoluzione dei segni clinici e dei sintomi senza la necessità di un cambio terapeutico. Giudizio clinico affidato a sperimentatori in cieco sul trattamento.

Risultati: 105 con FN sono stati inclusi ITT: 47 braccio "extended infusion (Ex)" e 58 nel gruppo standard (S) . Risposta complessiva in 35 **(74.4%)** Ex ; in 32 **(55.1%)** nel gruppo S (*P* = .044).

La "extended infusion" è risultata superiore nei pazienti con infezione clinicamente documentata.
In quelli con polmonite (80% [4/5] vs 0% [0/8]; *P* = .007).

Clinical Infectious Diseases
MAJOR ARTICLE
IDSA
Infectious Diseases Society of America

Increasing Evidence of the Nephrotoxicity of Piperacillin/Tazobactam and Vancomycin Combination Therapy—What Is the Clinician to Do?

Table 1. Studies on Nephrotoxicity from Vancomycin-Piperacillin/Tazobactam[a]

Authors, Year and Reference	Type of Study	Quality	Main Outcome	Comments
Hammond et al., 2017 [21]	Meta-analysis of 14 observational studies (n = 3549)	Good	VPT was more associated with AKI compared to vancomycin without PT (aOR, 3.11; 95% CI, 1.77–5.47)	Included studies on adults and children
Giuliano et al., 2016 [23]	Meta-analysis of 15 observational studies (n = 3258)	Good	Risk for AKI with VPT was higher compared to vancomycin ± β-lactam (OR, 3.649; 95% CI, 2.157–6.174)	Many of the same studies were included in the above meta-analysis
Navalkele et al., 2017 [24]	Retrospective matched cohort (n = 558)	Good	AKI rate was higher with VPT (81/279, 29%) vs. VC (31/279, 11%)	Showed more rapid onset of AKI with VPT (3 days) vs. VC (5 days)
Rutter et al., 2017 [25]	Retrospective matched cohort (n = 4103)	Good	VPT was 2.18 times more likely to cause AKI vs. VC (95% CI, 1.64–2.94)	Vancomycin doses between 3 and 4 g daily also increased the risk for AKI

Table 2. Suggested Approaches to Decrease Risk of Nephrotoxicity with Vancomycin-Piperacillin/Tazobactam

- Avoid coadministration of other nephrotoxic agents
- Avoid dehydration
- Avoid vancomycin loading dose when not indicated
- If available, adjust doses based on estimates of vancomycin exposure using Bayesian inputs
- Avoid unnecessarily prolonged administration of VPT
- Close monitoring of renal function
- Early and repeated reassessments of empiric antibiotic therapy with appropriate alterations
- Consider use of daptomycin (in absence of pneumonia) or linezolid in place of vancomycin
- Use alternatives to piperacillin/tazobactam such as cefepime or an anti-pseudomonal carbapenem

Clinical Infectious Diseases

SPECIAL SECTION/INVITED ARTICLE

HEALTHCARE EPIDEMIOLOGY: Robert Weinstein, Section Editor

Renal Dosing of Antibiotics: Are We Jumping the Gun?

Ryan L. Crass,[1] Keith A. Rodvold,[2] Bruce A. Mueller,[1] Manjunath P. Pai[1]

….. In questa review viene sottolineata l'importanza delle prime 48 ore di terapia spr per gli antibiotici ad eliminazione renale….. Usando un database su 18500 pz con diagnosi di infezione severa (varie) è stata verificata **una alta percentuale di pazienti con IRA (AKI)** in corso di polmonite (27.1%), cIAI (19.5%), UTI (20.0%), o SSTI (9.7%) che **entro le 48 ore si risolvono nel 57.2% dei casi**

……we suggest that deferred renal dose reduction of wide therapeutic index antibiotics could improve outcomes in patients with infectious diseases…..

→ **PIP/TZ, CAZ, Ceftolozane/TZ, CAZ-AVI, Telavancina** sono registrati per una riduzione della dose nei soggetti ClCr 30–50 mL/min

CID: published online September 13, 2018

Duration of therapy in documented infections

Continue targeted antibiotics for clinically- or microbiologically- documented infection

- *Until infection is microbiologically eradicated &*
- *Until all clinical signs of infection are resolved*
- *At least 7 days, of which at least 4 days afebrile*

BIII

Eggimann *et al., J Antimicrob Chemother* 1993
Cometta *et al., Antimicrob Agents Chemother* 1995
Cordonnier *et al., Clin Infect Dis* 1997
Biron *et al., J Antimicrob Chemother* 1998
Elting *et al., J Clin Oncol* 2000
Feld *et al., J Clin Oncol* 2000

Giamarellou *et al., Antimicrob Agents Chemother* 2000
Viscoli *et al., Clin Microbiol Infect.* 2002
Sanz *et al., J Antimicrob Chemother* 2002
Tamura *et al., Am J Hematol* 2002
Cometta *et al., Clin Infect Dis* 2003
Raad *et al., Cancer* 2003

Averbuch D, et al. Haematologica 2013;98:1826-35

Duration of antibiotics in FUO: Evidence & Recommendations

- Discontinue **iv** empirical antibacterials after ≥ 72h

  - *If patient has been afebrile ≥ 48h and is **stable***
  - *Irrespective of neutrophil count or **expected** duration of neutropenia **BII***

Joshi *et al., Am J Med* 1984
Jones *et al., J Pediatr* 1994
Cornelissen *et al., Clin Infect Dis* 1995
Horowitz *et al., Leuk Lymphoma* 1996
Santoloya *et al., Clin Infect Dis* 1997
Lehrnbecher *et al., Infection* 2002
Cherif *et al., Scand J Infect Dis* 2004
Slobbe *et al., Eur J Cancer* 2009

Averbuch D, et al. Haematologica 2013;98:1826-35

Colonizzazione ESBL-E: quale ruolo?

Clinical Infectious Diseases

MAJOR ARTICLE

Colonization With Levofloxacin-resistant Extended-spectrum β-Lactamase-producing Enterobacteriaceae and Risk of Bacteremia in Hematopoietic Stem Cell Transplant Recipients

CID 2018:67 (1 December) • Satlin et al

373 Pz. Tutti avevano effettuato profilassi pre-trapianto con levofloxacina. 41 (13%) hanno sviluppato CRO-R-E di cui 31 (10%) ESBL-E

Dei 31 colonizzati con ESBL-E : 10 (32%) hanno sviluppato una batteriemia ESBL-E durante il ricovero per trapianto, comparato a 1 (0.4%) dei 281 patienti non colonizzati con ESBL-E (*P* < .001).

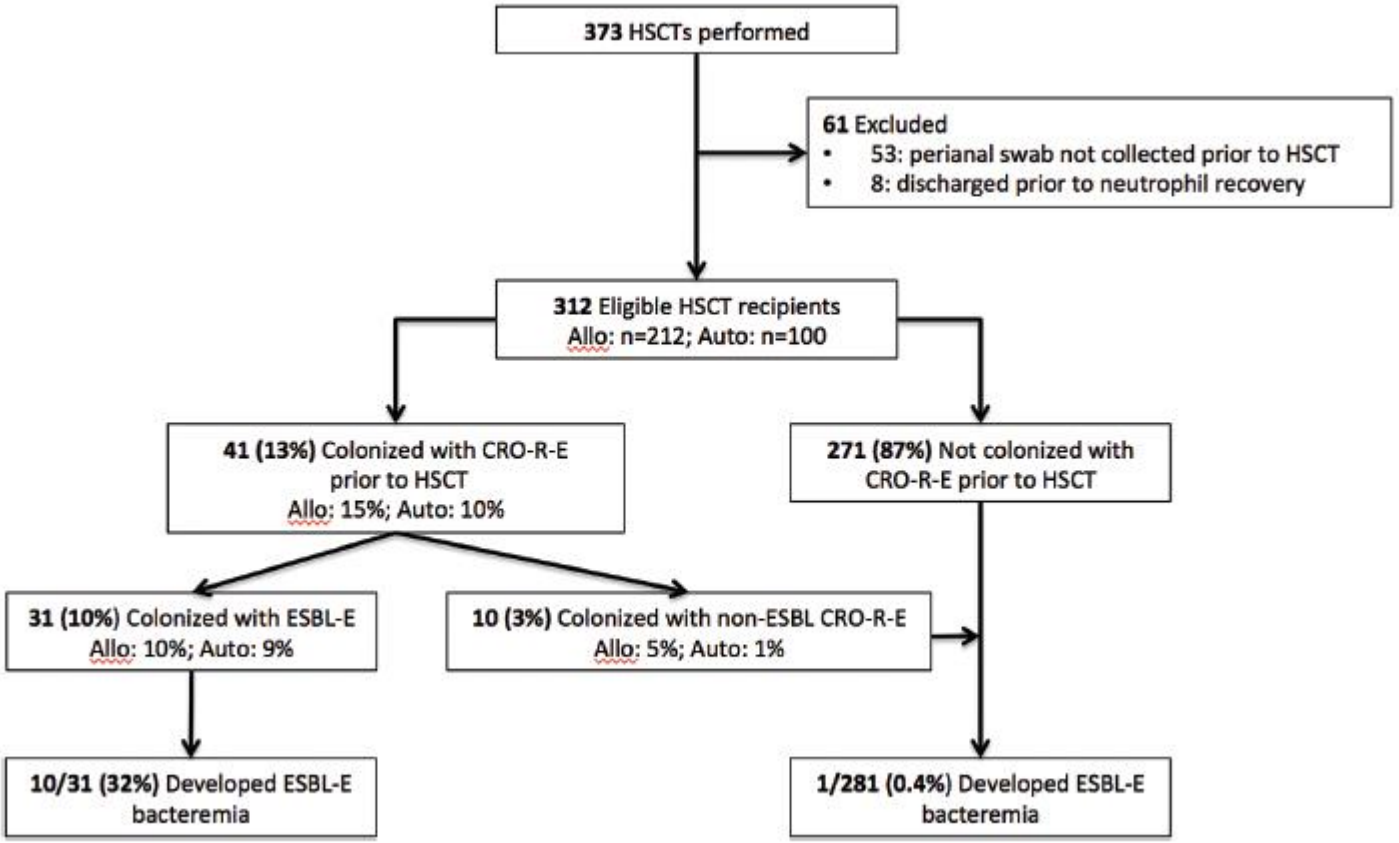
Tutte le BSI ESBL-E erano levofloxacina-resistenti e gli isolati identici genotipicamente a quelli rettali (PFGE) .

HSCT colonizzati con ESBL-E pre-trapianto e che hanno ricevuto profilassi con levofloxacina hanno un alto tasso di batteriemia (32%) durante la fase di neutropenia. L'avere una colonizzazione rettale da ESBL-E deve determinare una ottimizzazione della terapia antibatterica.

Clinical Infectious Diseases

MAJOR ARTICLE

Colonization With Levofloxacin-resistant Extended-spectrum β-Lactamase-producing Enterobacteriaceae and Risk of Bacteremia in Hematopoietic Stem Cell Transplant Recipients



batteriemia (32%)

Risk factors for, and clinical relevance of, faecal extended-spectrum β-lactamase producing *Escherichia coli* (ESBL-EC) carriage in neutropenic patients with haematological malignancies

Eur J Clin Microbiol Infect Dis (2011) 30:355–360

M. Arnan · C. Gudiol · L. Calatayud · J. Liñares · M. Á. Dominguez · M. Batlle · J. M. Ribera · J. Carratalà · F. Gudiol

observational prospective multicentre cohort study was conducted over 2 years at two teaching hospitals. Patients with acute leukaemia or undergoing stem cell transplanta-

217 pts, 63 ESBL-Ec carriers

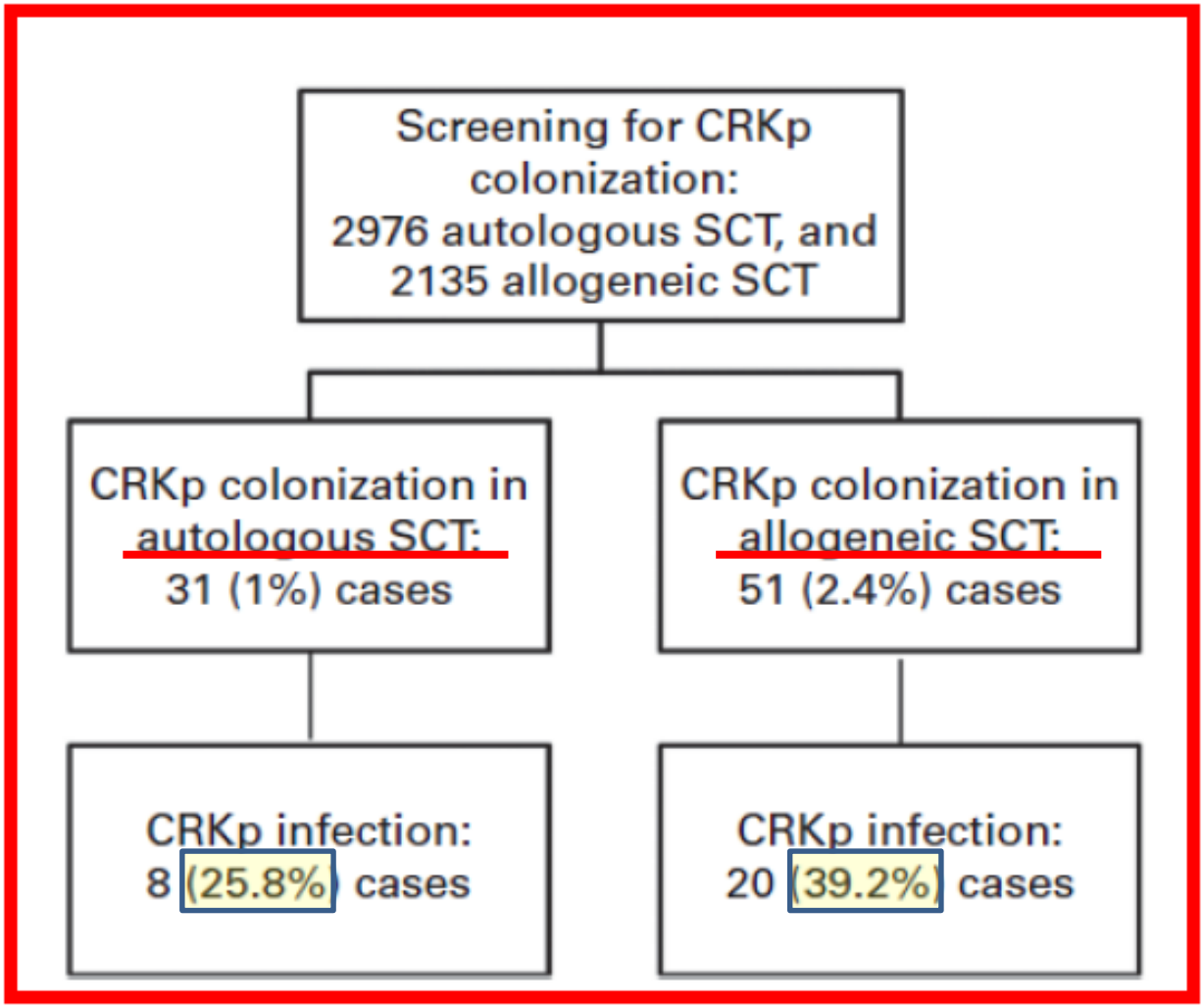
No association between ESBL-Ec carriage and ESBL-Ec BSI, or other clinical outcomes (lenght of hospitalization, mortality)

Thus, routine testing for ESBL-EC faecal carriage does not seem to be beneficial.

KPC ?

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]



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

EUCIC MEDICAL GUIDELINES ON DECOLONISATION OF MULTIDRUG RESISTANT GRAM-NEGATIVE ORGANISMS

- There is **low quality evidence of increased risk** of severe infections in ESBL-Enterobacteriaceae and CRE carriers in high risk settings (haematology, ICU and transplant).

- **Based on the evidence at the time of this guidelines the panel does not recommend routine decolonisation for MDR-GNO of hospitalised patients.**

- The panel suggests to consider decolonisation treatment with colistin with or without gentamicin **to temporary suppress ESBL- Enterobacteriaceae and CRE** colonisation in high risk population under controlled intervention and monitoring of resistance and side effects.

Ruolo di PCT nella diagnosi di CAP ?

Author, year	Relevant cases (n)	Procalcitonin cutoff (ng/mL)	Sensitivity (%)
Hedlund, 2000	27	0·50	77·8%
Masia, 2005	56	0·15	37·5%
Hirakata, 2008	40	0·50	45·0%
Daubin, 2009*	13	0·25	69·2%
Song, 2011*	11	0·35	81·8%
Ahn, 2011*	16	1·50	56·3%
Kasamatsu, 2012	113	0·50	39·8%
Musher, 2013	60	0·25	68·3%
Pfister, 2014*	55	0·25	90·9%
Rodriguez, 2016*†	196	0·25	78·0%
Self, 2017	236	0·25	66·9%

See appendix for full reference details. * All patients with mixed bacterial and influenza infection. †Includes 9 patients with *aspergillus* fungal infection.

***Table*: Sensitivity of procalcitonin concentrations for predicting bacterial infection in patients with community-acquired pneumonia**

The Lancet Infection- Vol 18 May 2018

Exp. Opinion su PCT in CAP/ICU

Manca una consensus ma Sept. 2018 Harvard School of Medicine:

PCT come guida per interrompere precocemente la terapia antibiotica:
nelle CAP se i livelli sono <0.5 ng/mL (o diminuiti ≥80% del picco se valori iniziali >5 ng/mL) → **SI**

PCT come guida per stabilire se partire con terapia antibiotica in CAP:
Molto controversa: la norma comportamentale del gruppo di esperti riuniti è di trattare indipendentemente dai livelli iniziali di PCT → **NO**

Concordanza nel considerare PCT un ausilio che mai deve sostituire il giudizio clinico spr in ambito ICU. Nella maggior parte dei trial si è constatato che **il giudizio medico è considerato prevalente sui livelli decisionali prestabiliti di PCT**

PCT è poco studiata nei soggetti immunodepressi, pz chirurgici e nei soggetti con **IRA/IRC**

Chanu Rhee, MD, MPH; Michael K Mansour, MD, PhD; Harvard School of Medicine; September 2018

PCT in ICU

PCT guida alla terapia in AECOPD/LRTI in ICU.

Daubin C. Int Care Med. Oct 2018;44(4):428

302 patienti randomizzati in due gruppi**: la mortalità a breve termine è risultata superiore nel gruppo in cui la tx era PCT–guidata vs trattamento SOC** da Linee Guida **(20% vs 14%)**.

Nel sottogruppo in cui si aspettava valori> cut off per avviare tx la mortalità era ancora superiore (31% vs 12%).

Viene ribadita l'importanza della terapia precoce in pazienti con interessamento clinico severo indipendentemente dai livelli di PCT

Punti chiave: Take Home messages

- **Infezioni:** Categorizzare bene il paziente, definire FR e foci infettivi. Le sepsi rappresentano il vero problema (spr HR)

- **Epidemiologia:** i GN-MDR sono un problema ↑ ma …..non sottovalutare i CoNS (CVC!) ↑↑. In pediatria: Entero

- **Tx empirica:** Stabile: PIP/TZ (Ex) o PIP/TZ +TIG
  Evitare PIP/TZ + Vanco (nefrotox)
  Instabile: Carb + Vanco/Dapto + ev Echino.
  Dosaggi pieni per le prime 48 H

- **Colonizzati da MDR:** Considerare spr se KPC o Ec ESBL

- **PCT ?:** Ausilio ma troppe variabili. Utile nel descalaggio


RINGRAZIO DELL'ATTENZIONE ….!!!