Strategie peritrapiantologiche di management del paziente candidato a trapianto allogenico di CSE con colonizzazione da germi multiresistenti

Corrado Girmenia

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Colonization in the management of MDR Gram-negative infections

Is colonization predictive of infection?

How to detect colonized subjects?

Is decontamination of colonized subjects a possible strategy?

Management of colonized subjects

> In the interest of the community

> In the interest of the patient

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ECCMID 2013; eP698

Prospective, cross-sectional observational study of hospitalised patients colonised with carbapenemase resistant Klebsiella pneumoniae (CR-KP)

M. Bartoletti et al (Bologna, IT)

To compare the incidence and outcome of CR-KP infections among patient cohorts

- Incidence N/1000 colonization days
  - medicine :4.3
  - Hematology: 26.3
  - ICU: 13.1
  - Surgical: 8.6
  - SOT: 7.4
  - Long Term Care: 4.7
- KPC-attributable mortality
  - Hematology:75%
  - ICU:11%
  - SOT:7%
  - LTC: 5%
  - Medicine: 2%
  - Surgery:2%

Medicine departments:
Lowest risk of infection in CRKp colonized
Lowest risk of death in CRKp infections

- In low risk departments CR-KP may be perceived as a clinically not relevant phenomenon.
- Low risk departments may represent the occult reservoir of CR-KP!!!!

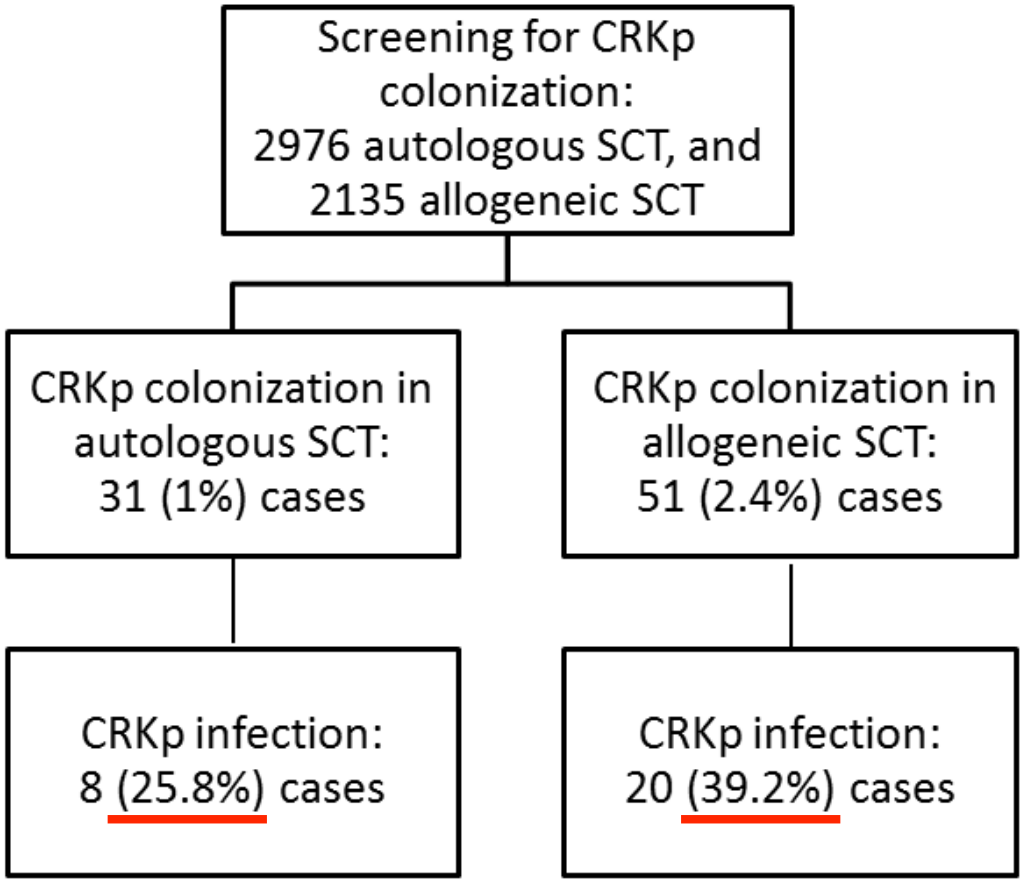
Bone Marrow Transplantation (2014), 1–7

www.nature.com/bmt

ORIGINAL ARTICLE

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]



A CRKp infection without previously documented colonization occurred in 10 autologous and 22 allogeneic SCT recipients

Bone Marrow Transplantation (2014), 1–7

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ORIGINAL ARTICLE

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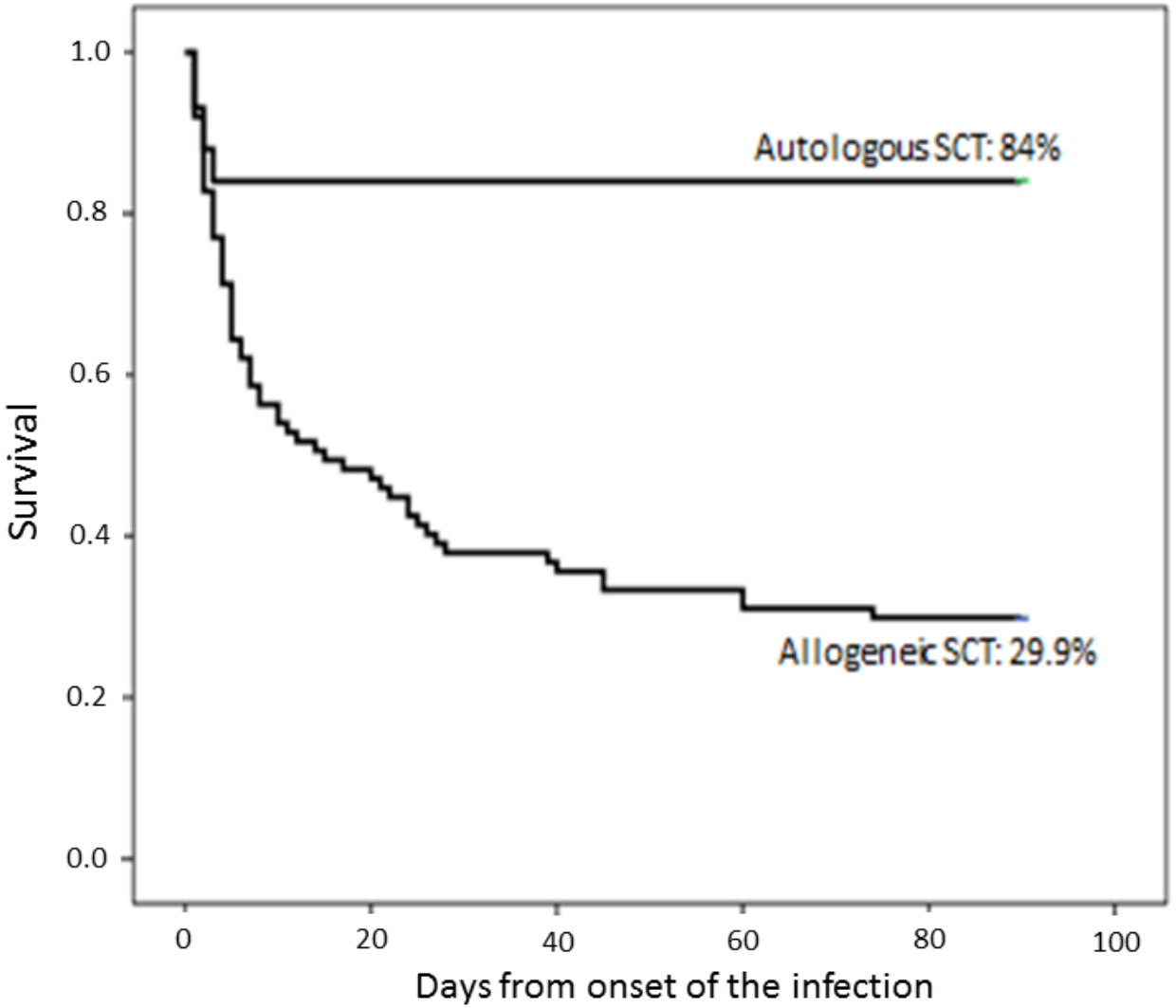
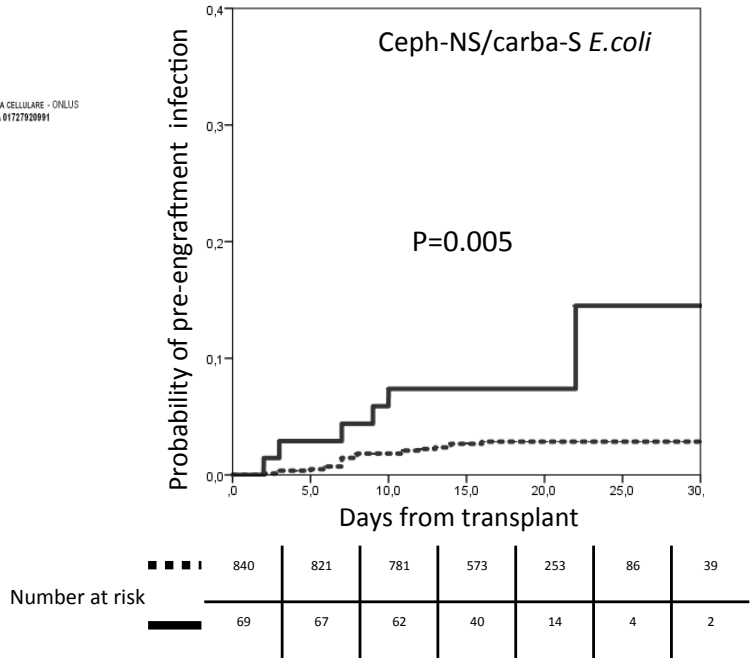


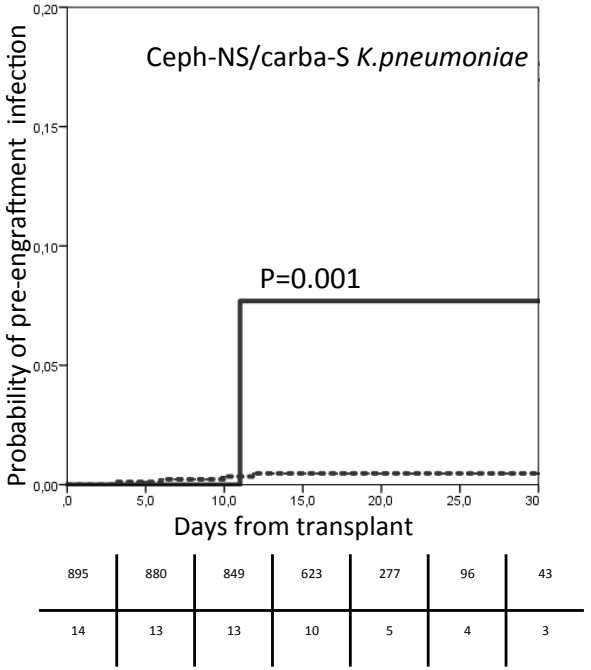
GITMO ONLUS

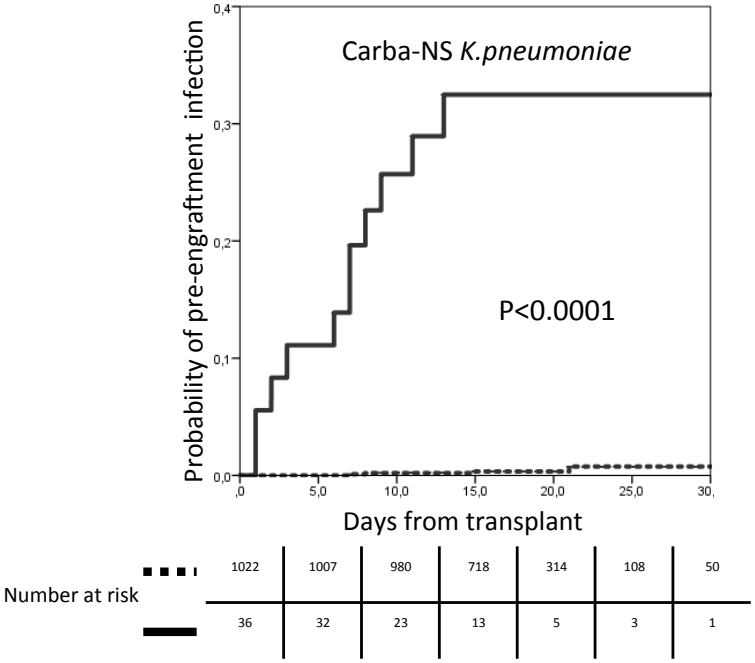
Gruppo Italiano per il Trapianto di Midollo Osseo, cellule staminali emopoietiche e terapia cellulare - ONLUS
Iscr. Registro Reg. Liguria – decr. n. 120 del 18/01/08 – cod. fisc. 95107000101 part. iva 01727920991

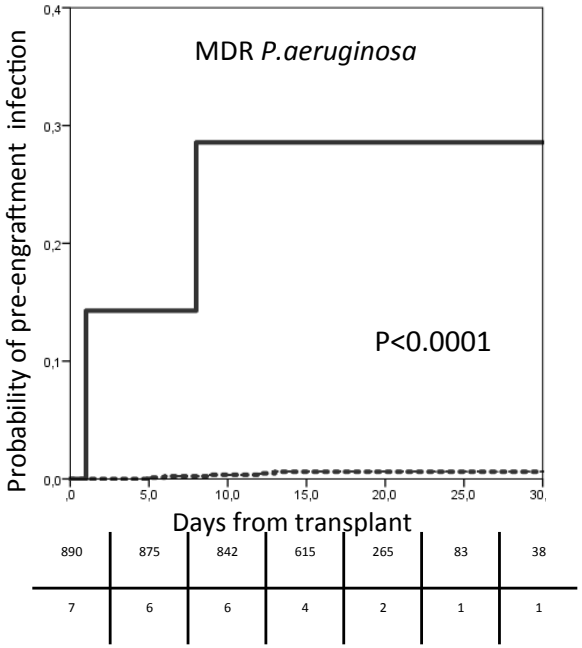
Incidence, risk factors and outcome of pre engraftment Gram negative bacterial infections after allogeneic and autologous hematopoietic stem cell transplantation: an Italian prospective multicenter survey.
(ClinicalTrials.gov,ID NCT02088840)

Colonization by resistant Gram neg, allo-HSCT









No colonization by the same species

The risk was not calculated for other resistant pathogens because the rate of colonization was very low

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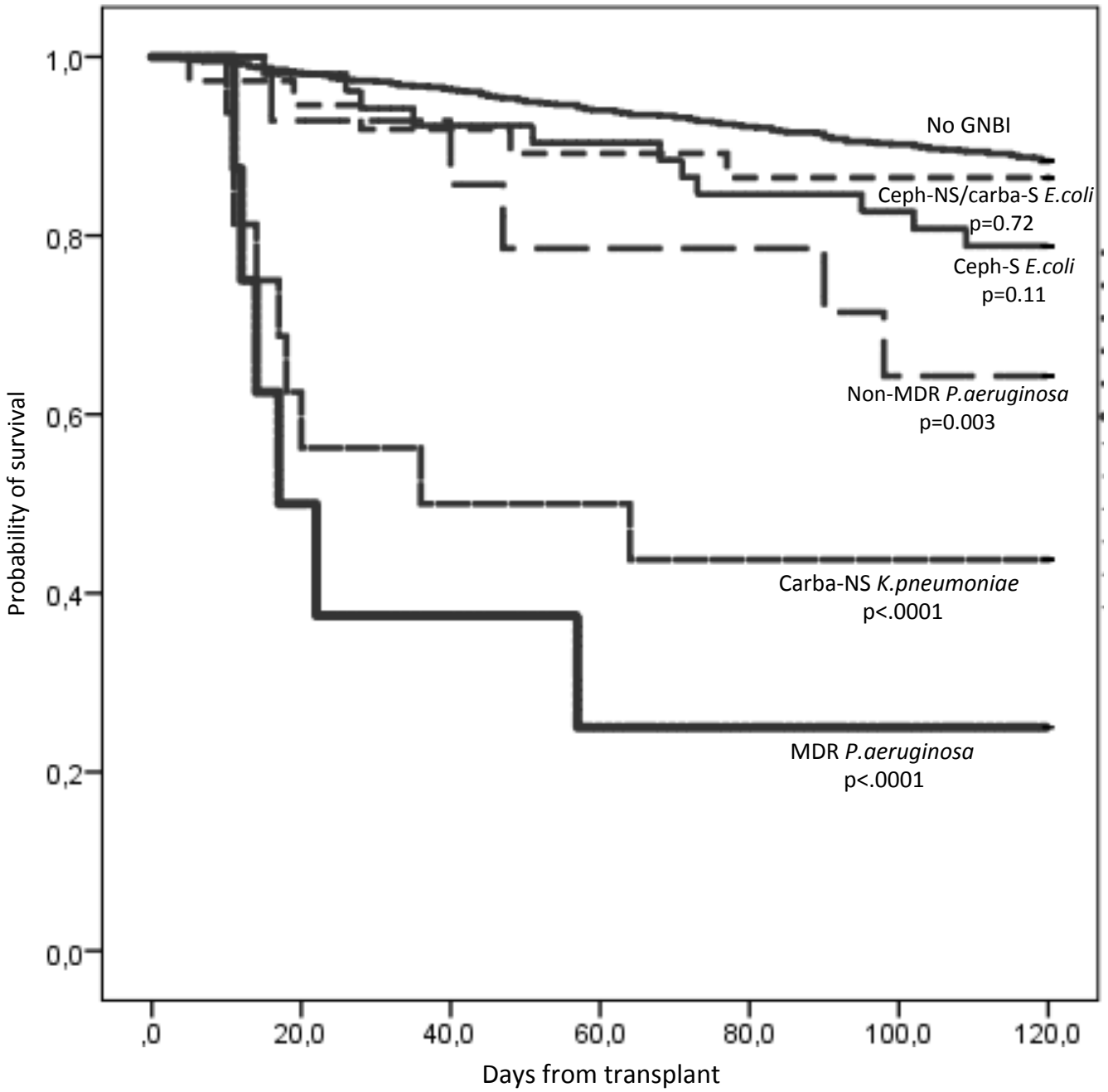
Survival according to Gram neg infection in allo-HSCT



Probability of survival was not calculated for other pathogens because the number of episodes was very low

AMCLI associazione microbiologi clinici italiani

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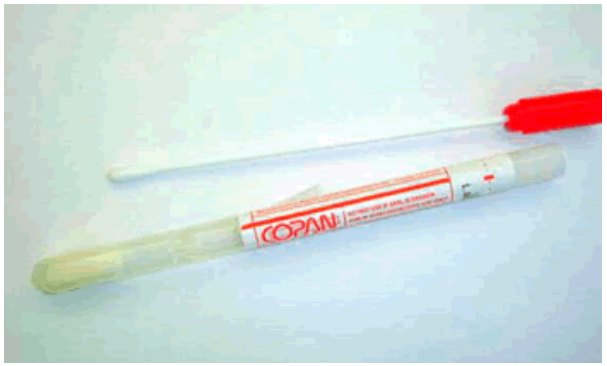
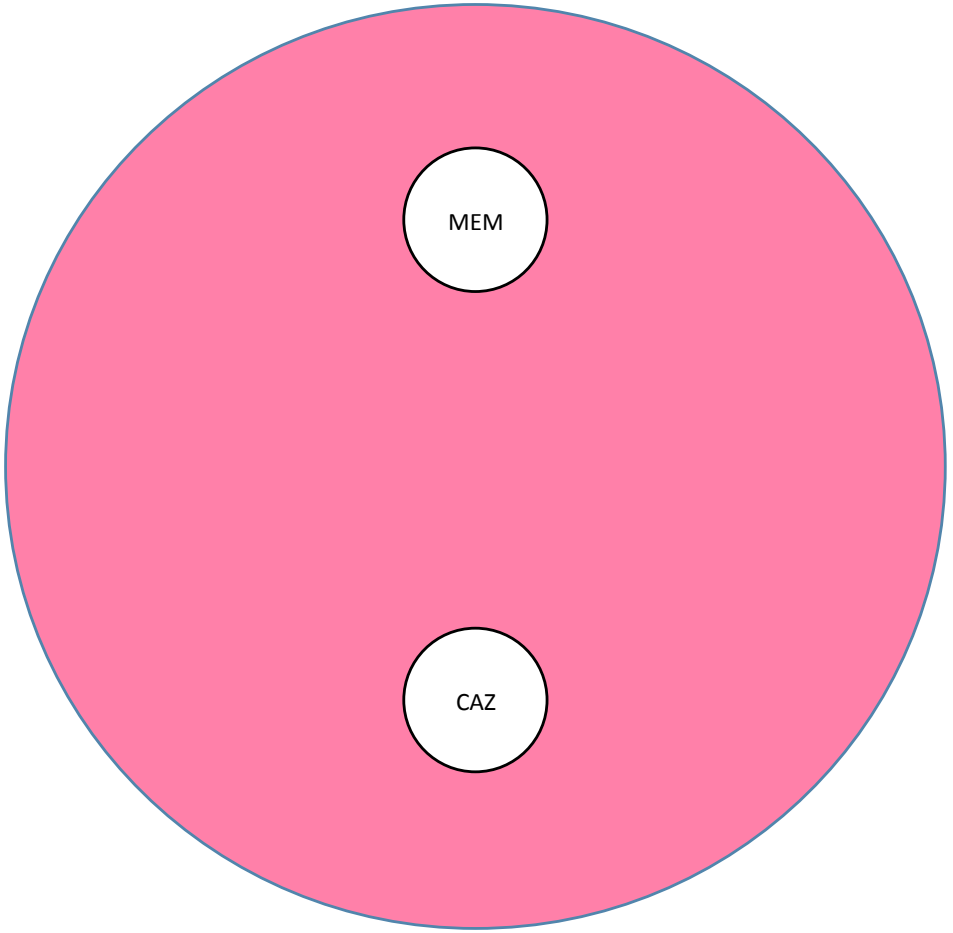
Detection of potential carriers

- PCR : investigational, not applicable il the 'real life'
- Surveillance cultures (directly by **rectal swab**)
  - MacConkey plates supplemented with antibiotics
    - Imipenem for KPC
    - cefotaxime and/or ceftazidime for ESBL
  - MacConkey plates with carbapenem disks for KPC and ceftazidime for ESBL
  - Chomogenic agar for ESBL and KPC

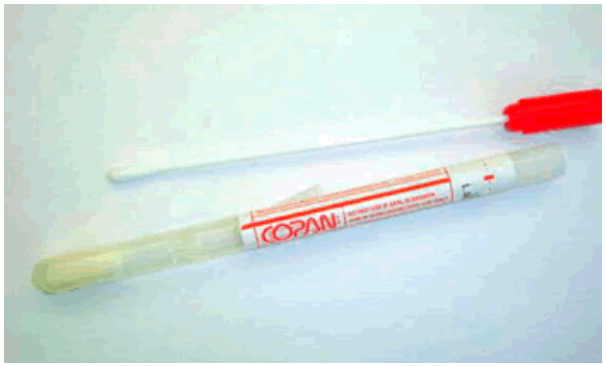
Detection of CEF-NS (ESBL) and Carba-NS (KPC, MBL, OXA-48) from surveillance cultures

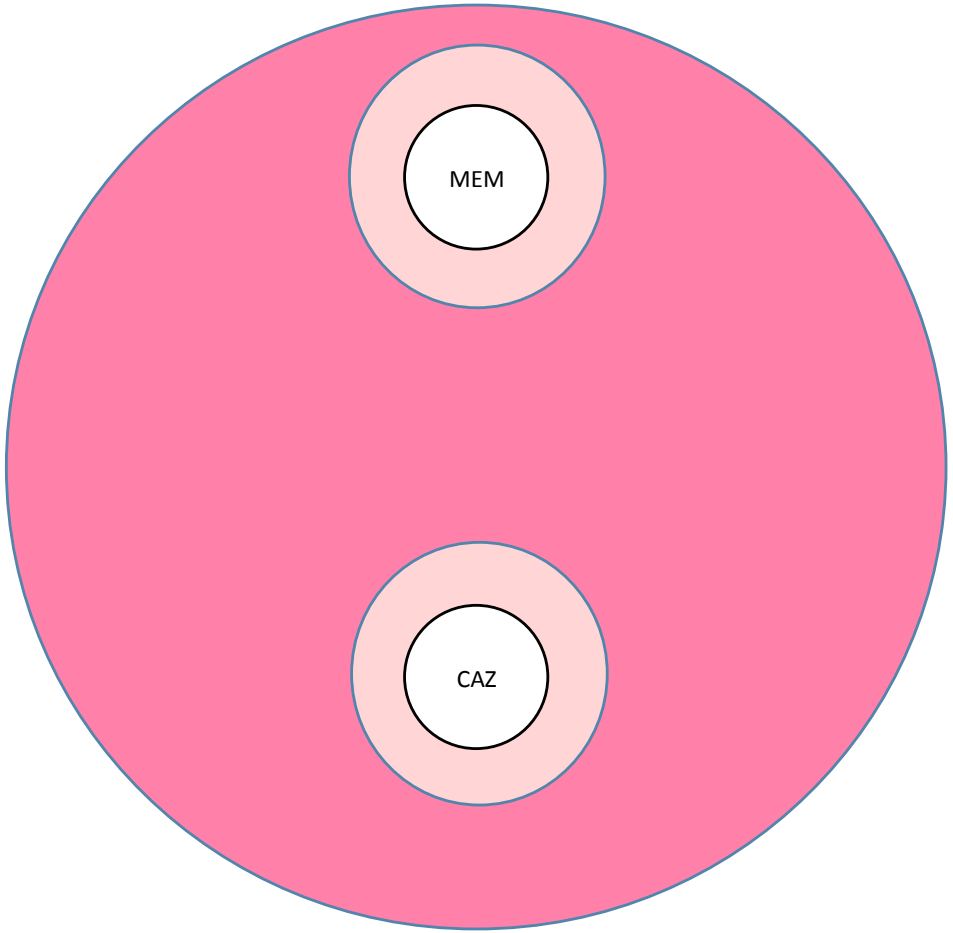




Also P.aeruginosa grows in MacConkey agar

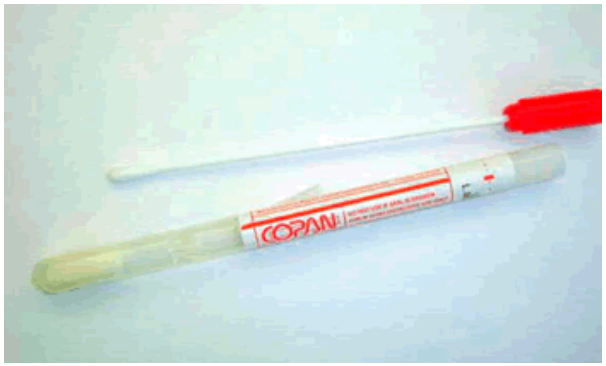
Detection of CEF-NS (ESBL) and Carba-NS (KPC, MBL, OXA-48) from surveillance cultures

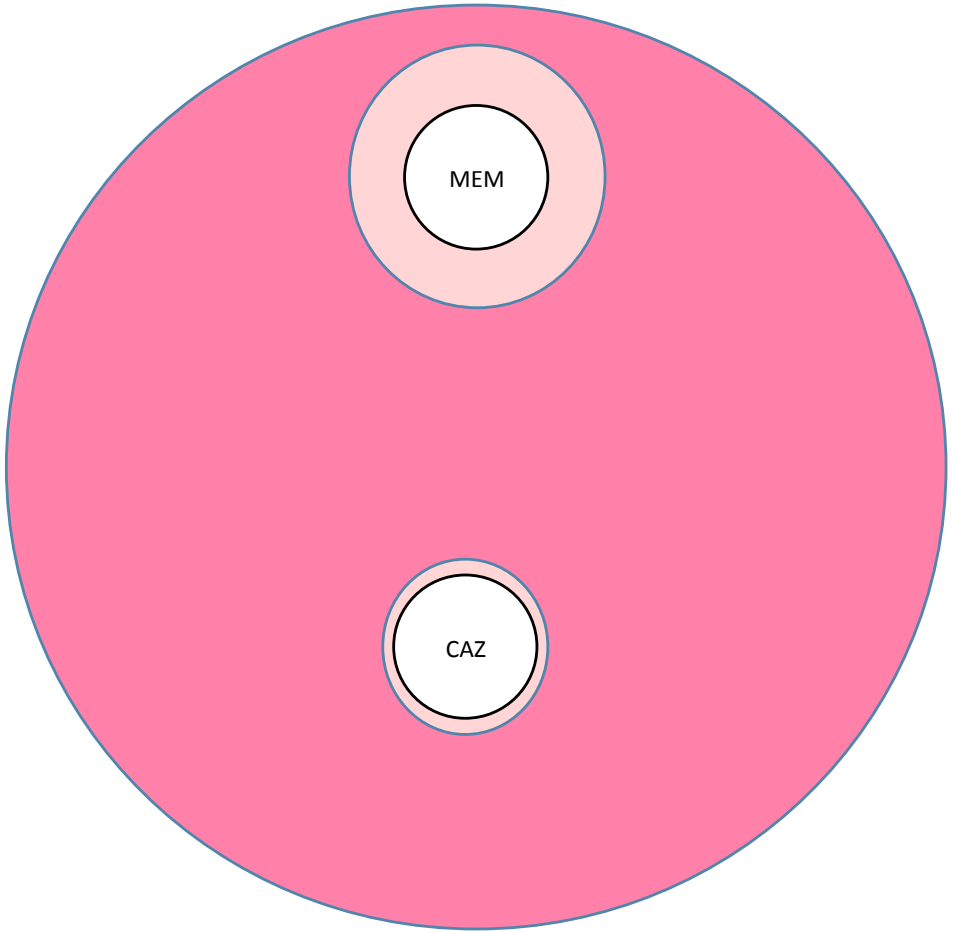




Susceptible to ceftazidime susceptible to meropenem: susceptible to batalactams

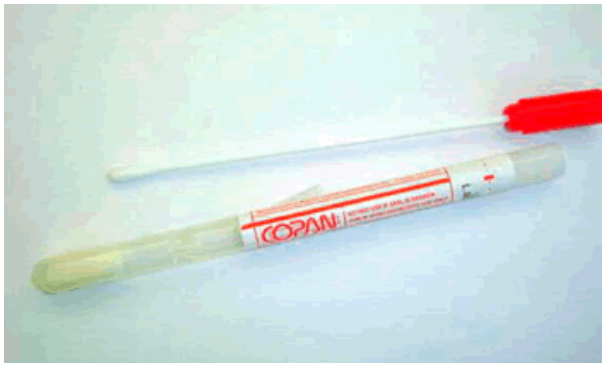
Detection of CEF-NS (ESBL) and Carba-NS (KPC, MBL, OXA-48) from surveillance cultures

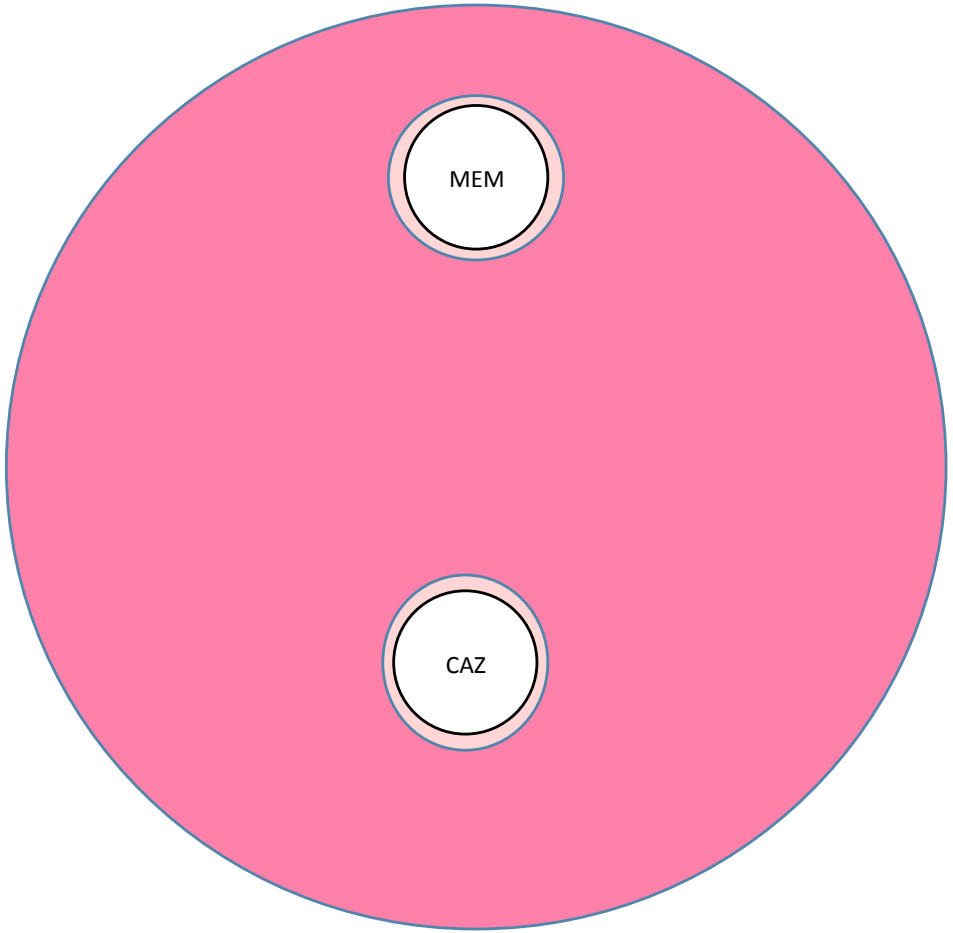




Resistant to ceftazidime susceptible to meropenem: suspect ESBL

Detection of CEF-NS (ESBL) and Carba-NS (KPC, MBL, OXA-48) from surveillance cultures





Resistant to ceftazidime and to meropenem: suspect of KPC or other MDR

CHROMagar™ ESBL

Click on the picture for Packaging / Colonies appearance

For overnight detection of Gram-negative bacteria producing Extended Spectrum Beta-Lactamase.

Typical Appearance of microrganisms

E.coli ESBL → Dark pink to reddish
Sensitive Gram negative strains → inhibited
Klebsiella, Enterobacter, Citrobacter → metallic blue
Proteus → brown halo

Order References

Please use these references when contacting your local distributor:
Product = base powder CHROMagar Orientation + CHROMagar ESBL Supplement

5000ml ESRT2
(base powder ref:RT412 + supplement ref:ES372)
25L ESRT3-25
(base powder ref:RT413-25 + supplement ref:ES373-25)

CHROMagar™ KPC

Click on the picture for Packaging / Colonies appearance

For Detection of gram-negative bacteria with a reduced susceptibility to most of the carbapenem agents.

Typical Appearance of microrganisms

E.coli CarbapenemR → Dark pink to reddish
Klebsiella, Enterobacter, Citrobacter CarbapenemR → Metallic blue
Pseudomonas CarbapenemR → Cream, translucent
Other bacteria → Usually inhibited

Order References

Please use these references when contacting your local distributor:
Product = base powder CHROMagar Orientation + CHROMagar KPC supplement

5000ml..... KPRT2
(base powder ref:RT412 + supplement ref:KP102)
25L..... KPRT3-25
(base powder ref:RT413-25 + supplement ref:KP103-25)

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EUROPEAN HEMATOLOGY ASSOCIATION
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Management of carbapenem resistant *klebsiella pneumoniae* infections in stem cell transplant recipients: an italian multidisciplinary consensus statement

by Corrado Girmenia, Claudio Viscoli, Alfonso Piciocchi, Laura Cudillo, Stefano Botti, Antonio Errico, Loredana Sarmati, Fabio Ciceri, Franco Locatelli, Maddalena Giannella, Matteo Bassetti, Carlo Tascini, Letizia Lombardini, Ignazio Majolino, Claudio Farina, Francesco Luzzaro, Gian Maria Rossolini, and Alessandro Rambaldi

Prior to hospital admission

Weekly if other colonized patients in the transplant unit or history of CRKp

In patients with other intestinal complications

In patients from endemic areas

- Timing of monitoring.
  - Transplant centers located in settings with known significant CRKp spread.
    - Monitoring of CRKp colonization is strongly recommended as part of the microbiological pre-transplant evaluation - prior to hospital admission - in both autologous and allogeneic SCT (**AII**). In patients not colonized, weekly post-transplant monitoring is indicated in the event of CRKp isolation from other patients in the same unit (**AII**). Patients with post-transplant intestinal complications, in particular Graft-versus-Host Disease, should undergo fecal culture including examination for CRKp (**AII**). A rectal swab should be repeated in patients who were not colonized and are re-hospitalized for post-transplant complications (**AIII**). CRKp colonized patients should be considered as persistent carriers regardless of the results of the subsequent cultures, thus rendering strict post-transplant monitoring as being no longer required (**BIII**). However, monitoring of the colonization status may be considered in patients with a previous CRKp isolation in order to document a decolonization and redefine the infection control strategy. Indeed, it is difficult to define the time after which a definitive decolonization can be established.
  - Transplant centers located in settings without significant CRKp spread.
    - Monitoring of CRKp colonization before or after SCT is not required (**BIII**). However, pre-transplant monitoring is recommended for patients transferred from CRKp endemic areas or in whom possible contact with the microorganism cannot be excluded, not only in the best interest of the patient, but also as part of hospital infection control measures (**AII**).

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Table 2. Oral decontamination for Carbapenem-resistant Enterobacteriaceae in general population and patients with hematologic malignancies.

Author (Reference)	Drugs	Study	N° patients included	N° (%) pts decontaminated	Pts with HM±SCT	N (%) G resistant stral	Follow-up
Zuckerman *et al.*[5]	GO	Observational	15	10/15 (66%)	15	0	30-300 days
Tascini *et al.*[6]	GO	Prospective	50	34/50 (68%)	2	4/16 (25%) persisters	180 days
Saidel-Odes *et al.*[10]	GCO1	Randomized Double Blind	20 GCO1 20 controls	12/20 (60%) GCO1; 3/20 (15%) controls	0	0	45 days
Oren *et al.*[15]	GO; CO2; GCO2	Semirandomized prospective plus controls	26 GO; 16 CO2; 8 GCO2 102 controls	11/26 (42%) GO; 8/16) 50% CO2; 3/8 (37%) GCO2; 7/102 (7%) controls	15 GO 15 CO2 4 GCO2 12 controls	6/15 (40%) persisters	31-140 days
Lubbert *et al.*[14]	GCO1	Observational plus controls	14 GCO1; 76 controls	6/14 (43%) GCO1; 23/76 (30%) controls	0	5/11 (45%)	48-53 days
Total	–	–	149 treated; 198 controls	84/149 (56%) treated; 33/198(16%) controls	51 treated 12 controls	13/42 (30%)	--

CRE: Carbapenem-resistant Enterobacteriaceae; G: gentamicin; GO: oral gentamicin (80 mg q.i.d.); CO2: oral colistin 2MU q.i.d.; GCO2: oral gentamicin (80 mg q.i.d.) plus oral colistin 2MU q.i.d.; GCO1: oral gentamicin (80 mg q.i.d.) plus oral colistin 1 MU q.i.d; HM±SCT: hematologic malignancies ± stem cell transplantation.

Decontamination of patients colonized by MDR Gram-neg bacteria

- The efficacy of a decontamination strategy has not been demonstrated in hematologic and HSCT pts
- The use of molecules active in therapy is questionable
- In other populations decontamination was not effective during systemic antibiotic therapy
- Relapse is frequent
- Clinical trials are required (i.e. fecal transplant)

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Why detection of MDR Gram-neg carriers is important?

- For the interest of the community:
  - Carriers are the main source of MDR bacteria spread, particularly for enterobacteria
  - Prevention of infection transmission is a cornerstone of any «infection control» strategy
- For the interest of the patient:
  - Colonization is highly predictive of invasive infection
  - Is colonization a contraindication to transplant?
  - Tailored management based on colonization data

Figure 1: Facility Approach to Evaluation of Newly Recognized CP-CRE Colonized or Infected Patients

New CRE-colonized or CRE-infected patient identified

▼

- Notify appropriate personnel (i.e., clinical staff, infection prevention staff)
- Notify public health (if required)

▼

- Place patient on Contact Precautions in single room (if available)-see discussion about use in long-term care
- Reinforce hand hygiene and use of Contact Precautions on affected ward/unit
- Educate healthcare personnel caring for patient about preventing CRE transmission

▼

- Consider screening epidemiologically-linked patient contacts (e.g., roommates) for CRE with at least stool, rectal, or peri-rectal cultures; consider review of microbiology records to identify previous cases
- Consider point prevalence survey of affected unit particularly if more than one CRE patient identified

▼

- If screening cultures or further clinical cultures identify additional CRE-colonized or -infected patients, consider additional surveillance cultures of contacts or ongoing point prevalence surveys of affected units until no further transmission identified
- Consider admission CRE surveillance cultures (i.e., active surveillance) of high-risk patients particularly in higher prevalence areas
- Consider cohorting patients and staff

▼

- Ensure if patient transferred within the facility that precautions are continued. Ensure, if discharged and readmitted, there is a mechanism to identify patient at readmission
- Ensure if patient transferred to another facility, CRE status is communicated to accepting facility

Notify

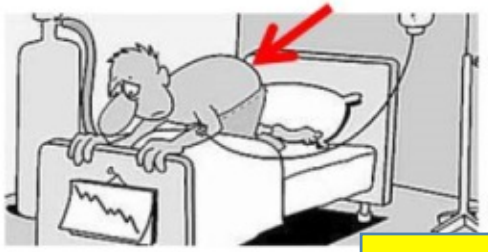
Contact precautions

Screening of contacts

Consider additional surveillance

Communicare CRE status if patient transferred

New Admission



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RESEARCH ARTICLES

Long-term control of carbapenemase-producing Enterobacteriaceae at the scale of a large French multihospital institution: a nine-year experience, France, 2004 to 2012

S Fournier (sandra.fournier@sap.aphp.fr)[1], C Monteil[1], M Lepainteur[1], C Richard[2], C Brun-Buisson[3], V Jarlier[4], AP-HP Outbreaks Control Group[5]

Eurosurveillance 2014

CPE

- se
- es
- or
- The CIC I visited all the hospitals where an outbreack occurred to **help** the local team to apply the programme

Local and central supervision = help!!!!

Resistance of Klebsiella pneumoniae Isolates to Carbapenems in Italy, France, Greece, Spain and Austria, 2009 - 2015 -

Country	Year	Total N	%R
Austria	2009	463	0.0 %
	2010	509	0.6 %
	2011	610	0.2 %
	2012	738	0.8 %
	2013	910	1.2 %
	2014	971	0.6 %
	2015	1022	0.8 %
France	2009	1268	0.2 %
	2010	1432	0.1 %
	2011	1640	0.0 %
	2012	1627	0.5 %
	2013	1842	0.7 %
	2014	2013	0.5 %
	2015	2244	0.5 %
Spain	2009	575	0.2 %
	2010	1161	0.0 %
	2011	1144	0.3 %
	2012	1152	0.8 %
	2013	1241	1.6 %
	2014	1266	2.3 %
	2015	1483	2.2 %

Country	Year	Total N	%R
Greece	2009	1627	43.5 %
	2010	1687	49.1 %
	2011	1636	68.2 %
	2012	1460	60.5 %
	2013	1209	59.4 %
	2014	1088	62.3 %
	2015	1185	61.9 %
Italy	2009	304	1.3 %
	2010	731	15.2 %
	2011	615	26.7 %
	2012	845	29.1 %
	2013	1453	34.3 %
	2014	1315	32.9 %
	2015	1999	33.5 %

Containment of a Country-wide Outbreak of Carbapenem-Resistant *Klebsiella pneumoniae* in Israeli Hospitals via a Nationally Implemented Intervention

Clinical Infectious Diseases 2011;52(7):848–855

Mitchell J. Schwaber,[1] Boaz Lev,[2] Avi Israeli,[2] Ester Solter,[1] Gill Smollan,[1] Bina Rubinovitch,[1] Itamar Shalit,[1] Yehuda Carmeli,[1] and the Israel Carbapenem-Resistant Enterobacteriaceae Working Group[a]

[1]National Center for Infection Control, Israel Ministry of Health, Tel Aviv, and [2]Israel Ministry of Health, Jerusalem, Israel

- 2006: several Israeli hospitals faced a clonal outbreak of CRKp that was not controlled by local measures .
- March 2007: the Israeli Ministry of Health launched a nationwide intervention and issued guidelines mandating
  - patient and staff cohorting
  - professional task force
    - site visits at acute-care hospitals,
    - evaluated infection-control policies and laboratory methods
    - supervised adherence to the guidelines
    - provided daily feedback on performance to hospital directors
    - made additional interventions when and where necessary.

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[1]National Center for Infection Control, Israel Ministry of Health, Tel Aviv, and [2]Israel Ministry of Health, Jerusalem, Israel

Professional task force supervision = help!!!!

79% relative reduction of the incidence compared with the previous year

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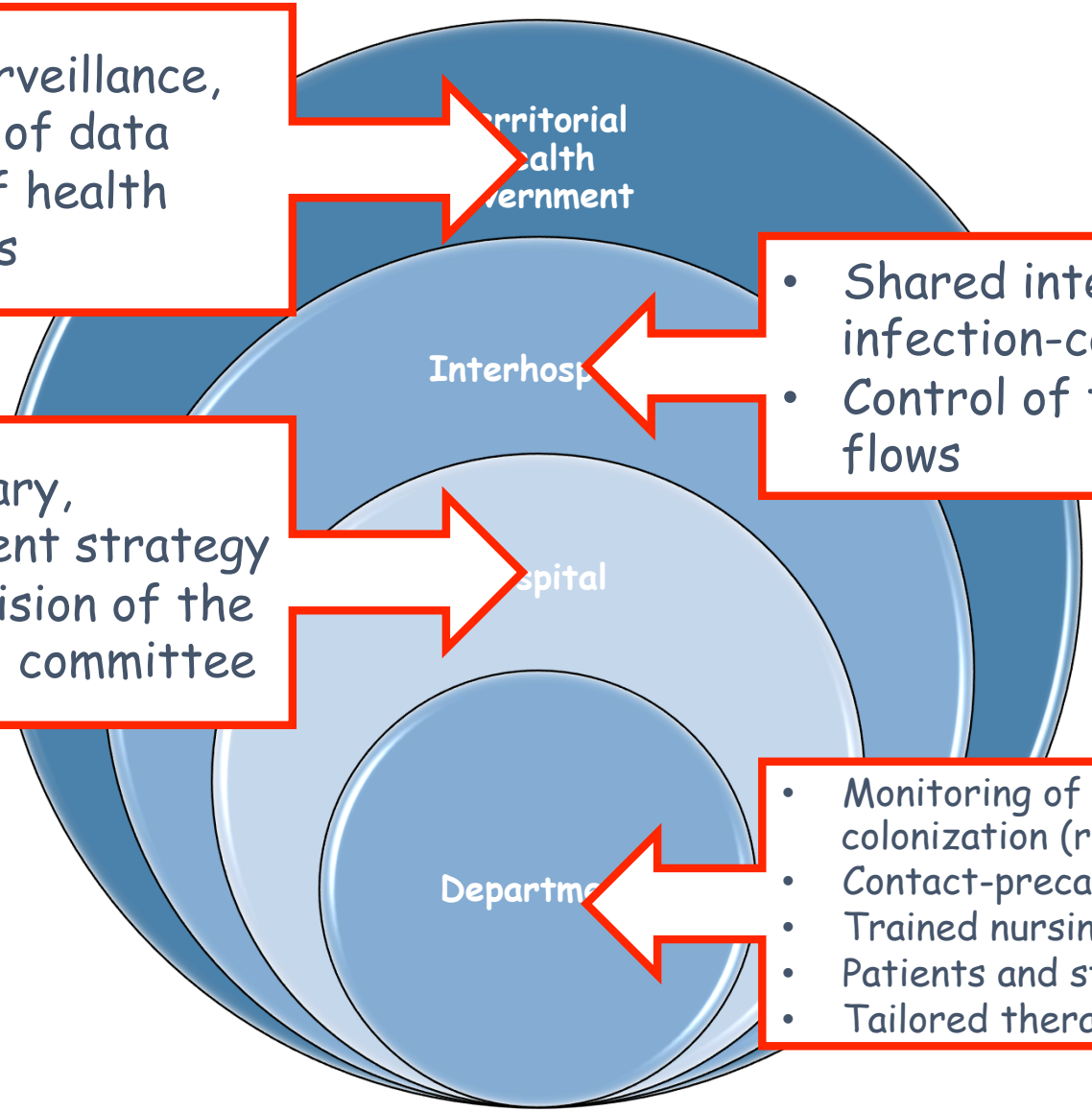
Management of carbapenem resistant *klebsiella pneumoniae* infections in stem cell transplant recipients: an italian multidisciplinary consensus statement

Infection control strategies in SCT populations in an era of antibiotic resistance

- Territorial surveillance, dissemination of data
- Supervision of health policy agencies



- Shared interhospital infection-control strategy.
- Control of the patients flows

- Multidisciplinary, interdepartment strategy
- Active supervision of the infect-control committee

- Monitoring of MDR/XDR colonization (rectal swab).
- Contact-precautions
- Trained nursing staff
- Patients and staff cohorting
- Tailored therapeuitc strategies

Why detection of MDR Gram-neg carriers is important?

- For the interest of the community:
  - Carriers are the main source of MDR bacteria spread, particularly for enterobacteria
  - Prevention of infection transmission is a cornerstone of any «infection control» strategy
- For the interest of the patient:
  - Colonization is highly predictive of invasive infection
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Colonization is not a contraindication to transplant

If possible consider delay of transplant

The choice of conditioning regimen or stem scell source with a reduced infectious risk may be considered

Impact of the CRKp issues on patients eligibility for SCT and on SCT strategies

- Pre-transplant CRKp colonization does not represent *per se* an absolute contraindication to both autologous and allogeneic-SCT (**AII**). In patients who do not require urgent SCT, transplantation may be delayed to allow for CRKp decolonization (**AIII**).
- In patients with recent CRKp infection before SCT – a condition with a high-risk of an early, life-threatening relapse after transplant – careful evaluation of the risk-benefit ratio for performing SCT is necessary. For this particular condition, transplantation may be contraindicated in favor of a less intensive therapeutic choice, or postponed (**BIII**).
- With regard to transplant procedures there is no contraindication for any type of autologous-SCT in CRKp carriers. As for allogeneic-SCT, the choice of conditioning regimen or stem cell source associated with a reduced infectious risk (engraftment time is generally shorter with peripheral stem cells as compared to bone marrow and cord blood) may be considered. However, no recommendation can be actually given and the decision remains at the discretion of the attending team.

Bone Marrow Transplantation (2015) 50, 282–288

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ORIGINAL ARTICLE

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]

Table 2. Probability of OS at 3 months from CRKp infection in 87 allo-SCT patients

	OS, %	*Univariate*		*Multivariate*	
		HR (95% CI)	*P*	*HR (95% CI)*	*P*
Male vs female	28 vs 32	1.04 (0.62–1.73)	0.88		
Age, ⩽43 years vs >43 years	37 vs 22	0.67 (0.40–1.10)	0.11	0.59 (0.34–1.01)	0.056
Underlying disease, acute leukemia vs others	27 vs 35	1.30 (1.30–0.76)	0.33		
Status of the underlying disease at transplant, CR/stable vs active	36 vs 18	0.56 (0.33–0.44)	0.03	0.61 (0.35–1.06)	0.080
CRKp infection during the 3 months before transplant, no vs yes	32 vs 10	0.51 (0.25–1.04)	0.06	0.33 (0.15–0.74)	0.007
Myeloablative conditioning, yes vs no	29 vs 32	1.22 (0.74–2.03)	0.44		
Donor type					
Matched related vs mismatched related or unrelated volunteer donor or cord blood	31 vs 28	0.95 (0.56–1.61)	0.85		
Level of CRKp infection documentation, proven vs probable	31 vs 20	0.89 (0.42–1.87)	0.76		
Time of onset of the infection after transplant,_⩽40 days vs >40 days	34 vs 22	0.94 (0.56–1.56)	0.80		
Neutrophil count at the time of infection, <500/cmm vs ⩾500/cmm	29 vs 32	1.5 (0.88–2.61)	0.13		
Acute grade II–IV or chronic severe GVHD at the time of infection, no vs yes	33 vs 22	0.98 (0.58–1.66)	0.94		
First-line antibiotic therapy, not CRKp-targeted vs CRKp-targeted	21 vs 45	1.76 (1.05–3.10)	0.04	2.67 (1.43–4.99)	0.002

Abbreviations: CI=confidence interval; CRKp=carbapenem-resistant *K. pneumoniae*; HR=hazard ratio; OS=overall survival.

Bone Marrow Transplantation (2014), 1–7

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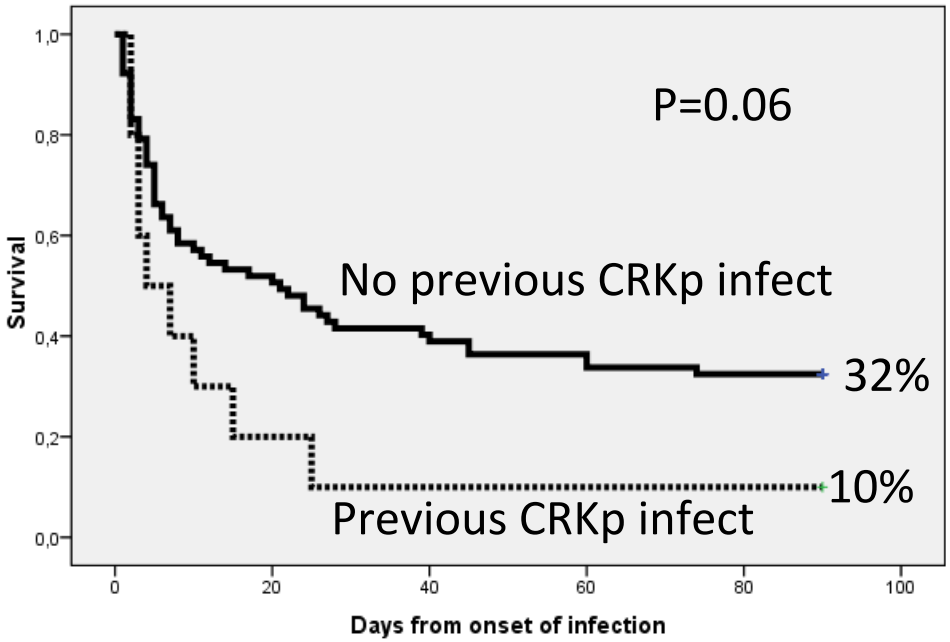

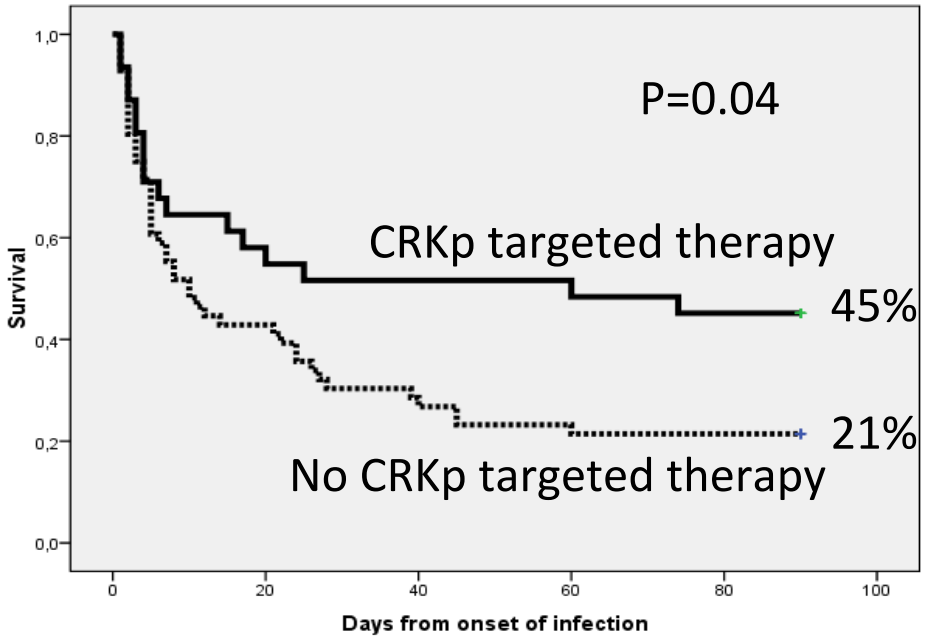

Prevention of colonization is the «cornerstone» of CRKp infection-control

Micozzi et al. BMC Infectious Diseases (2017) 17:203
DOI 10.1186/s12879-017-2297-9

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

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

Alessandra Micozzi[1*], Giuseppe Gentile[1], Clara Minotti[2], Claudio Cartoni[2], Saveria Capria[2], Daniele Ballarò[1], Stefania Santilli[2], Emanuele Pacetti[1], Sara Grammatico[1], Giampaolo Bucaneve[3] and Robin Foà[1]

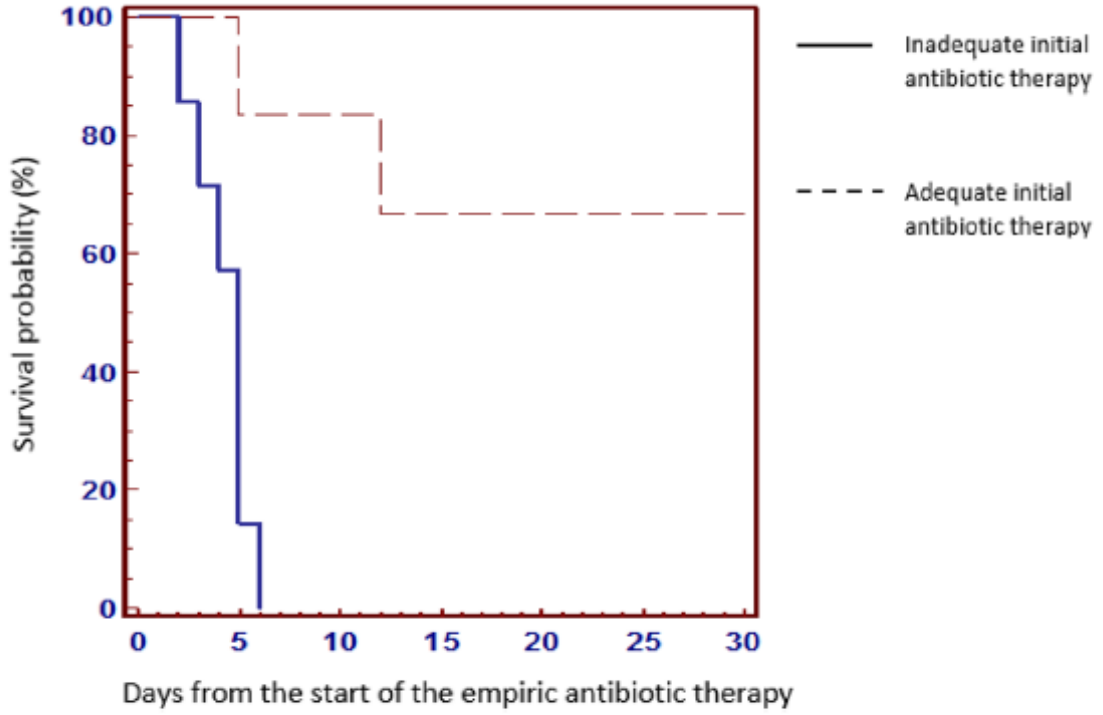

Fig. 2 Kaplan–Meier curves showing the impact of initial adequate antibiotic therapy on survival at 30 days in patients with CRKP bacteremia (log rank test =9.17, $p = 0.002$)

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EUROPEAN HEMATOLOGY ASSOCIATION
haematologica
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Management of carbapenem resistant *klebsiella pneumoniae* infections in stem cell transplant recipients: an italian multidisciplinary consensus statement

by Corrado Girmenia, Claudio Viscoli, Alfonso Piciocchi, Laura Cudillo, Stefano Botti, Antonio Errico, Loredana Sarmati, Fabio Ciceri, Franco Locatelli, Maddalena Giannella, Matteo Bassetti, Carlo Tascini, Letizia Lombardini, Ignazio Majolino, Claudio Farina, Francesco Luzzaro, Gian Maria Rossolini, and Alessandro Rambaldi

Susceptibility pattern of the colonizing isolate

At least two active agents

Standard empiric antibiotic therapy discouraged in patients with colonization by MDR bacteria

- CRKp carriers, at onset of febrile neutropenia or other signs of possible infection.
  - CTAT based on the susceptibility pattern of the colonizing isolate with the inclusion of at least two active agents, if possible, is strongly recommended (**AII**).
  - The use of standard empiric antibiotic therapy, not including CRKp-active drugs, is discouraged (**AII**).
  - In SCT centers with an ongoing outbreak of CRKp, the choice of empiric CTAT may be considered also in febrile patients who are not colonized, or with an unknown colonization status. (**BII**). Prompt withdrawal of CTAT with downgrading to more traditional drugs is recommended if cultures come back negative for CRKp, also taking into consideration the clinical findings (**AII**).

Consider active empiric therapy also in noncolonized patients during an ongoing outbreak

The choice of antibiotic therapy in patients colonized by MDR Gram-neg bacteria

- Detailed susceptibility (MIC) of the colonizing isolate is required
- Antibiotics (high doses) against isolates with MICs over the breackpoint may be used but a certain activity is needed:
  - Colistin $\leq$ 4 mcg/ml (S $\leq$ 2 mcg/ml)
  - Meropenem $\leq$ 16-32 mcg/ml (S $\leq$ 2 mcg/ml)
  - Tygeciclin $\leq$ 4 (S $\leq$ 1 mcg/ml)
  - Fosfomycin ?? (S $\leq$ 32 mcg/ml
  - Gentamycin $\leq$ 4 mcg/ml (S $\leq$ 2 mcg/ml)
- The appropriate antibiotic therapy should be defined in colonized patients before the onset of a febrile episode.

The role of fluoroquinolone prophylaxis in an era of MDR Gram-neg bacteria

- Is fluoroquinolone decontamination still effective in the prevention of Gram-neg infections?
- Can a fluoroquinolone decontamination effect favouring the emergence of MDR Gram-negative bacteria be excluded?

GITMO ONLUS
Gruppo Italiano per il Trapianto di Midollo Osseo, cellule staminali emopoietiche e terapia cellulare - ONLUS
Iscr. Registro Reg. Liguria – decr. n. 120 del 18/01/08 – cod. fisc. 95107000101 part. iva 01727920991

AMCLI associazione microbiologi clinici italiani

Incidence, risk factors and outcome of pre engraftment Gram negative bacterial infections after allogeneic and autologous hematopoietic stem cell transplantation: an Italian prospective multicenter survey.

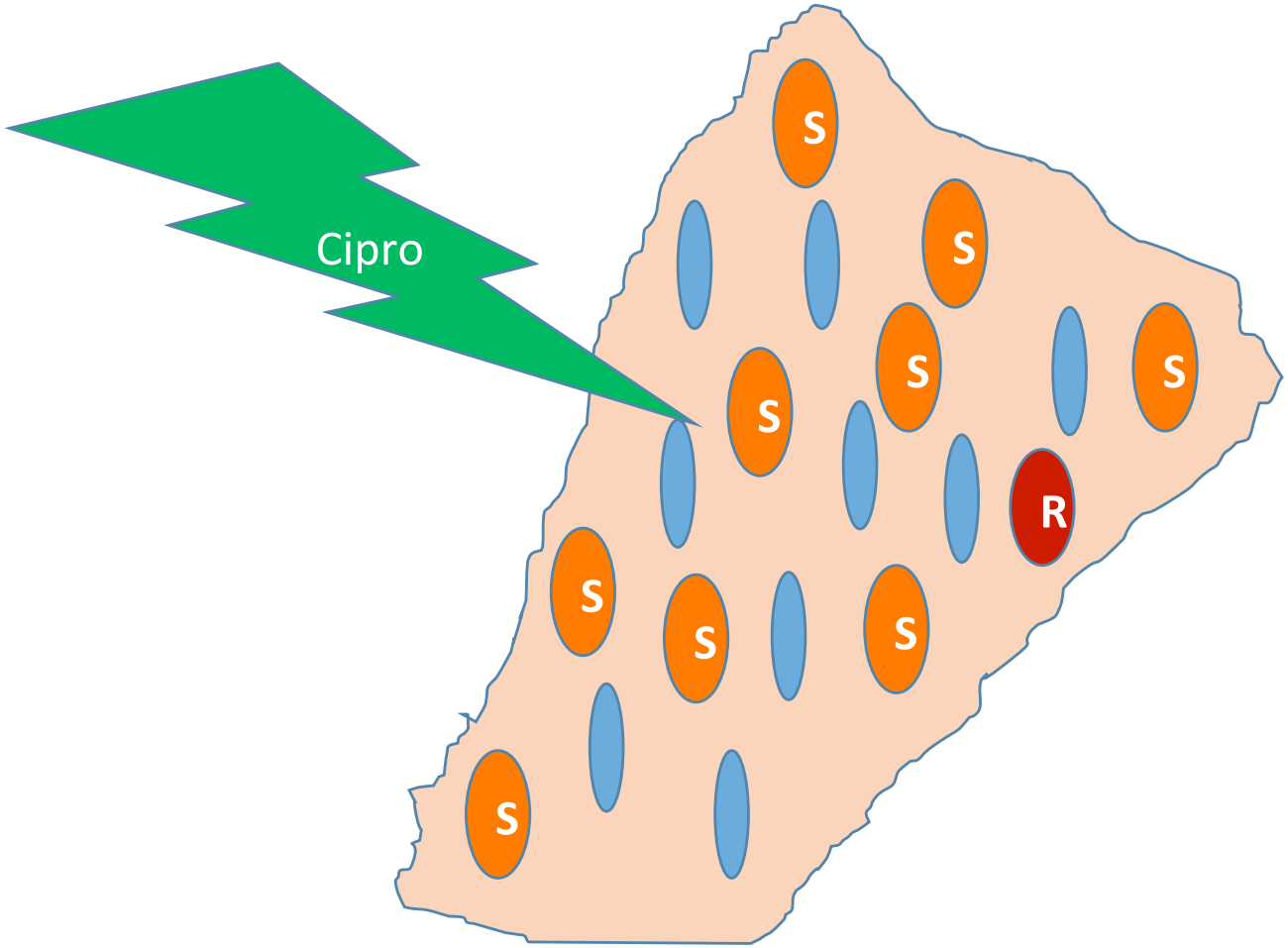
(ClinicalTrials.gov,ID NCT02088840)

Risk factors for pre-engraftment Gram negative infections

Multivariate analysis

Allo-HSCT		Auto-HSCT	
Variable	**HR (95% CI), p**	Variable	**HR (95% CI), p**
Age (+10y)	1.15 (1.05-1.25), 0.016	Age (+10y)	1.18 (1.05-1.33), 0.006
Other diseases vs acute leukemia	0.64 (0.46-0.89), 0.009	Lymphoma vs other diseases	1.84 (1.31-2.61), 0.0005
Donor MMR MMU CB	 3.74 (2.15-6.50), <0.0001 2.91 (1.50-5.64), 0.001 3.77 (1.50-9.45), 0.005	Antibacterial prophylaxis vs no prophylaxis	0.46(0.32-0.68), <0.0001
Days of pre-engraftment neutropenia	1.02 (1.01-1.03), 0.0004		

Possible effects of fluoroquinolones intestinal decontamination in high risk patients



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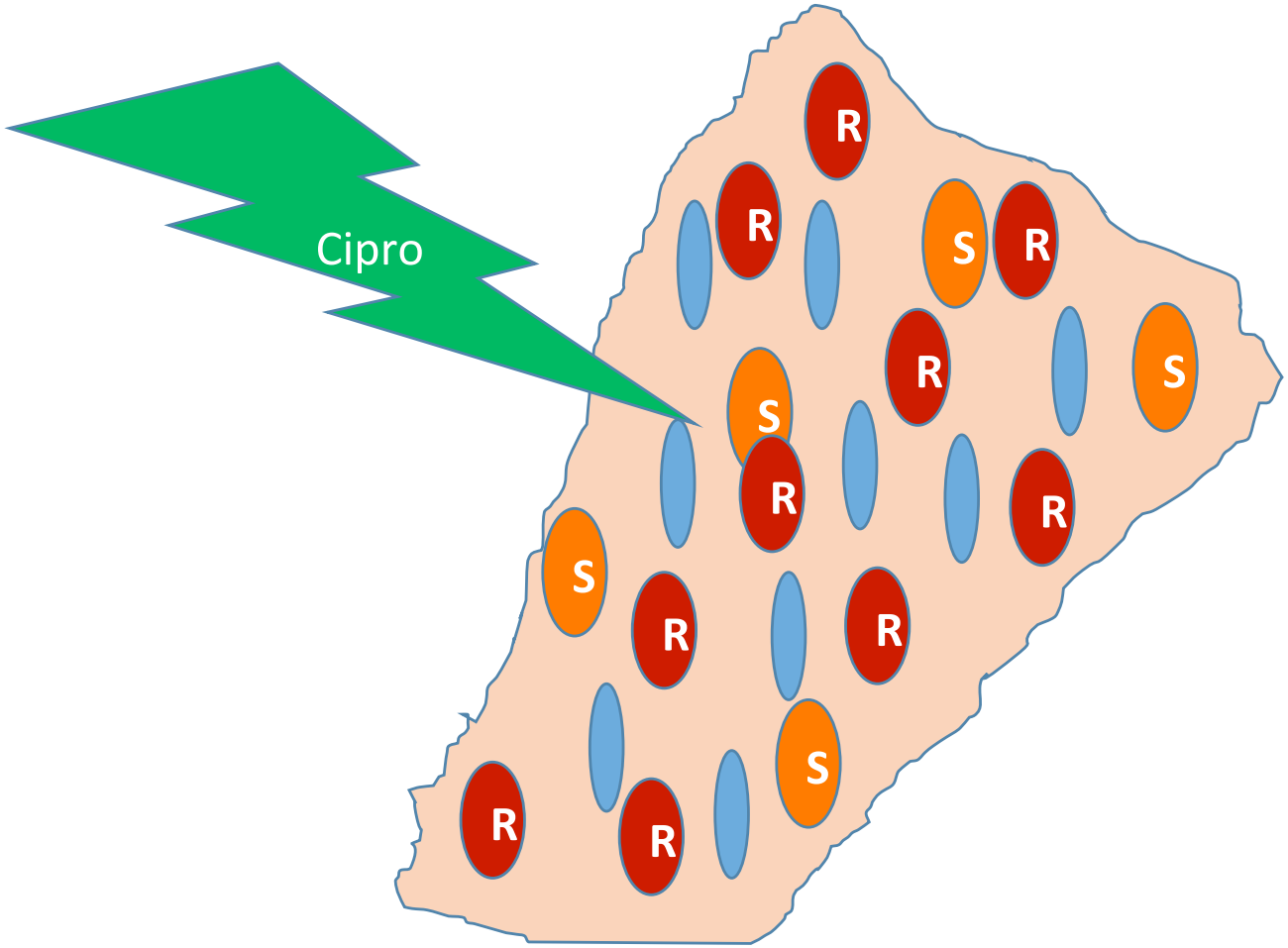

Ciprofloxacin prophylaxis in neutropenic allo-HSCT recipients: a placebo-controlled study

- **Background**: ciprofloxacin is no more effective in the prevention of Gram-neg infections
- **Objective**: non inferiority of placebo vs ciprofloxacin

- **Background**: ciprofloxacin may favour infections by MDR Gram-neg bacteria
- **Objective**: superiority of placebo vs ciprofloxacin