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

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Running title: KPC infections in SCT recipients

The increasing incidence of infections by carbapenem-resistant enterobacteria (CRE), in particular carbapenem-resistant *Klebsiella pneumoniae* (CRKp), is a significant public health challenge worldwide (1). The interim results of the last European survey on CRE (EuSCAPE project 2013) indicate that CRKp is endemic in Italy, and that this endemicity is mostly contributed by strains producing KPC-type carbapenemases (http://www.ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-carbapenemase-producing-bacteria-europe.pdf;EARS-NETreport 2012;7).

CRKp infections are associated with high morbidity and mortality rates, particularly among Intensive Care Units (ICU) patients, recipients of solid organ transplants (SOT) and patients with hematological malignancies (1-3). The Gruppo Italiano Trapianto Midollo Osseo (GITMO) recently performed a retrospective study (2010-2013) which involved 52 stem cell transplant (SCT) centers to assess the epidemiology and the prognostic factors of CRKp infections in autologous and allogeneic SCT (4). Cases of CRKp infection were reported in 53.4% of centers and were documented in 0.4% of autologous and 2% of allogeneic SCTs. A CRKp colonization was followed by an infection in about 30% of cases. The infection-related mortality rate was 16% in autologous and 64.4% in allogeneic SCT. A pre-transplant CRKp infection and an inadequate first-line treatment were independent factors associated with an increased mortality in allogeneic SCT patients who developed a CRKp infection. Indeed, despite the administration of a first-line CRKp-targeted antibiotic therapy (CTAT) (see below), 55% of patients who received a CTAT still died. These data underscored the challenge about CRKp infections, particularly in the allogeneic-SCT setting, in terms of outcome and management of post-transplant complications, and raised an issue about the transplant eligibility among patients who got colonized or had developed a CRKp infection before transplant.

Based on these original data and on the recent literature, a multidisciplinary group of experts from GITMO, the Italian Association of Clinical Microbiologists (Associazione Microbiologi Clinici Italiani; AMCLI), the Italian Society of Infectious and Tropical Diseases (Società Italiana

Malattie Infettive e Tropicali; SIMIT), and the Italian National Transplant Center (Centro Nazionale Trapianti; CNT) was convened with the aim of providing consensus recommendations about the management of CRKp infection/colonization in autologous and allogeneic-SCT recipients.

The Expert Panel (EP) included 17 specialists in hematology, infectious diseases, clinical microbiology and nursing, selected in view of their expertise in research and clinical practice of infections in SCT. The areas of major concern were defined by generating clinical key issues using the criterion of clinical relevance, i.e. impact on patient management and risk of inappropriateness, and recommendations were obtained according to a nominal group technique.

The EP focused its discussion on four key-issues considered relevant for the present recommendations that are shown in Table 1.

1. Detection of CRKp carriers before and after SCT.

Colonization by CRKp represents a condition predictive of a subsequent infection in immunocompromised patients (4-8). The EP agreed that the detection of CRKp carriers seems to be the crucial mean for infection-control and appropriate therapy, but well-defined colonization survey strategies (i.e. timing and frequency of tests) have not been standardized. Considering that the primary colonization site of enterobacteria is the intestinal tract, screenings are focused on the detection of intestinal carriage of CRKp, usually by analysis of rectal swabs. Three levels of isolation may be considered in the infection-control strategy: known to be colonized, known to be not colonized and results pending.

2. Infection-control strategies and management of CRKp carriers in the SCT setting.

Infection-control of CRE should be planned at each department, in the entire hospital, and at regional, national or multinational level. The differences in morbidity and mortality of infections due to CRE in populations of patients with various underlying diseases and comorbidity profiles should be considered for a comprehensive infection-control strategy (3,4,7,8). In a recent survey in a tertiary teaching Italian hospital, compared to internal medicine patients (4.3/1000 colonization

days), the highest incidence of CRKp infections among colonized patients was observed in hematology (26.3; P=0.04) and ICU (13.1; P=0.0004), followed by surgery (8.6; P=0.14), transplant (7.4; P=0.34), and long-term care (4.7; P=0.99). CRKp attributable mortality was highest in hematology (75%) followed by ICU (11%), transplant (7%), long term care (5%), internal medicine and surgery (both 2%) (7). In a further multicenter matched case–control study of adult CRKp rectal carriers, the rates of infections among carriers in hematology, SOT, ICU and medicine were 38.9%, 18.8%, 18.5% and 16%, respectively (8). These experiences underline the unique impact of CRKp infection in hematologic patients, including SCT recipients, and the importance in considering colonized patients in lower risk units likely as an occult reservoir and a source of microorganisms spread to high-risk patients in the hospital.

Candidates to SCT often come to the transplant-unit from centers located in other regions or countries with different risk of carrying CRE. This extensive inter-facility sharing of patients has the potential to facilitate widespread regional and even international transmission of CRE. Recent experiences from Israel and France demonstrated the importance of infection-control strategies applied at regional/national level when clonal outbreaks of CRE cannot be controlled by local measures (9,10). The central program for controlling CRE spread included recommendations to isolate, and screen for resistant microorganisms, patients previously hospitalized abroad, and bundled measures to control cross transmission. A quick implementation of nursing staff-cohorting to avoid cross contamination was a crucial tool of the infection control. A supervised adherence to the guidelines with a feedback on performance to hospital directors, and the addition of specific interventions when and where necessary, guaranteed the effectiveness of the interventions. The main results of these national infection-control strategies were the decrease in the total number of outbreaks and the containment of the intrahospital and interhospital spread of CRE infections in a few months. The EP agreed that a centralized coordination at any level is essential in the epidemiological control of CRKp infections in high risk populations including SCT recipients.

3. **Criteria for timing of antibiotic therapy and choice of the appropriate regimen in patients at risk for and with documented CRKp infection**.

An Expert-Panel convened by the 4th European Conference on Infections in Leukemia (ECIL-4) group has recently published guidelines for the management of empirical and targeted therapy in an era of emerging resistant gram-negative pathogens in leukemia patients and SCT recipients (11,12). This group has recommended that empirical therapy should be tailored according to local epidemiology, adopting an escalation/de-escalation approach in order to reduce to the indispensable the use of carbapenems and colistin. An appropriate CTAT was defined as combination including at least two among colistin/polymyxin B, tigecycline and gentamicin, preferably with the addition of meropenem, and eventually also fosfomycin. The use of high, unconventional doses for some drugs was suggested (12). The GITMO study confirmed the independent role of a first line CTAT on survival; however, half the patients who received a first line CTAT still died due to the infection (4). Of note, in this study, out of 22 patients with a CRKp infection documented before allogeneic SCT, 10 (45.4%) relapsed early after transplant, and 9 (90%) of them died despite early CTAT. These findings raise the crucial problem of the unsatisfactory efficacy of the available treatments and the need of infection prevention in patients at risk avoiding the contact with these pathogens and trying to eradicate the colonization. In the last few years, the efficacy and safety of selective digestive decontamination (SDD) with non absorbable antibiotics for the eradication of CRE carriage was evaluated in populations with various underlying conditions (5,6,13-15) (Table 2). The available data seem to show that SDD, in particular with oral gentamicin, may be in general a suitable option in CRKp carriers with a moderate risk to develop resistance to gentamicin (see table 2), especially in persistent carriers during decontamination. However, in view of the small experience in hematologic populations and of the need of further data about safety there is poor evidence to support a recommendation on SDD in SCT patients colonized by CRKp, but this topic may deserve appropriate investigation.

4. Impact of the CRKp issues on patients eligibility to SCT and on SCT strategies

The EP found no data in the literature about the impact of the CRKp issue on eligibility to SCT and other related strategies and based the discussion on the GITMO experience (4) and the expert opinions. The EP agreed that, considering the crucial importance of SCT in the comprehensive treatment strategy for some hematological patients, CRKp colonization does not represent a contraindication to both autologous and allogeneic-SCT. On the contrary, a recent CRKp infection before SCT, being associated with a high risk of a fatal relapse, requires a careful evaluation of the risk-benefit ratio for performing SCT.

In conclusion, CRKp infections in SCT patients have a dramatic impact on outcome, particularly in the allogeneic setting. Carrier detection represents a critical aspect, and any intervention requires coordination at intrahospital and interhospital level. In the present report, experts in the field produced recommendations for prevention and management of CRKp infection/colonization in SCT patients and suggested some topics of investigation. The questions raised by and the conclusions drawn from this consensus conference may form the basis for improving infection-control of CRE infections in the SCT populations.

Authorship and disclosures

All authors provided substantial contributions to conception and design, acquisition of evidence and analysis and interpretation of data, in particular during panel meetings. All authors also participated in drafting the article and revising it critically, and gave final approval of the version to be published. C. Girmenia, G. M. Rossolini, C. Viscoli and A. Rambaldi were responsible for manuscript preparation. All the authors critically revised the final version of the paper.

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Table 1. Recommendations for the management of carbapenem-resistant *Klebsiella pneumoniae* (CRKp) infections in stem cell transplant recipients.*

Detection of CRKp carriers before and after SCT

- **Site/s and sample/s for microbiological surveillance.**
  - A rectal swab should be preferred and is probably sufficient for standard microbiological monitoring of CRKp colonization **(AII)**. Repeated swabs and culture from other sites/fluids (i. e. inguinal skin, vagina, stools, urine, oral swabs, sputum) may improve the sensitivity of the colonization screening **(BII)**.
- **Microbiological methods.**
  - Direct plating of rectal swabs to selective agar media appear adequate **(AII)**. A preliminary broth enrichment step aimed at increasing the sensitivity of the test may be used to detect subjects with low-level colonization if the delay in the results is not critical (i.e. in pre-transplant screening) **(BII)**. Molecular methods can be faster and more sensitive compared to cultural methods, but only culture may allow susceptibility testing which is obviously crucial **(AII)**.
  - Simultaneous culture of the rectal swab onto nonselective media for detection of the presence of enterobacterial microbiota should always be included, to assess the quality of the rectal swab (AII).
- **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 - before 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 search for CRKp **(AII)**. A rectal swab should be repeated in patients that 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 following cultures, thus rendering strict post-transplant monitoring 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 a possible contact with the microorganism cannot be excluded, not only in the best patient interest, but also as part of hospital infection-control measures (**AII**).

Infection-control strategies and management of CRKp carriers in the SCT setting.

- **Precautions to use in the SCT unit.**
  - The presence of a nursing staff competent and familiar with infection-control procedures is one of the most relevant measures to avoid cross infection-transmission. A continuous process to educate, monitor and improve health care personnel adherence to infection-control precautions should be ensured **(AII)**.

- Hand hygiene is pivotal for preventing CRKp transmission **(AI)**. Facilities should ensure that healthcare personnel, patients and visitors are familiar and adherent with proper hand hygiene.
- Patients who are colonized or infected with CRKp, as well as those with a previous history of CRKp, should be housed in single rooms and placed on contact-precautions **(AII)**. If single rooms are not available, patient may be cohorted **(AII)**. Cohorting practice should also consider the risk of acquiring additional resistance. Patients with a colistin-susceptible CRKp strain should not be cohorted with patients with colistin-resistant strains, given the ability for cross-transmission shown by colistin-resistant CRKp **(AIII)**. Patients entering the transplant unit should be considered as potentially colonized and managed consequently, until proven otherwise **(BII)**. In cases with a high suspicion of colonization by resistant pathogens, three consecutive negative culture or molecular test results separated by ≥48 h each may be presumably required to exclude CRKp colonization **(BIII)**. In addition to patient cohorting, staff cohorting should be considered **(AII)**.

- **Prevention of intrahospital and interhospital transmission of CRKp.**
  - A coordinated control effort involving the clinical microbiology laboratory and the various departments of the hospital is recommended **(AI)**. Any connection between the transplant unit and other departments or health-care facilities of the same or another hospital in which CRKp are common (or are suspected so) should be carefully monitored. Monitoring of occult CRKp carriers also in non-intensive departments, such as internal medicine and general surgery, should be considered as it may be crucial for the prevention of CRKp spread to high-risk units **(AIII)**.
  - The prevalence or incidence of CRKp should be investigated by performing some form of territorial surveillance for these organisms, and surveillance data should be regularly disseminated **(AII)**. Transfer of patients from one hospital to another should be conditioned by specific monitoring procedures of the CRKp carriers. The supervision of the adherence to guidelines for infection control at the highest levels of health policy agencies is needed to ensure that core prevention measures are being implemented at interhospital and intrahospital level **(AII)**.

Criteria for timing of antibiotic therapy and choice of the appropriate regimen in patients at risk for and with documented CRKp infection.

- CRKp carriers, at the first documentation before or after SCT
  - SDD with oral gentamicin or oral colistin in susceptible CRKp carriers starting from CRKp documentation and, at least, until engraftment might be considered. However, in view of the small experience in hematologic populations and of the need of further data about safety (risk for resistance selection) there is poor evidence to support a recommendation **(CIII).** The EP advised particular caution in the use of oral colistin/polymyxin for SDD considering the consequence of resistance selection, being colistin a drug pivotal for treatment**.**
- CRKp carriers, at onset of post-conditioning neutropenia
  - Starting a CTAT in CRKp carriers at the onset of neutropenia, instead of onset of fever and in absence of any sign of infection, might be a sort of preemptive strategy. However, the EP considered this approach a very unorthodox procedure considering the lack of any experience on the efficacy and safety of this practice, the risk of an overtreatment and the risk of inducing resistance **(CIII).**
- 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 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, considering also the clinical findings **(AII)**.
- Patients with documented CRKp infection
    - A CTAT guided by the in vitro susceptibility results is recommended **(AII)**
- Patients with a recent history of CRKp infection before transplant
    - Considering the high probability of an early, fatal post-transplant relapse the EP discussed on the feasibility of starting CTAT at the onset of neutropenia regardless of fever or other infectious signs. A consensus on this issue was not reached. Despite the recognition of the relevance of this novel strategy to face a dramatic complication, the risk of overtreatment and toxicity represented the main reasons for disagreement by some components of the EP.

Impact of the CRKp issues on patients eligibility to 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 that 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 for an early, life-threatening relapse after transplant - careful evaluation of the risk-benefit ratio for performing SCT is needed. For this particular condition, transplantation may be contraindicated, in favor of a less intensive therapeutic choice, or postponed **(BIII)**.
- With regard to the 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.

* A systematic weighting of the level and grade of evidence was used (reference 12).
SDD=selective digestive decontamination; CTAT= CRKp-targeted antibiotic therapy

TABLE 2: Oral decontamination for Carbapenem-resistant Enterobacteriacaee 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 strains	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 (13)	GCO1	Randomized Double Blind	20 GCO1 20 controls	12/20 (60%) GCO1; 3/20 (15%) controls	0	0	45 days
Oren et al (14)	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 (15)	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 Enterobacteriacaee; 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.