Short communication

Management of carbapenem-resistant *K. pneumoniae* in allogenic stem cell transplant recipients: the Turin bundle

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SUMMARY

Carbapenem resistance has evolved rapidly since 2001 and the distribution of Carbapenemase-producing *Klebsiella pneumoniae* (CR-Kp) is currently a public health concern worldwide. In the haematological setting, especially in allogenic transplant, CR-KP infections were associated with a mortality up to 65%.

Aim of this report is to describe the management of patients colonized by CR-Kp and undergoing allo-HSCT with a multiple-step intervention strategy: the "Turin bundle". Steps included oral gentamicin (GO) within 20 days before allo-HSCT, avoidance of levofloxacin prophylaxis during neutropenia, treatment of febrile neutropenia with tigecycline 100 mg *bid* and piperacillin-tazobactam at standard dosages and early appropriate combination therapy for patients with severe sepsis. In our small series all patients survived, no resistance to oral gentamicin was observed and 60% of patients had negative rectal swabs after transplant.

Key words: Carbapenemase-producing *Klebsiella pneumonia*, Allogenic haematopoietic stem cell transplant (HSCT), Carbapenem-sparing strategies, Decontamination, Mortality.

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Carbapenem resistance has evolved rapidly since 2001 and the distribution of Carbapenemase-producing *Klebsiella pneumoniae* (CR-Kp) is currently a public health concern worldwide (De Rosa et al., 2015). In Europe, epidemiological determinants now vary substantially by geography and according to the European Antimicrobial Resistance Surveillance Network (EARS-Net), the European population-weighted mean percentage for carbapenem resistance was 8.1% in 2015 (European Centre for Disease Prevention and Control, 2014).

Italy is in second place after Greece in terms of resistance and CR-Kp is now endemic in Italy (Albiger et al., 2015), with some reports of a new epidemiological trend, with CR-Kp infections even developing within 5 days from hospital admission (Corcione et al., 2014).

The GITMO recently reported data on 52 stem cell transplant centers in Italy, describing 53.4% of cases of carbapenem-resistant Enterobacteriaceae, with a higher incidence in allogenic transplant (allo-HSCT) with a related mortality up to 65% (Pagano et al., 2014). Moreover, it has not been well established whether chronic carriers of CR-Kp may undergo allogenic HSCT due to the risks of severe infections and high mortality (Girmenia et al., 2015).

Gut colonization is the human reservoir of CR-Kp and represents one of the main risks for CR-Kp bloodstream infections, requiring active surveillance for carrier identification and isolation (De Rosa et al., 2015b). Gut decontamination for CR-Kp decolonization is an interesting option for infection control purposes, also reducing cross-transmission and allowing patients to further proceed to HSCT. Moreover, the efficacy and safety of selective digestive decontamination (SDD) with non-adsorbable antibiotics has been evaluated in different settings in the last few years, showing that SDD in particular with gentamicin may be an option in CR-Kp carriers (Zuckerman et al., 2011; Saidel-Odes et al., 2012; Oren et al., 2013; Tascini et al., 2014).

From the above considerations it seems that appropriate management is complex and requires infection control protocols and timely and appropriate therapeutic strategies in the setting of febrile neutropenia or clinically documented infections (Girmenia et al., 2015). Accordingly, we report here the results of a bundle intervention applied to the management of CR-Kp haematological carriers undergoing allo-HSCT.

Even before the publication of an Italian Consensus (Girmenia et al., 2015), we aimed to manage patients colonized by CR-Kp and undergoing allo-HSCT with a multiple-step intervention strategy at the City of Health and Science, Molinette Hospital, in Turin, Italy, between 2013 and 2015.

All haematological patients with a positive rectal swab for CR-Kp and undergoing allo-HSCT were included in the study. Rectal swabs for multi-drug-resistant (MDR) bacteria surveillance were routinely performed at the time of hospital admission and weekly throughout hospitalization in all

high-risk patients according to a regional Infection Control Policy protocol (Piedmont Region n° 30335/DB.2001).

For all patients, demographic and clinical data were collected. Microbiology data included the surveillance rectal swab results for identification of CR-Kp carriers identified through automatic seeding with the WASPTM system (ADA) followed by biochemical identification of isolated colonies and antimicrobial sensitivity test with MicroScan system (Siemens). Antimicrobial susceptibility was tested with MicroScan system and defined according to the EUCAST breakpoint definitions (http://www.eucast.org).

After identification of CR-Kp carriers with weekly rectal swabs, the multi-step intervention strategy included oral gentamicin (GO) within 20 days before HSCT in the best window of opportunity (no concomitant antibiotic treatment), no levofloxacin prophylaxis of febrile neutropenia, carbapenem-sparing combination therapy for febrile neutropenia with tigecycline 100 mg *bid* and piperacillin-tazobactam at standard dosages and early appropriate therapy covering CR-Kp pathogens for patients with severe sepsis or septic shock (Table 1).

Eight patients were colonized by CR-Kp among 167 patients (4.8%) undergoing allo-HSCT. All patients were given GO (80 mg four times daily) without concomitant systemic antibiotic therapy for a median duration of five days (IQR, 5 to 6 days) and the decontamination rate was 25% (2/8), without any side-effect or any resistance to gentamicin. Three patients did not have full adherence to the Turin bundle due to penicillin allergies, febrile episodes before or after transplantation that were treated with piperacillin/tazobactam or meropenem, respectively, plus 100 mg *bid* tigecycline for a median duration of seven days. Of the remaining five patients, listed in Table 2, one patient did not have febrile neutropenia; four patients were persistently colonized after GO decontamination and all had febrile neutropenia after a median of seven days (IRQ, 5.5 to 9.8 days) by HSCT (Table 2). Two patients had positive blood cultures for CR-Kp and treatment was switched to colistin, tygecicline and meropenem after initial empiric treatment with tigecycline and piperacillin-tazobactam. There were no deaths at 6-month follow-up and three patients had persistently negative rectal swabs (Table 2).

CR-Kp infections are a major concern especially in haematological patients (Girmenia et al., 2015). Data from the literature underline the need of non-conventional agents for treatment of CR-Kp infections guided by *in vitro* susceptibility data, and a better outcome was associated with combination therapy (Tumbarello et al., 2015). Several approaches have been proposed to reduce endogenous source in colonized patients with contrasting results (Tascini et al., 2014; Lubbert et al., 2013). Moreover, data from the literature attempting to manage febrile neutropenia in an endemic setting for MDR bacteria showed that tigecycline plus piperacillin/tazobactam was associated with

a lower number of bacteremia-related early deaths (Bucaneve et al.2014). As described by Bucaneve et al., the combination of piperacillin/tazobactam and tigecycline was safe, well tolerated, and effective in febrile high-risk haematologic patients, highlighting the role that this combination therapy might have as a first line empiric therapy in epidemiologic settings characterized by a high prevalence of infections due to MDR microorganisms (Bucaneve et al., 2014).

To our knowledge, this is the first report of a multiple-step intervention in patients colonized by CR-Kp undergoing HSCT. In our small series all patients survived, no resistance to oral gentamicin was observed and 60% of patients had persistently negative rectal swabs after transplant. A main issue regarding the effectiveness of strategies of eradication is the role of negative rectal swabs that may reflect only a reduction of colonization burden rather than a true decolonization.

A successful bundle deserves special consideration to reduce the burden of CR-Kp infections in immunocompromised patients, integrating early identification of rectal carriers, GO in the best available window of opportunity, avoidance of levofloxacin prophylaxis and pursuing appropriate antibiotic management of febrile neutropenia or early appropriate combination treatment for patients with severe sepsis or septic shock.

We believe that an integrated treatment strategy may be implemented for all haematological patients colonized by CR-Kp including a decolonization strategy without concomitant antibiotic treatment, because even a reduction of the amount of gut colonization, best achieved before transplant, may be of enormous benefit in reducing the possibility of haematogeneous dissemination of CR-Kp.

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Table 1. The "Turin bundle": Multi-step intervention for CR-Kp carriers in A haematological setting.

Intervention	Therapeutic window	Comment
Gentamicin *per os*	Before allo-HSCT	Reduction of CR-Kp enteric burden
NO levofloxacin prophylaxis	Neutropenia	Avoid further gastrointestinal dismicrobism
Tigecycline 100 mg q12h + piperacillin/tazobactam 4.5 mg q6-8h	Febrile neutropenia	Carbapenem sparing strategy
Colistin 9 MU then 4.5 MU q12h + tigecycline 100 mg q12h + meropenem 2 gr q8h	Severe sepsis/Septic shock	Timely appropriate empiric treatment Other regimens have been suggested according to known strain susceptibilities (Bassetti et al., 2016)

Table 2. Characteristics, treatment and outcomes of patients following the "Turin Bundle".
M= male; F=female; LAM= myeloid acute leukemia; LLA B= acute lymphoblastic leukemia B; GO= oral gentamicin; += positive; -= negative; S=susceptible

Patient	Age & gender	Diagnosis	Duration GO (days)	Rectal swabs after GO	Gentamicin MIC pre / after GO	Follow-up rectal swabs	Neutro-penia febrile	Severe sepsis / septic shock	Clinical Outcomes
1	58, M	LAM	6	+	S / S	-	Yes	No	Alive
2	58, M	LAM	5	+	S / S	-	Yes	No	Alive
3	44, M	LLA B	10	+	S / S	+	Yes	No	Alive
4	54, M	LAM	7	+	S / S	+	Yes	No	Alive
5	55, F	LAM	5	-	S / S	-	No	No	Alive