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MAJOR ARTICLE

Targeted peri-operative prophylaxis in patients colonized with Carbapenem Resistant Enterobacterales undergoing Liver Transplantation: a multinational cohort study

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Background. Targeted perioperative prophylaxis (T-PAP) has been proposed to mitigate the impact of Carbapenem-Resistant Enterobacterales (CRE) infections in patients colonized with CRE who are undergoing liver transplantation (LT). This study aims to investigate the impact of T-PAP versus standard perioperative prophylaxis (S-PAP) in preventing CRE infections.

Methods. Observational, multinational cohort study of adults with CRE colonization at LT. The endpoints were CRE infection within 15 and 30 days after LT. Exposure was T-PAP defined as the use of agents with *in vitro* activity against the colonizing strain. T-PAP was differentiated into T-PAP with old drugs (T-PAPold) and T-PAP with novel drugs (T-PAPnew) according to the regimens used. T-PAPnew included patients exposed to new betalactam/betalactamse inhibitors (BL/BLIs) or cefiderocol. Treatment-effect models with augmented inverse probability weighting were employed to assess the average treatment effect (ATE) of T-PAPold and T-PAPnew versus S-PAP on CRE infection.

Results. A total of 408 CRE pre-transplant carriers were included. T-PAPold was administered to 112 patients (27.5%), and T-PAPnew was administered to 28 patients (6.9%). Post-transplant CRE infection at 15 and 30 days occurred in 87 (21.4%) and 106 (26.0%) patients, respectively. The ATE of T-PAPnew at 15 and 30 days post-transplant was -0.146 (p=0.002) and -0.056 (p=0.320), respectively. The ATE of TPAPold at 15 and 30 days post-transplant was 0.003 (p=0.941) and -0.005 (p=0.897) respectively.

Conclusions. The protective effect of T-PAPnew in preventing CRE infections is significant within the first 15 days, but its effectiveness decreases within the first month.

Keywords: CRE, targeted perioperative antibiotic prophylaxis, liver transplant

INTRODUCTION

Carbapenem-resistant Enterobacterales (CRE) colonization is one of the main risk factors for further developing CRE infection (1,2). Among solid organ transplant recipients, those undergoing liver transplantation (LT) are at highest risk of CRE colonization and infection, considering complexity of surgery, previous exposure to broad-spectrum antibiotics, and need of immunosuppressive treatments (3). A recent meta-analysis reported an increased risk of 1-year mortality after solid organ transplantation (SOT) in patients colonized with multidrug resistant organisms (MDRO) and this risk was highest for subgroups of CRE carriers and patients undergoing LT (4). The link between carriage and death seems to be an increased risk of CRE infection after transplantation as shown in the same metanalysis (4). For these reasons, transplant centers are advocating for robust recommendations and novel approaches capable of reducing the impact of CRE carriage on post-transplant outcome. In LT candidates colonized with CRE, gut decolonization and targeted perioperative antibiotic prophylaxis have been proposed to reduce the risk of CRE infection after LT. However, selective decolonization strategies in this specific setting failed to demonstrate a real benefit, and the role of targeted peri-operative antibiotic prophylaxis (T-PAP) remains controversial (5,6). To date, none of available studies specifically focused on the impact of T-PAP in LT recipients colonized with CRE before transplant, and the existing evidence is based on T-PAP based on old drugs (T-PAPold) with *in vitro* activity (e.g. aminoglycosides) but with recognized PK/PD limitations (7). With this assumption, we conducted this study to explore the relationship between different regimens of prophylaxis and the risk of developing CRE infection after LT in patients with CRE colonization at transplant.

MATERIALS AND METHODS

Study design, population & setting

The present study is part of the CRECOOLT project (NCT05594901) a large multinational cohort of adult (≥18 years) patients who underwent LT from January 2010 to October 2024, and were found to be colonized with CRE within 60 days before or after transplant. Follow-up was of 180 days after LT. As the aim of this study was to investigate the relationship between peri-operative antibiotic prophylaxis and the risk of developing CRE infection within 15 or 30 days after LT, only patients with CRE colonization at LT were analyzed.

The study was first approved by the institutional review board of the promoting center (n. 697/2022/Oss/AOUBo), then by the institutional review boards of all participating centers. Informed consent to participate in the study was obtained contacting patients via email or phone

call. In case of deceased or unreachable patients, the informed consent was waived considering the observational nature of the study.

Eighteen hospitals performing LT participated in the study: 9 from Italy (2 centers in Milan, Bologna, Modena, Turin, Padua, Genoa, Palermo, and Udine); 6 from Brazil (3 in Rio de Janeiro, 2 in São Paulo, and Fortaleza); 2 from Spain (Madrid and Majadahonda); and 1 from Israel (PetahTikva). An active surveillance screening for CRE colonization was required by the study protocol. All centers performed systematic screening of CRE carriage by rectal swab at inclusion in waiting list, at LT, and weekly after LT until hospital discharge. Screening of CRE colonization in sites other than gastrointestinal tract was requested by attending physician and was not dictated by the study protocol. Patients receiving prolonged prophylaxis >48 hours were excluded.

Data sources were clinical charts and hospital electronic records, they were deidentified before entry into a standardized electronic case report form and managed using REDCap capture tool hosted by Alma Mater University of Bologna. Collected data were periodically checked for accuracy by an investigator of the coordinating center. Queries for incongruous or missing data were submitted to investigators to ensure high quality and completeness.

Study definitions & endpoint variables

CRE was defined as any *Enterobacterales* displaying *in vitro* nonsusceptibility to any of the carbapenems according to the criteria (Clinical and Laboratory Standards Institute or European Committee on Antimicrobial Susceptibility Testing) adopted at the participating center during the study period. The colonization status was defined as isolation of CRE from rectal swab or other samples other than blood cultures or sterile fluids (e.g., urine, respiratory samples, superficial skin samples) in absence of symptoms and/or signs of infection. The identification of the carbapenem resistance mechanism was performed in all centers using selective culture media complemented by nucleic acid amplification tests (NAAT). Multisite colonization was defined when CRE was concomitantly isolated from more than one sample.

The primary endpoint was CRE infection within 15 days from LT, defined as/or according to Centers for Disease Control and Prevention criteria (8). The secondary endpoint was CRE infection, defined as above, within 30 days after LT. The assessment of CRE infection was made by the local investigator and revised by an investigator of the promoting center, in case of no agreement a third investigator of the promoting center was asked to review the case for establishing the final diagnosis.

The main exposure variable was perioperative antibiotic prophylaxis (PAP) defined as standard-PAP (S-PAP) consisting of regimens with no *in vitro* activity against CRE. S-PAP protocol varied across participating centers, 12 (66.7%) used beta-lactam/beta-lactamase inhibitors primarily ampicillin/sulbactam (6 centers), piperacillin/tazobactam (3 centers), and amoxicillin/clavulanate (3 centers). The remaining centers utilized either ampicillin plus cefotaxime (3 centers) or cefazolin (3 centers). PAP including drugs with *in vitro* activity against CRE was defined as

targeted-PAP (T-PAP). This group was further differentiated according to the type of antibiotic regimen used: old (*e.g.* regimens including colistin, tigecycline, amikacin or high-dose meropenem, either alone or in combination) versus novel (T-PAPnew) (*e.g.* ceftazidime-avibactam ± aztreonam, meropenem-vaborbactam or cefiderocol). Other exposure collected variables included: demographic data (age and sex); comorbidities according to Charlson Comorbidity index (CCI); underlying liver disease, and severity of liver disease according to MELD at inclusion in waiting list and at LT. In addition, data about CRE colonization status were collected. For secondary endpoint, CRE infection within 30-day from LT, also complications after LT such as AKI, need of continuous renal replacement therapy (CRRT), prolonged mechanical ventilation and rejection were considered.

Statistical analysis

Categorical variables were expressed as absolute numbers and their relative frequencies. Continuous variables were expressed as mean ± standard deviation if normally distributed, or as median and interquartile range (IQR) if non-normally distributed and for variables reporting durations. Clinical characteristics were compared between type of prophylaxis (S-PAP, T-PAPold, T-PAPnew) and presence of CRE infection at 15 and at 30 days with bivariate analyses.

We used treatment-effects models with the augmented inverse probability weighting (AIPW) estimator to analyze the relationship between the type of prophylaxis and CRE infection. Treatment-effects models with AIPW entail three different steps: 1) treatment-effect models apply the counterfactual framework, mimicking randomization with observational data; 2) separate regression models of the outcome are estimated for each treatment level (outcome models); 3) inverse probability weights, which correct for the conditional probability of treatment, are calculated by a treatment model and applied to the treatment-specific predicted outcomes (11, 12). In our analysis, the treatment model was a multinomial logit, to accommodate for the three different regimens. We used the same treatment model for both endpoints of 15- and 30-day CRE infection, which included the following baseline variables: patient age, underlying liver disease (metabolic, HCC, or HCV), Charlson Comorbidity Index (CCI), MELD score, time in days from colonization to OLT, presence of multisite colonization, and presence of the KPC strain. These variables were selected based on established clinical practice criteria and evidence of a relationship with treatment from bivariate analysis. The outcome model was a logit regression with a weighted non-linear least squares estimator. The logit model of 15-day CRE infection included only IPW-corrected treatment (S-PAP, T-PAPold, T-PAPnew) as predictor. The logit model of 30-day CRE infection included IPW-corrected treatment and the binary indicators of surgical reintervention, prolonged mechanical ventilation (>48 hours), and the need for renal replacement therapy. The comparability of baseline characteristics in the weighted groups was assessed by checking the weighted distribution of treatment, the standardized differences of weighted means and the weighted variance ratio of all covariates. A complete case analysis was carried out if the missing data in the models did not exceed 5% of the study population. In all multivariable models, robust standard errors were obtained accounting for patients' clustering into the 29 centers. All analyses

were carried out using Stata v.19.5, specifically the teffects aipw command was used for the treatment-effect analysis with inverse probability weighting.

RESULTS

A total of 408 LT recipients colonized with CRE before transplantation were enrolled. The characteristics of the study population are shown in **Table 1**. Median age was 54 (IQR 45-62) years and 63.6% were male. Alcoholic cirrhosis and viral hepatitis were the primary indications for LT in 121 (29.7%) and 120 (29.4%) cases, respectively. A total of 69 (16.9%) patients had hepatocellular carcinoma (HCC). The median CCI was 5 (IQR 3-7). MELD score at waiting list inclusion and at LT was 21 (IQR 15-27) and 25 (IQR 18-32), respectively. The median time from CRE colonization to LT was 11 (IQR 1-36) days. The all-cause mortality rate at 180 days was 26.3%, with a median time from LT of 32 (IQR 10-66) days.

As for peri-operative prophylaxis, 268 (65.7%) patients were managed with S-PAP, 112 (27.5%) with T-PAPold, and 28 (6.9%) with T-PAPnew. The use of T-PAP increased over the study period from 25.1% in 2010-2017 to 43.5% in 2018-2024. The use of novel drugs was introduced in the second period. Fifteen-day CRE infection rates according to prophylaxis regimen and study periods are shown in **Figure 1**.

Of the 112 patients who received the T-PAPold, data about the specific regimen adopted was available for 61/112 patients (54.5%). Of these, 44 patients received an aminoglycoside-based regimen, 14 patients received a tigecycline-based regimen, and 3 patients received a colistin-based regimen. For the T-PAPnew, 21 patients received ceftazidime/avibactam, 6 patients received meropenem/vaborbactam, and 1 patient received cefiderocol. The main characteristics of patients according to type of prophylaxis are shown in **Table 1.**

Risk factors for CRE infection within 15-day after LT

Overall, 87 patients (21.4%) developed CRE infection within 15 days from LT, with a median time form LT to CRE infection of 6 (IQR 2-10) days. Detailed information on the sites of CRE infection can be found in **Table 2**. Crude incidence rates by type of PAP were 20.9% in SPAP (56/268), 25.9% for TPAPold (29/112), 7.1% for TPAPnew (2/28). The comparison of patients with vs. those without CRE infection within 15 days after LT showed significant differences for HCC (9.1% vs. 19.1%, p=0.027), median MELD at transplant (29 vs. 24, p<0.001), induction with basiliximab (26.1% vs. 40.6%, p=0.004), maintenance with prednisone (85.1% vs. 68.2%, p<0.001), respiratory colonization (6.9% vs. 1.2%, p=0.003) and KPC as mechanism of resistance (79.5% vs. 66.2%, p=0.017). A trend toward statistical significance was observed for TPAPnew (2.3% vs. 8.1%; p=0.058). Finally, LT recipients with CRE infection showed an increased length of ICU (15 vs. 6 days, p<0.001) and hospital stay (30 vs. 21 days, p=0.014), as well as higher 180-day mortality (50.6% vs. 19.6%, p<0.001) (see **Suppl. Table 1**).

The treatment-effect analysis with AIPW was carried out on 394 patients with complete data (**Table 3**); overall the missingness rate was 3.4%, with 1/28 (3.6%) missing in the TAPnew group, therefore no data imputation was applied. The potential outcome mean (POM) of S-PAP was 0.214 (95% CI: 0.155 to 0.273), the average treatment effect (ATE) of TAPold was 0.003 (95% CI: -0.069 to 0.075, p=0.941), the ATE of TAPnew was -0.146 (95% CI: -0.238 to -0.054, p=0.002). These results indicate that if all patients were treated with S-PAP 21.4% of them would be expected to become infected within 15 days, while if all patients were treated with TAPnew this proportion would be reduced by 14.6% and if all patients were treated with TAPold the infection rate would be substantially the same as if they were treated with S-PAP. Covariate balance after weighting is displayed in **Suppl. Tables 2, 3 and 4**: the AIPW estimator balanced most of the covariates, except for MELD score and time from colonization to OLT, that in the TAPnew group showed either a standardized mean not close to 0 or a variance ratio not close to 1. All the details of the AIPW model are given in **Suppl. Table 5**.

Risk factors for 30-day CRE infection after LT

Overall, 106 (26.0%) LT recipients developed CRE infection within 30-day after LT (**Suppl. Table 6**). Crude incidence rates by type of PAP were 24.6% in SPAP (66/268), 31.3% for TPAPold (35/112), 17.9% for TPAPnew (5/28). Conditions associated with 30-day CRE infection were MELD at LT (29 vs. 24, p<0.001), bolus of steroid as induction regimen (85.8% vs. 74.5%, p=0.015) and steroids as maintenance regimen (84.9% vs. 67.2%, p<0.001), as well as multisite colonization (21.7% vs. 13.6%, p=0.048) and KPC-producing strain (79.2% vs. 65.6%, p=0.010). Considering post-LT complications, acute renal failure (72.6% vs. 41.4%, p<0.001), the need of CRRT (61.3% vs. 26.5%, p<0.001), prolonged mechanical ventilation (45.3% vs. 17.9%, p<0.001) and re-intervention (43.4% vs. 26.2%, p=0.001) were more frequently observed in patient with CRE infection.

In **Table 3** we show that the POM of S-PAP was 0.258 (95% CI: 0.186 to 0.331), the ATE of TAPold was -0.005 (95% CI: -0.074 to 0.064, p=0.897), the ATE of TAPnew was -0.056 (95% CI: -0.165 to 0.054, p=0.320). Among the three post-transplant candidate predictors of the outcome, mechanical ventilation for more than 48 hours was removed because it did not allow the model to converge. These results indicate that if all patients were treated with S-PAP 25.8% of them would be expected to become infected within 30 days, while if all patients were treated with TAPnew this proportion would be reduced by 5.6% and if all patients were treated with TAPold there would be no substantial difference in the infection rate. Covariate balance after weighting is provided in **Suppl. Tables 2, 3 and 4**. All the details of the AIPW model are given in **Suppl. Table 7**.

DISCUSSION

In this multicenter international study conducted among LT recipients colonized with CRE before transplantation, we found that T-PAP using novel drugs active against CRE appears to play a protective role in reducing the risk of developing CRE infection within 15 days after LT, while T-PAP using old regimens for CRE do not. We further observed that the protective effect of T-PAP with novel drugs diminishes over a longer observation period, during which post-LT complications such as the need of CRRT and reintervention play a role in infection development.

Although the SOT population generally exhibits better survival following Gram-negative bacteremia compared to patients with hematological malignancies or solid tumors (9,10), CRE infection after LT nonetheless demonstrated a dramatic impact on patient survival in our cohort. Specifically, mortality rates among infected patients reached 50.6%, significantly higher than the 19.6% observed in those colonized but who did not develop post-transplant CRE infection. This excess of mortality aligns with findings from previous studies (11,12). Of consequence, several strategies have been proposed to mitigate such risk, including active screening, selective decolonization and T-PAP (2).

As endorsed by the European guidelines, active screening for CRE carriage before LT is strongly recommended, as it allows to identify patients at risk of subsequent CRE infection (13). As for targeted prophylaxis, the same document endorsed it in patients colonized with extended spectrum cephalosporin resistant strains despite the limited and low-quality evidence supporting such an approach, while no recommendation was done for CRE colonized patients due to the lack of studies (13). Nevertheless, T-PAP is gaining more and more interest, as highlighted in a recent survey conducted among 55 respondents from 14 countries (14), where for LT candidates colonized with CRE a T-PAP approach was preferred by 58% of responders with the majority also considering the use of novel drugs. However, studies assessing the use of these drugs as for targeted prophylaxis have to be reported yet. Indeed, available studies focused on CRE-colonized LT candidates described T-PAP strategies with older regimens. The largest study conducted among LT recipients showed an independent protective effect of targeted surgical prophylaxis based on amikacin and ampicillin in patients at risk for MDRO colonization/infection (7). On the other hand, a multinational study conducted by the CRECOOLT group, where T-PAP was administered in 26% of 203 CRE-colonized LT recipients, found no significant difference between the T-PAP and S-PAP groups (12). In the present study, we confirmed that managing LT candidates with an old regimen-based T-PAP did not reduce the infection risk after transplant. Instead, despite a limited sample size, we observed a potential protective effect of T-PAP with new drugs in CRE infection development within 15-day after LT.

However, the potential benefit of T-PAP seems to diminish over time. Post-LT complications, such as CRRT and prolonged mechanical ventilation, significantly impact the CRE infection risk within the first month post-transplant. Our findings are aligned with previous data on this topic (15–17) and the final question remains if "Should programs expand prophylaxis regimen to cover

more resistant organisms, or should they reserve broader spectrum agents to treat infections as they arise?" (18). This issue is crucial from an ecological point of view (19). In this regard, among the 5/28 LT recipients managed with TPAPnew who developed a CRE infection within 30 days post-LT, none of the clinical isolates obtained after prophylaxis showed new resistance to the agent administered. In one case, the ceftazidime/avibactam MIC (administered as T-PAP) increased from 2 to 4 mg/L.

However, it is important to note that the majority of CRE infections developed with a median onset of 6 days after transplantation. Thus, T-PAP with novel regimens could play a role in preventing CRE infection in those patients at highest risk for early post-transplant infection as those with higher MELD and high colonization burden (e.g. positive respiratory samples). Indeed, these variables were associated with increased risk of early CRE infection in our multivariable model adjusted for unbalances between prophylaxis groups.

The current research has intrinsic limitations due to its observational design. Nonetheless, a data quality check was performed from the coordinating center, and queries were raised in case of discordant or inconclusive data. Unfortunately, data for only 54.5% of T-PAP regimens involving old drugs were available. Furthermore, multisite colonization, especially in the lower respiratory tract, was not routinely assessed, potentially leading to the selection of a more severe patient group. The TPAPnew group was quite small, and despite our efforts to control for confounding factors, the treatment-effect model failed to perfectly balance the MELD score and time to colonization. This may have left potential bias in our results uneliminated, therefore conclusions about the real impact of T-PAP with new drugs should be taken with precaution. In addition, we did not explore the potential impact of different PAP regimens on preventing other non-CRE infections. To minimize center-related biases, we adjusted multivariable analysis for centers and main variables potentially associated with increased risk of infection, but some unrecognized factors could have occurred.

In conclusion, LT candidates colonized with CRE and presenting with a higher MELD score and respiratory colonization were found to be at the highest risk of early CRE infection after transplant. T-PAP involving novel drugs appears to be a reliable intervention to mitigate this risk within the first two weeks post-LT, while its effect within the first month seems to be reduced. In addition, the overall impact of prophylaxis strategies should be evaluated also in terms of early non-CRE infections to provide a more comprehensive assessment of infectious outcomes after LT. Future clinical trials specifically focused on this topic are strongly needed.

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The other authors declare no conflict of interest related to the content of this manuscript.

DATA AVAILABILITY STATEMENT: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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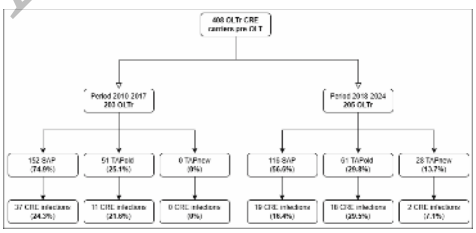
Figure 1. Rates of perioperative antibiotic prophylaxis and relative 15-day CRE infections in the two periods.



REFERENCES

1. Pérez-Galera S, Bravo-Ferrer JM, Paniagua M, Kostyanev T, Kraker MEA de, Feifel J, et al. Risk factors for infections caused by carbapenem-resistant Enterobacterales: an international matched case-control-control study (EURECA). eClinicalMedicine [Internet]. 2023 Mar 1 [cited 2025 Jun 30];57. Available from: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(23)00048-2/fulltext
2. Giannella M, Bartoletti M, Campoli C, Rinaldi M, Coladonato S, Pascale R, et al. The impact of carbapenemase-producing Enterobacteriaceae colonization on infection risk after liver transplantation: a prospective observational cohort study. Clin Microbiol Infect. 2019 Dec;25(12):1525–31.
3. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med. 2007 Dec 20;357(25):2601–14.
4. Almohaya A, Fersovich J, Weyant RB, Fernández García OA, Campbell SM, Doucette K, et al. The impact of colonization by multidrug resistant bacteria on graft survival, risk of infection, and mortality in recipients of solid organ transplant: systematic review and meta-analysis. Clin Microbiol Infect. 2024 Oct;30(10):1228–43.
5. Fariñas MC, González-Rico C, Fernández-Martínez M, Fortún J, Escudero-Sanchez R, Moreno A, et al. Oral decontamination with colistin plus neomycin in solid organ transplant recipients colonized by multidrug-resistant Enterobacterales: a multicentre, randomized, controlled, open-label, parallel-group clinical trial. Clin Microbiol Infect. 2021 Jun;27(6):856–63.
6. Righi E, Mutters NT, Guirao X, Dolores Del Toro M, Eckmann C, Friedrich AW, et al. ESCMID/EUCIC clinical practice guidelines on perioperative antibiotic prophylaxis in patients colonized by multidrug-resistant Gram-negative bacteria before surgery. Clin Microbiol Infect. 2022 Dec 22;S1198-743X(22)00632-2.
7. Freire MP, Song ATW, Oshiro ICV, Andraus W, D'Albuquerque LAC, Abdala E. Surgical site infection after liver transplantation in the era of multidrug-resistant bacteria: what new risks should be considered? Diagn Microbiol Infect Dis. 2021 Jan;99(1):115220.
8. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008 Jun;36(5):309–32.
9. Toschi A, Pascale R, Gibertoni D, Pasquali R, Grechi A, Grassi I, et al. Epidemiological characteristics and management of Gram-negative bacteraemia in different immunocompromised hosts: Observational single-center study. PLoS One. 2025;20(7):e0327535.
10. Boutzoukas AE, Dai W, Cober E, Abbo LM, Komarow L, Chen L, et al. Carbapenem-resistant Enterobacterales in solid organ transplant recipients. American Journal of Transplantation. 2025 Apr 1;25(4):848–59.
11. Anesi JA, Lautenbach E, Thom KA, Tamma PD, Blumberg EA, Alby K, et al. Clinical Outcomes and Risk Factors for Carbapenem-resistant Enterobacterales Bloodstream Infection in Solid Organ Transplant Recipients. Transplantation. 2023 Jan 1;107(1):254–63.
12. Giannella M, Freire M, Rinaldi M, Abdala E, Rubin A, Mularoni A, et al. Development of a Risk Prediction Model for Carbapenem-resistant Enterobacteriaceae Infection After Liver Transplantation: A Multinational Cohort Study. Clinical Infectious Diseases. 2021 Aug 15;73(4):e955–66.

13. Aguado JM, Silva JT, Fernández-Ruiz M, Cordero E, Fortún J, Gudiol C, et al. Management of multidrug resistant Gram-negative bacilli infections in solid organ transplant recipients: SET/GESITRA-SEIMC/REIPI recommendations. Transplant Rev (Orlando). 2018 Jan;32(1):36–57.
14. Bonazzetti C, Rinaldi M, Cosentino F, Gatti M, Freire MP, Mularoni A, et al. Survey on the approach to antibiotic prophylaxis in liver and kidney transplant recipients colonized with 'difficult to treat' Gram-negative bacteria. Transpl Infect Dis. 2024 Apr;26(2):e14238.
15. Chen Y, Wang W li, Zhang W, Zhang Y tao, Tang S xiao, Wu P ping, et al. Risk Factors and Outcomes of Carbapenem-Resistant Enterobacteriaceae Infection After Liver Transplantation: A Retrospective Study in a Chinese Population. Infect Drug Resist. 2020 Nov 10;13:4039–45.
16. Freire MP, Oshiro ICVS, Pierrotti LC, Bonazzi PR, de Oliveira LM, Song ATW, et al. Carbapenem-Resistant Enterobacteriaceae Acquired Before Liver Transplantation: Impact on Recipient Outcomes. Transplantation. 2017 Apr;101(4):811–20.
17. Rinaldi M, Bonazzetti C, Gallo M, Ferraro G, Freire M, Terrabuio DRB, et al. Validation of the INCREMENT-SOT-CPE score in a large cohort of liver transplant recipients with carbapenem-resistant Enterobacterales infection. Transplant Infectious Disease [Internet]. 2023;25(2). Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85149382709&doi=10.1111%2ftid.14036&partnerID=40&md5=e867b4ac749175224c439f69a81c4573
18. Viehman JA, Clancy CJ, Clarke L, Shields RK, Silveira FP, Kwak EJ, et al. Surgical Site Infections After Liver Transplantation: Emergence of Multidrug-Resistant Bacteria and Implications for Prophylaxis and Treatment Strategies. Transplantation. 2016 Oct;100(10):2107–14.
19. Sucu S, Basarir KE, Mihaylov P, Balik E, Lee JTC, Fridell JA, et al. Impact of gut microbiota on liver transplantation. Am J Transplant. 2023 Oct;23(10):1485–95.

ALT TEXT (Figure 1): Flowchart of the study population involving 408 OLT recipients who were CRE carriers pre-transplant. The diagram illustrates the distribution of patients into two time periods (2010-2017 and 2018-2024) and their subsequent stratification into three prophylaxis groups (SAP, TAPold, and TAPnew), showing the respective CRE infection rates for each group.

Table 1. Comparison of CRE colonized liver transplant recipients according to the type of prophylaxis

	S-PAP (N=268, 65.7%)	**T-PAPold (N=112, 27.5%)**	**T-PAPnew (N=28, 6.9%)**	**Total N=408 (100%)**	**p-value**
Demographic data					
Age (years) (median, IQR)	54 (45-61)	53 (45-59)	58 (43-65)	54 (45-61)	0.226
Sex, male	170 (63.7)	72 (64.3)	17 (60.7)	259 (63.6)	0.940
Period of enrolment					<0.001
2010-17	152 (56.7)	51 (45.5)	0 (0)	203 (49.7)	
2018-24	116 (43.3)	61 (54.5)	28 (100)	205 (50.3)	

Comorbidities					
CCI (median, IQR)	5 (3-6)	5 (4-7)	5 (4-7)	5 (3-7)	0.074
Underlying liver disease					
Viral hepatitis	90 (33.6)	21 (18.8)	9 (32.1)	120 (29.4)	0.014
Alcoholic cirrhosis	76 (28.4)	37 (33.0)	8 (28.6)	121 (29.7)	0.655
Metabolic disease	25 (9.3)	19 (17.0)	6 (21.4)	50 (12.3)	0.036
Autoimmune disease	25 (9.3)	10 (8.9)	4 (14.3)	39 (9.6)	0.673
Fulminant hepatitis	6 (2.2)	5 (4.5)	0 (0)	11 (2.7)	0.313
Prior LT	22 (8.2)	9 (8.0)	6 (21.4)	37 (9.1)	0.062
HCC	54 (20.1)	12 (10.7)	3 (10.7)	69 (16.9)	0.054
MELD at inclusion list (median, IQR)	21 (15-27)	20 (16-27)	20 (14-26)	21 (15-27)	0.727
Time from inclusion in list to LT (median, IQR) (days)	63 (12-229)	68 (17-177)	30 (7-114)	57 (13-192)	0.203
Information about transplant					
MELD at LT (median, IQR)	23 (17-30)	29 (22-34)	24 (19-29)	25 (18-32)	<0.001
Combined transplant	11 (4.1)	7 (6.3)	1 (3.6)	19 (4.7)	0.630
Coledoco-jejunal anastomosis	49 (18.3)	19 (17.0)	8 (28.6)	76 (18.6)	0.358
Prolonged surgery	83 (31.4)	37 (33.0)	9 (32.1)	129 (31.9)	0.955
Intraoperative bleeding	90 (34.6)	32 (28.6)	8 (32.0)	130 (32.7)	0.521
Donor age (years) (median, IQR)	55 (41-68)	43 (32-56)	61 (53-78)	52 (37-66)	<0.001
Induction regimen					
Bolus of steroids	187 (69.8)	105 (93.8)	24 (85.7)	316 (77.5)	<0.001
ATG	4 (1.5)	1 (0.9)	1 (3.6)	6 (1.5)	0.574
Basiliximab	95 (35.4)	42 (37.5)	16 (57.1)	153 (37.5)	0.078
Maintenance regimen					
Prednisone	179 (66.8)	98 (87.5)	16 (57.1)	293 (71.8)	<0.001
Tacrolimus	246 (91.8)	103 (92.0)	26 (92.9)	375 (91.9)	0.981
Cyclosporine	9 (3.4)	1 (0.9)	1 (3.6)	11 (2.7)	0.383
MMF	101 (37.7)	47 (42.0)	7 (25.0)	155 (38.0)	0.251
CRE colonization					
Rectal swab	251 (93.7)	102 (91.1)	28 (100)	381 (93.4)	0.225
Respiratory sample	8 (3.0)	2 (1.8)	0 (0)	10 (2.5)	0.540
Urinary tract	24 (9.0)	22 (19.6)	5 (17.9)	51 (12.5)	0.011
Multisite colonization	30 (11.2)	28 (25.0)	6 (21.4)	64 (15.7)	0.002
Time from CRE colonization to LT (days) (median, IQR)	7 (0-29)	15.5 (5-40)	29 (13-71)	11 (1-36)	<0.001
KPC	198 (73.9)	67 (59.8)	17 (60.7)	282 (69.1)	0.016
OXA-48	13 (4.9)	5 (4.5)	4 (14.3)	22 (5.4)	0.117
NDM	3 (1.1)	5 (4.5)	5 (17.9)	13 (3.2)	<0.001
VIM	5 (1.9)	3 (2.7)	1 (3.6)	9 (2.2)	0.778
Post-LT complications					
Acute renal failure	116 (43.3)	74 (66.1)	12 (42.9)	202 (49.5)	<0.001

Need of CRRT	93 (34.7)	45 (40.2)	7 (25.0)	145 (35.5)	0.288
Mechanical ventilation >48h	68 (25.4)	26 (23.2)	8 (28.6)	102 (25.0)	0.818
PGNF	21 (7.8)	18 (16.1)	3 (10.7)	42 (10.3)	0.055
Re-intervention	80 (29.9)	38 (33.9)	7 (25.0)	125 (25.7)	0.586
Re-LT	9 (3.4)	7 (6.3)	4 (14.3)	20 (4.9)	0.029
Biopsy proven rejection	25 (9.3)	6 (5.4)	2 (7.1)	33 (8.1)	0.425
CMV disease	50 (18.7)	23 (20.5)	5 (17.9)	78 (19.1)	0.900
Outcomes					
15-day CRE infection	56 (20.9)	29 (25.9)	2 (7.1)	87 (21.3)	0.085
30-day CRE infection	66 (24.6)	35 (31.3)	5 (17.9)	106 (26.0)	0.243
Time from LT to CRE infection (days) (median, IQR)	8 (4-17)	8.5 (3-19.5)	18 (12-21)	11 (1-34)	0.546
LOS (days) (median, IQR)	22 (13-40)	23 (13-36)	21.5 (13-47.5)	22 (13-39)	0.959
LIS (days) (median, IQR)	6 (3-14)	8 (5-24)	5 (3-10)	7 (3-17)	0.037
15-day all-cause death	23 (8.6)	15 (13.4)	0 (0)	38 (9.3)	0.059
30-day all-cause death	32 (11.9)	20 (17.9)	0 (0)	52 (12.7)	0.021
180-day all-cause death	69 (26.4)	32 (28.8)	4 (14.8)	105 (26.3)	0.332
Time from LT to death (days) (median, IQR)	36 (11-73)	20 (7-58)	49.5 (44-70.5)	32 (10-66)	0.187

Abbreviations: S-PAP standard antibiotic prophylaxis, T-PAPold targeted antibiotic prophylaxis with old regimens, T-PAPnew targeted antibiotic prophylaxis with novel regimens, IQR interquartile range, CRE Carbapenem-resistant Enterobacterales, CCI Charlson comorbidity index, LT liver transplant, HCC hepatocellular carcinoma, MELD model for end-stage liver disease, ATG anti-thymocyte globulins, MMF mofetil mycophenolate, PGNF primary graft non function, CRRT continuous renal replacement therapy, CMV cytomegalovirus, LOS length of overall hospital stay, LIS length of ICU stay.

Table 2. Sites of CRE infection within 15- and 30-day according to PAP used.

	S-PAP, (N=268, 65.7%)	**T-PAPold, (N=112, 27.5%)**	**T-PAPnew, (N=28, 6.9%)**	**P-value**
BSI	28 (50)	5 (17.2)	0 (0)	0.007
LRTI	14 (25)	7 (24.1)	0 (0)	0.719
IAI	7 (12.5)	5 (17.2)	2 (100)	0.018
UTI	2 (3.6)	3 (10.3)	0 (0)	0.407
SSI	12 (21.4)	15 (51.7)	0 (0)	0.010
Other	3 (5.4)	1 (3.4)	0 (0)	0.879
Overall: 15-day	**56/268 (20.9)**	**29/112 (25.9)**	**2/28 (7.1)**	
BSI	30 (45.5)	6 (17.1)	0 (0.0)	0.014
LRTI	17 (25.8)	7 (20.0)	1 (20.0)	0.795
IAI	10 (15.2)	6 (17.1)	3 (60.0)	0.062
UTI	3 (4.5)	3 (8.6)	1 (20.0)	0.345

SSI	17 (25.8)	17 (48.6)	0 (0)	0.019
Other	3 (4.5)	3 (8.6)	0 (0)	0.604
Overall: 30-day	**66/268 (24.6)**	**35/112 (31.3)**	**5/28 (17.9)**	

Abbreviations: S-PAP standard antibiotic prophylaxis, T-PAPold targeted antibiotic prophylaxis with old regimens, T-PAPnew targeted antibiotic prophylaxis with novel regimens, BSI bloodstream infection, LRTI lower respiratory tract infection, IAI intra-abdominal infection, UTI urinary tract infection, SSI surgical site infection.

Table 3. Treatment-effect estimation with augmented inverse probability weights for CRE infection within 15 days and within 30 days (n=394).

Variable	coefficient	95%CI	p-value
Infection within 15 days			
ATE T-PAPold vs. S-PAP	0.003	-0.069 to 0.075	0.941
ATE T-PAPnew vs S-PAP	-0.146	-0.238 to -0.054	0.002
POM (S-PAP)	0.214	0.155 to 0.273	<0.001
Infection within 30 days			
ATE T-PAPold vs. S-PAP	-0.005	-0.074 to 0.064	0.897
ATE T-PAPnew vs S-PAP	-0.056	-0.165 to 0.054	0.320
POM (S-PAP)	0.258	0.186 to 0.331	<0.001

Abbreviations: CI=confidence interval, ATE=average treatment effect, POM=potential mean outcome, S-PAP standard peri-operative prophylaxis, T-PAPold targeted antibiotic prophylaxis with old regimens, T-PAPnew targeted antibiotic prophylaxis with novel regimens.