ESCMID/EUCIC clinical practice guidelines on perioperative antibiotic prophylaxis in patients colonized by multidrug-resistant Gram-negative bacteria before surgery

Guidelines

ESCMID/EUCIC clinical practice guidelines on perioperative antibiotic prophylaxis in patients colonized by multidrug-resistant Gram-negative bacteria before surgery

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Abstract

Scope: The aim of the guidelines is to provide recommendations on perioperative antibiotic prophylaxis (PAP) in adult inpatients who are carriers of multidrug-resistant Gram-negative bacteria (MDR-GNB) before surgery.

Methods: These evidence-based guidelines were developed after a systematic review of published studies on PAP targeting the following MDR-GNB: extended-spectrum cephalosporin-resistant Enterobacterales (ESCR-E), carbapenem-resistant Enterobacterales (CRE), aminoglycoside-resistant Enterobacterales, fluoroquinolone-resistant Enterobacterales (FQR-E), cotrimoxazole-resistant *Stenotrophomonas maltophilia*, carbapenem-resistant *Acinetobacter baumannii* (CRAB), extremely drug-resistant *Pseudomonas aeruginosa*, colistin-resistant GNB, and pan-drug-resistant GNB. The critical outcomes were the occurrence of surgical site infections (SSIs) caused by any bacteria and/or by the colonizing MDR-GNB, and SSI-attributable mortality. Important outcomes included the occurrence of any type of postsurgical infectious complication, all-cause mortality, and adverse events of PAP, including development of resistance to targeted (culture-based) PAP after surgery and incidence of *Clostridioides difficile* infections. The last search of all databases was performed until April 30, 2022. The level of evidence and strength of each recommendation were defined according to the GRADE approach. Consensus of a multidisciplinary expert panel was reached for the final list of recommendations. Antimicrobial stewardship considerations were included in the recommendation development.

Recommendations: The guideline panel reviewed the evidence, per bacteria, of the risk of SSIs in patients colonised with MDR-GNB before surgery and critically appraised the existing studies. Significant knowledge gaps were identified, and most questions were addressed by observational studies. Moderate to high risk of bias was identified in the retrieved studies, and the majority of the recommendations were supported by low level of evidence. The panel conditionally recommends rectal screening and targeted PAP for FQR-E before transrectal ultrasound-guided prostate biopsy and for ESCR-E in patients undergoing colorectal surgery and solid organ transplantation. Screening for CRE and CRAB is suggested before transplant surgery after assessment of the local epidemiology. Careful consideration of the laboratory workload and involvement of antimicrobial stewardship teams before implementing the screening procedures or performing changes in PAP are warranted. High-quality prospective studies to assess the impact of PAP among CRE and CRAB carriers performing high-risk surgeries are advocated. Future well-designed clinical trials should assess the effectiveness of targeted PAP, including the monitoring of MDR-GNB colonization through postoperative cultures using EUCAST clinical breakpoints.

Keywords

Multidrug-resistant Gram-negative bacteria

Perioperative antibiotic prophylaxis

Rectal colonization

Surgical site infections

ESCMID

GRADE

Scope and context

The World Health Organization (WHO) has defined, among multidrug-resistant Gram-negative bacteria (MDR-GNB), carbapenem-resistant *Acinetobacter baumannii* (CRAB), CR *Pseudomonas aeruginosa* (CRPA), CR Enterobacterales (CRE) such as *Klebsiella pneumoniae* (CRKP) as well as extended-spectrum cephalosporin-resistant Enterobacterales (ESCR-E) as bacteria of critical importance for research and development of new antibiotics [1]. An insufficient antibiotic pipeline, substantial healthcare burden, and partly effective or not well-defined preventability in the healthcare setting were among the prioritizing criteria for MDR-GNB selection in the WHO list [1]. In the hospital setting, infection risks for surgical site infections (SSIs) development are well characterized and classified according to patient and procedural factors such as age, comorbidities, surgery type, degree of wound contamination, and duration of surgery [2, 3]. SSIs represent frequent postoperative complications, ranging from 10 to 25% according to the type of surgery in prospective clinical studies, and have a negative impact on patients' morbidity, mortality, and associated healthcare costs [4, 5]. The increase of antimicrobial resistance at global level has also affected SSIs, leading to prolonged hospitalisation, extended duration of antibiotic treatment, need for surgical revisions, and increased mortality [6]. A meta-analysis investigating the efficacy of perioperative antibiotic prophylaxis (PAP) in colorectal surgery showed that SSIs steadily increased between 1980 and 2005, irrespective of the type of PAP or surgical technique [7]. The reduction in PAP efficacy could be explained by a rise in intestinal colonization with resistant Enterobacterales that may not be covered by routine PAP, usually including a cephalosporin combined with metronidazole to target the aerobic and anaerobic intestinal microbiota [5]. Increasing rates of SSIs caused by MDR-GNB have been reported [8-11] along with emerging evidence that rectal colonization precedes infection [12-15]. Decolonization of MDR-GNB carriers before surgery is not routinely recommended due to the lack of long-term efficacy and the potential risk for antibiotic resistance selection [1]. The 2013 European Centre for Disease Prevention and Control (ECDC) guidance suggests that periodical active surveillance of MDR bacteria should be performed by trained personnel to adjust the selection of PAP [16]. To date, no other international guidelines provided specific recommendations on targeted PAP for MDR-GNB carriers [3, 5, 17, 18]. The WHO guidelines on the prevention of SSIs, reviewing studies up to 2015, did not advise for or against MDR-GNB rectal screening and/or culture-directed PAP, expressing concern on presurgical ESCR-E screening implementation as a potential risk for carbapenem-based PAP and CRE selection [3, 19].

The objective of these guidelines is to provide evidence-based recommendations for PAP in adult inpatients with preoperative MDR-GNB rectal colonization, with no restrictions on the type of surgery or associated comorbidities. Anticipated users include surgeons, anesthetists, infection control and infectious diseases specialists, clinical microbiologists, hospital staff (e.g., clinical medical, nursing, and paramedical staff), and policy makers.

Questions addressed by the guidelines

The target MDR-GNB (listed in the subsequent section) and the guideline questions were selected by consensus during the first panel meeting. To address the benefits of pre-surgical screening for MDR-GNB to inform targeted PAP in carriers before surgery, the articles reporting the rates of postoperative infections in MDR-GNB carriers vs. noncarriers were reviewed.

Sampling techniques and microbiological practices were not reviewed or discussed since they were beyond the scope of these guidelines.

The main research questions addressed by the guidelines include:

(a) Should screening for MDR-GNB be recommended prior to surgery and when?

(b) Which PAP have been evaluated for patients colonized with the target MDR-GNB?

(c) Should PAP be adapted in patients colonized with MDR-GNB before surgery?

(d) Should other interventions, such as decolonization therapy, preoperative digestive decontamination (PDD) regimen, or bundled interventions be performed as a potential adjunct to PAP in MDR-GNB carriers before surgery?

(e) Should the duration of PAP change in patients colonized with MDR-GNB before surgery?

The recommendations are summarized in Table 1.

Methods

These guidelines were developed by a multidisciplinary group of experts including infectious diseases specialists, clinical microbiologists, and surgeons, according to the ESCMID guidance document (www.escmid.org). The panel reviewed the articles and discussed evidence-based tables, evidence certainty classification, and recommendation strength. The recommendations were revised until consensus was reached and the final list of recommendations was approved by the whole panel.

Further details on the guideline development process are reported in the Supplementary Material.

Literature search and data extraction

A systematic review of the published literature was performed, including studies evaluating PAP in adult inpatients (aged 18 years and older) colonized with MDR-GNB before surgery. The review protocol followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and was registered on the International Prospective Register of Systematic Reviews (PROSPERO - N. CRD42021170244) [20].

Because of the expected limited number of randomized controlled trials (RCTs), any type of study except for case reports was reviewed. Data retrieved exclusively from outpatients and from pediatric populations as well as studies omitting patients' carrier status prior to surgery were excluded. The articles were identified through literature searches using Medline, Embase and Cochrane databases for full-text articles from January 2010 until December 2021. The search started from January 2010 due to

existing guidelines reporting no evidence to support screening for MDR-GNB and targeted PAP up to 2010 and 2015 (3, 5). A focused search for any recently published, relevant study was also performed from January until April 30, 2022, using Medline and Google Scholar. References from the retrieved articles were screened for potential inclusion in the review.

A combination of Medical Subject Headings and equivalent terms and keywords were used for each MDR-GNB, as detailed in the Supplementary material (Appendix S1), and a two-stage selection process was performed by two independent reviewers (E.L.A.C. and A.V.). All retrieved abstracts were screened against eligibility criteria and duplicates were discarded. If eligibility could not be determined, the full article was retrieved. Disagreements were resolved by consultation with a third party (E.C. and further reviewed by E.R. and N.M.). Flowcharts of assessed studies are reported in Appendix S1.

Data were extracted into a pre-defined Excel database to record the study relevant features, specifically: country and year of publication, study design, type of surgery, target bacteria, type of culture-directed (reported as "targeted") PAP, and outcomes.

A PICO (population/participant, intervention, comparator/control, outcome) framework was implemented defining the following elements:

- Population: adult surgical inpatients with screening samples before surgery yielding one of the following MDR-GNB: ESCR-E, CRE, aminoglycoside-resistant Enterobacterales (AGRE), fluoroquinolone-resistant Enterobacterales (FQR-E), extremely drug-resistant *Pseudomonas aeruginosa* (XDRPA), cotrimoxazole-resistant *Stenotrophomonas maltophilia* (CRSM), CRAB, colistin-resistant GNB (CoRGNB), pan-drug-resistant GNB (PDR-GNB). According to the 2012 international consensus definitions [21], MDR was defined as nonsusceptibility to at least one agent in 3 or more antibiotic classes, XDR as nonsusceptibility to at least one agent in all but 2 or fewer antibiotic classes, and pandrug-resistant (PDR) GNB as nonsusceptibility to all licensed and routinely available antibiotics
- Intervention: targeted PAP, defined as a regimen selected according to bacterial culture results and their susceptibility pattern (or predefined according to the effective antibiotic) to target the colonizing MDR-GNB. Other interventions, such as decolonization therapy (defined as any measure that may lead to the loss of detectable MDR-GNB carriage), PDD regimens, or bundled interventions performed as a potential adjunct to PAP in MDR-GNB carriers before surgery were also considered
- Controls: patients receiving routine PAP (defined as PAP performed according to the locally established protocols and not targeting specific MDR-GNB)
- Outcomes:

  (a) Critical: occurrence of SSIs caused by any bacteria and/or by the colonizing MDR-GNB; SSIs-attributable mortality

  (b) Important: occurrence of any type of postsurgical infectious complication (reported as postoperative infection, e.g., bacteremia, pneumonia, urinary tract infections, etc.) in patients

colonized by MDR-GNB; all-cause mortality; length of hospital stay; adverse events (including resistance development, defined as postoperative colonization by bacteria resistant to the regimen used for targeted PAP, *Clostridioides difficile* infections, and PAP-related toxicity).

A section of these guidelines is dedicated to MDR-GNB colonized solid organ transplant (SOT) recipients. Urologic surgery recommendations are discussed in a separate section due to the specific characteristics associated with this type of surgery.

Quality assessment and grading recommendations

The risk of bias of the included studies is reported in Appendix S2. The quality assessment was performed using the Effective Practice and Organization of Care guidelines for RCTs and the Newcastle-Ottawa Scale for uncontrolled studies (Appendix S1) [22, 23]. The certainty of evidence was classified as high, moderate, low, or very low, and the strength of recommendations was reported as strong or conditional (weak) according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [24]. According to GRADE, good practice statements were designated based on expert opinion and reported as ungraded [25].

Further research propositions, indications for infection prevention, and antimicrobial stewardship considerations were not developed formally and therefore were not graded.

Recommendations

The guidelines are reported according to the colonizing bacteria, except for organ transplant surgery and urologic surgery for which, due to the specific characteristics and type of infections associated, an additional section was added. Each section reports the questions addressed by the guidelines, the recommendations graded according to the available evidence, and the recommendations for research. If relevant, infection prevention and stewardship considerations were also reported.

No RCTs were available for inclusion. Regarding question (d), no articles targeting MDR-GNB carriers through decolonization protocols, PDD, or bundled interventions before surgery were retrieved.

Reports comparing SSIs or, in general, postoperative infections between colonized and noncolonized patients before surgery included 7 observational studies for ESCR-E, 4 for CRE, and 2 for CRAB (Table 2) mainly with moderate or high risk of bias (Appendix 2). No evidence was found for XDR-PA, AGRE, CRSM, CoRGNB, or PDR-GNB. Very few reports directly compared the efficacy of targeted versus routine PAP in reducing postoperative infections among MDR-GNB carriers and are summarized in Appendix S2.

1. Extended spectrum cephalosporin-resistant Enterobacterales (ESCR-E)

Question 1.1: Should patients be screened for ESCR-E prior to surgery?

Recommendation

We suggest rectal screening to identify ESCR-E carriers before colorectal and liver transplant surgery according to the local epidemiology (conditional recommendation, low certainty of evidence).

It might be good practice to screen all SOT recipients for ESCR-E before surgery according to the local epidemiology (ungraded good practice statement).

Specific aspects of screening in SOT recipients are discussed in the following sections.

Infection and prevention considerations

- The implementation of screening procedures should follow a careful assessment of local prevalence of ESCR-E colonization and infection among patients admitted or transferred to the surgical wards
- The choice of targeted versus universal screening should be based on the local work organization (e.g., outpatient ambulatory or preadmission screening) and integrated within diagnostic and antibiotic stewardship guidance.
- Changes in screening and PAP policies should be based on local epidemiology, microbiological capacity, locally available financial resources, and patient's risk factors for ESCR-E acquisition.
- A cut-off for considering changes in antibiotic treatment according to local resistance prevalence is not established [26]. According to the 2016 WHO guidelines that consider ESCR-E high-prevalence ≥ 10% [3], it is reasonable to use it as a cut-off for implementation evaluation. Previous data reported that, in a scenario with 10% ESCR-E prevalence, the number of patients needed to be screened to avoid one SSI is 150 [27].
- Standard operating procedures should be agreed upon according to national indications and evidence-based institutional protocols, including sampling site technique and microbiological methods.

Review of the evidence

Infections in ESCR-E carriers versus noncarriers

Seven observational studies (6 prospective, 2 with medium and 4 with high risk of bias; one retrospective with high risk of bias; one prospective, multicentric, with low risk of bias), 3 including liver transplant recipients (LTR), showed an increased risk of postoperative infections in ESCR-E carriers versus noncarriers (Table 2) [28-34]. Dubinsky-Pertzov et al. included 3600 patients from 3 hospitals in Israel, Switzerland, and Serbia screened for ESCR-E before colorectal surgery and receiving cephalosporin-based PAP showing significantly higher SSIs in carriers compared with noncarriers (24.8% vs. 11.1%, P<0.001). Multivariable analysis confirmed that ESCR-E carriage status was an independent predictor doubling the risk of SSIs (OR 2.36; 95% CI 1.50–3.71), with even higher odds for SSIs caused by ESCR-E (OR 4.23, 95% CI 1.70–10.56) [31]. Golzarri *et al.* included 171 (30 ESCR-E carriers) patients with gastrointestinal and gynecological malignancies reporting higher rates

of SSIs (RR 2.20, 95% CI 1.20-3.90) and bloodstream infections (RR 4.0, 95% CI 2.36-6.87) in carriers versus noncarriers, respectively [32]. The sample size was limited, and carrier status was a risk factor for postoperative infections only at univariable analysis. Apisarnthanarak *et al.* included 129 ESCR-E carriers among 360 patients undergoing abdominal surgery receiving various PAP, reporting ESCR-E colonization as a risk factor for SSIs (adjusted OR [aOR] 2.40, 95% CI 1.19-19.91); all ESCR-E SSIs occurred in ESCR-E carriers [33]. Among LTR, Bert *et al*. reported increased rates of ESCR-E colonization over time (from 0% in 2001–2003 to 11% in 2009–2010 in LTR) [29]. Logre *et al*. enrolled 100 colonized LTR, reporting a sensitivity of 0.62 and a specificity 0.91 for pre-LT ESCR-E rectal carriage in predicting post-LT ESCR-E infections. Compared with other Enterobacterales, ESCR-*K. pneumoniae* carrier status was an independent predictor of ESCR-E infection [34].

The 6 observational studies retrieved mainly involved abdominal and liver transplant surgery showing moderate or high risk of bias (only one multicentric study in colorectal surgery had low risk of bias) and reported an increased rate of postoperative infections in general and of SSIs in ESCR-E carriers compared with noncarriers, suggesting that screening for carriers would define a population at risk that may be benefit of interventions to reduce postoperative infections.

Question 1.2: Should PAP be adapted in patients colonized with ESCR-E before surgery?

Recommendation

We conditionally recommend targeted PAP in patients colonized with ESCR-E undergoing colorectal surgery (conditional recommendation for use, low certainty of evidence).

We conditionally recommend targeted PAP in patients colonized with ESCR-E undergoing liver transplant surgery (conditional recommendation for use, very low certainty of evidence).

It might be good practice to consider targeted PAP for all SOT recipients who are colonized with ESCR-E before surgery (ungraded good practice statement)

Specific aspects of PAP in SOT recipients are discussed in the following sections.

Antimicrobial stewardship considerations

Regimens that may be used for targeted PAP in ESCR-E carriers are listed in Table 3, according to the potential impact on antimicrobial resistance following the WHO Access, Watch, and Reserve (AWaRe) classification [35, 36] and considering the current indicatons for the treatment of MDR-GNB [37].

Under the consideration of antimicrobial stewardship, the use of carbapenems should be limited if other antibiotic options are available against ESCR-E. Reserve antibiotics that may be used for the treatment of extensively resistant bacteria, including novel molecules (e.g., ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, cefiderocol, imipenem-relebactam), should not be routinely used for targeted PAP in ESCR-E carriers [37].

Review of the evidence

Targeted PAP in ESCR-E carriers

Two reports, including a prospective multinational study and a retrospective, single-center study (with low and high risk of bias, respectively) analyzed targeted PAP effectiveness in reducing postoperative infections [34, 38]. Nutman *et al.* performed a multicenter, non-randomized, non-blinded interventional study involving 3 hospitals in Israel, Serbia, and Switzerland between 2012-2017 and including 3600 patients screened before elective colorectal surgery [38]. Of these, 14% (9 - 29%) were ESCR-E carriers and 468 received either routine PAP with cefuroxime, or cefazolin, or ceftriaxone plus metronidazole (baseline phase) or ertapenem (interventional phase). There was a suboptimal adherence to the study phases, with 4% of patients receiving ertapenem in the baseline phase, 20% receiving routine PAP in the interventional phase, and 1% receiving other or no antibiotics. Patients receiving routine PAP had higher National Nosocomial Infections Surveillance (NNIS) scores, while increased stoma creation was reported in the ertapenem group. The multivariable model (including NNIS score and stoma creation) showed a decreased SSIs risk of 33%, with a statistically significant difference favoring ertapenem (adjusted risk difference, ARD –7.7%, 95% CI –14.6% - –0.8%). Moreover, SSIs caused by ESCR-E were significantly lower in the ertapenem (0.9%) vs. the routine PAP group (6.5%, ARD –5.6%, 95% CI, –8.9% to –2.3%) showing an 86% reduction. The NNT to prevent one SSI among ESCR-E carriers was 13. The number needed to screen (NNS) to prevent one SSI ranged from 45 to 138 by study site. The study was underpowered to detect the effect of the intervention on deep SSIs. No differences in mortality, *C. difficile* infection, acute renal failure, or intensive care unit (ICU) admission were detected between groups. Overall length of hospital stay and emergence of antibiotic resistance were not reported [38]. In a related, nested study from the same group including 225 patients at a single site, colonization by ESCR-E and CRE after surgery was significantly lower in the ertapenem vs. the routine arm [39].

Logre *et al.* retrospectively analyzed 100 ESCR-E colonized LTR in France [34]. A total of 35 postoperative infections caused by ESCR-E (11 SSIs, 10 urinary tract infections, 9 pulmonary infections, and 5 sepsis) were reported at day 30. Only 68 patients could be assessed according to PAP, showing higher rates of ESCR-E postoperative infections among LTR receiving routine (7/11, 63%) compared with targeted (17/57, 30%) PAP (P=0.04). Targeted PAP included cefoxitin (40%), a carbapenem (31%), or piperacillin/tazobactam (29%). Although the results favored targeted PAP, the quality of the study was low, with high risk of bias due to the retrospective nature, the limited sample size (with only 11 patients receiving routine prophylaxis), and the lack of outcome according to each regimen. Mortality rates between infected and noninfected patients at day 28 and 90 were similar, while ICU stay was longer in infected versus noninfected patients (P<0.001). Hospital length of stay and PAP-associated adverse effects or antibiotic resistance were not reported [34].

Other two reports on targeted PAP were analyzed but showed major limitations. Apisarnthanarak *et al*. reported no association between the use of carbapenem-based PAP, received by 23% of carriers and 6% of noncarriers, and SSIs reduction (aOR, 0.89; 95% CI, 0.55-14.24), however no comparison with

other PAP was provided [33]. De Pastena *et al*. performed an interventional nonrandomized prospective study in 76 ESCR-E carriers undergoing pancreatic surgery, comparing postoperative infections in patients receiving PAP with ampicillin/sulbactam (period 1) or piperacillin/tazobactam (period 2) [30]. Although significantly higher rates of postoperative infections (30% versus 11%, P=0.025) and superficial SSIs (34% versus 0, P<0.001) were shown in period 1 versus 2, PAP was not selected according to preoperative cultures, and prolonged PAP (up to 3 days) was allowed during period 1 in case of biliary stent placement [30].

Given the paucity of data and the observational study design, there was a low (for colorectal surgery) to very-low (for liver transplant surgery) certainty of evidence supporting targeted PAP in ESCR-E carriers. Due to the high risk for infections in SOT recipients and the evidence for liver transplant surgery, the panel believes it may be good practice to consider targeted PAP for all SOT.

Research and conditional use in restricted trials

Due to the very low evidence for targeted PAP effectiveness in ESCR-E carriers undergoing liver transplantation and the lack of evidence for other transplant surgeries, further studies are needed to investigate the impact of targeted PAP in reducing post-transplant infections among ESCR-E colonized SOT candidates. Research protocols should include the post-surgical monitoring of antibiotic resistance (e.g., CRE colonization through rectal cultures, especially if carbapenem-based PAP is used) and report antimicrobial susceptibility according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST, https://www.eucast.org/clinical_breakpoints/) results.

Furthermore, due to the limited evidence on the effectiveness of targeted PAP in other specific surgical groups, the panel suggests designing clinical trials in ESCR-E carriers undergoing high-risk surgical procedures (e.g., major cardiothoracic surgery, pancreatic surgery, major oncologic general surgery or gynecologic surgery). The trial design should consider the local burden of ESCR-E and patient-related risk factors for carrier status (e.g., previous ESCR-E infections, recent use of broad-spectrum antibiotics, prior hospital or long-term care facility admission or prolonged stay, ICU stay, mechanical ventilation, renal failure). Post-surgical monitoring of resistance development to the antibiotics used for targeted regimens is recommended. Same-strain colonization and infection relatedness, as well as the mechanisms of resistance of newly isolated MDR-GNB detected after surgery, should be investigated.

2. Carbapenem-resistant Enterobacterales (CRE)

Question 2.1: Should patients be screened for CRE prior to surgery?

Recommendation

We suggest implementing rectal screening to identify CRE carriers before liver transplant surgery according to the local epidemiology (conditional recommendation, low certainty of evidence).

It might be good practice to screen, according to the local epidemiology, all SOT recipients for CRE before surgery (ungraded good practice statement).

Infection and prevention considerations

- Any change in screening procedures should follow a careful assessment of local prevalence of CRE colonization and infection among patients admitted or transferred to the surgical wards; although a prevalence threshold is not clearly defined to recommend the implementation of screening procedures, it is reasonable to consider a prevalence ≥ 10% as a cut-off for implementation evaluation according to previous recommendation [3].
- The choice of targeted versus universal screening should be based on the local work organization and integrated within antibiotic and diagnostic stewardship guidance.
- Irrespective of the PAP, the panel considers the knowledge of the colonization status before SOT essential for the early implementation of infection control procedures (e.g., reducing the risk of intrahospital and community spreading).

Review of the evidence

Infections in CRE carriers versus noncarriers

Four observational studies (2 retrospective, with high and medium risk of bias and 2 prospective, with medium risk of bias), all including LTR, 3 performed in Italy and one in Brazil, compared the rates of postoperative infections between CRE carriers and noncarriers (Table 2) [13, 14, 40, 41]. Mazza *et al.* identified 10 out of 310 (3%) patients who CRKP carriers before LT; 30% developed CRKP infections documented up to 70 days post-LT with a mortality of 100% [13]. Pre-transplant colonization was significantly associated with infection (OR 10.76, 95% CI 2.60-44) but was detected only by univariable analysis. Giannella *et al*. performed a prospective, single-centre study analyzing 237 LTR and 10 (4%) CRKP carriers, showing lower rates of post-LT infections in noncolonized versus CRKP colonized within 120 days after LT (2% versus 18% respectively, P<0.001) [40]. The same transplant center included 553 LTR between 2010 and 2017 showing that CRE colonization increased significantly over time (RR 1.21, 95% CI 1.05-1.39) [41]. Multivariable analysis identified CRE colonization before transplantation as an independent risk for CRE infection (HR 18.50, 95% CI 6.76-50.54). Freire *et al.* reported 72 (40%) CRKP carriers among 181 LTR; 42% became CRKP infected compared with 1 out of 139 noncarriers [42]. CRKP carriers were more likely to develop an infection caused by CRKP compared with those who were colonized by other MDR-GNB (RR 1.28; 95% CI 1.04-1.58). The study, however, combined pre- and post-transplant colonization. The same authors performed a study enrolling 98 (13%) LTR who were CRE carriers, showing higher rates of CRE SSIs in carriers versus

noncarriers (P=0.001) [14]. CRE acquisition before transplantation was identified as an independent risk factor for SSIs caused by any type of bacteria (OR 2.32, 95% CI 1.43-3.77) and by MDR-GNB (OR 3.17, 95% CI 1.46-6.89). Although these studies highlight an increased rate of postoperative infections among CRE carriers vs. noncarriers, several limitations were detected, including the study design (all observational single-site studies, retrospective in 2 cases) and the variable, or not reported, follow-up time for infection detection (Table 2).

Question 2.2: Should PAP be adapted in patients colonized with CRE before surgery?

Recommendation

There is insufficient evidence for or against targeted PAP for patients who are colonized with CRE before surgery at the time of writing and therefore no recommendation can be issued.

Review of the evidence

Targeted PAP in CRE carriers

Two retrospective studies, a Brazilian single-center study and a multicentric study performed in the US and Brazil (with moderate and high risk of bias, respectively) were retrieved [14, 43]. In a cohort of 762 LTR enrolled between 2010-2018, PAP was changed from 2014 replacing cefotaxime with amikacin (in association with ampicillin) if an increased risk of developing MDR infections (e.g., vancomycin-resistant enterococci, CRAB, and CRE) was documented [14]. Risk factors included pretransplant CRE colonization, treatment with a broad-spectrum antibiotic in the past 30 days, need of dialysis, or MELD>24. A total of 229 (30%) SSIs were detected, including 109 caused by MDR bacteria. When targeted PAP was performed, the rates of SSIs caused by any MDR bacteria decreased to 13% (14/109) compared with 30% (25/120) of those caused by nonresistant bacteria (OR 0.35, 95% CI 0.15-0.80). The study, however, was limited by the lack of susceptibility profiles for MDR bacteria receiving targeted PAP and by the lack of data for CRE infections, therefore the efficacy of the modified PAP could not be clearly assessed [14]. Taimur *et al*. included 60 SOT recipients (50% liver, 28% heart, and 12% kidney transplant recipients) with either previous CRE infection or carrier status. Post-transplant CRE infections were documented in 40% of cases, and 35% SOT recipients received targeted PAP for CRE. Targeted PAP, however, was not known for most patients and mainly consisted of a combination of 2 to 3 agents such as carbapenems, polymyxins, and tigecycline [43]. At univariable analysis, targeted PAP was more commonly reported in patients with post-SOT CRE infections (13/24, 54%) compared with those without CRE infections (8/36, 22%, P=0.015). Study limitations included the small sample size and the associated impossibility to perform a multivariable analysis. Furthermore, data on CRE colonization could not be dissected from previous CRE infection, and most patients on targeted prophylaxis had prior CRE bacteremia [43]. None of the studies provided data on adverse

events or emergence of antibiotic resistance following targeted PAP. No conclusions could be drawn from these studies on the effects of targeted PAP in CRE carriers undergoing transplant surgery.

Antimicrobial stewardship considerations

Although there is no evidence for recommending targeted PAP for CRE carriers, the knowledge of CRE colonization in high-risk patients, such as those receiving transplant surgery, is relevant not only for infection control purposes but also for the adaption of post-surgical empirical treatment, for example in case of sepsis or severe infections [44].

Research and conditional use in restricted trials

The panel recommends designing clinical trials to assess the impact of CRE rectal screening in high-risk surgeries. A recommendation is made also to design trials of targeted PAP in CRE carriers undergoing SOT and other high-risk surgical procedures to evaluate the effectiveness, applicability, and safety of the intervention following antimicrobial stewardship principles, specifically:

- clinical trials of targeted PAP should be designed considering rectal culture results
- the choice of targeted PAP should take into consideration the limited number of options that are available for the treatment of CRE infections, avoiding novel compounds that may be required for the treatment of post-surgical infections
- Resistance monitoring should be performed through detection of MDR-GNB carriage after surgery and to detect emerging resistance to the regimens used for targeted PAP. In SSIs, the clonal relationship between MDR bacteria detected after surgery and preoperative colonizing bacteria should be determined, and both short- and long-term post-surgical colonization investigated.

3. Carbapenem-resistant Acinetobacter baumannii (CRAB)

Question 3.1: Should patients be screened for CRAB prior to surgery?

Recommendation

We conditionally recommend implementing rectal screening to identify CRAB carriers before liver transplant surgery according to the local epidemiology (conditional recommendation, low certainty of evidence).

It might be good practice to screen, according to the local epidemiology, all SOT recipients for CRAB before surgery (ungraded good practice statement).

Infection and prevention considerations

- Any change in screening procedures should follow a careful assessment of local prevalence of CRAB colonization and infection among patients admitted or transferred to the surgical wards; although a prevalence threshold is not clearly defined to recommend the implementation of screening procedures, it is reasonable to consider a prevalence ≥ 10% as a cut-off for implementation evaluation according to previous recommendation [3].
- Any change in procedures should consider evidenced-based screening protocols, including the screening of different body sites (e.g., skin) [45].
- The choice of targeted versus universal screening should be based on the local work organization and integrated within antibiotic and diagnostic stewardship guidance.
- The panel considers the knowledge of the colonization status of the patient before SOT essential for early implementation of infection control procedures (e.g., reducing the risk of intrahospital and community spreading).

Review of the evidence

Infections in CRAB carriers versus noncarriers

Only two cohort studies (one prospective and one retrospective with medium and high risk of bias, respectively), performed at the same transplant center in Brazil, assessed CRAB postoperative infections among LTR [14, 46] showing increased infection risk in carriers vs. noncarriers (Table 2). In the first study, 24 CRAB carriers were identified among 196 LTR [46]. Post-LT infections caused by CRAB were detected in 56 (29%) LTR and associated with 60-day mortality (P<0.001). Pretransplant colonization was predictive of post-LT CRAB infection (relative risk, RR, 1.48, 95% CI 0.96-2.26) and mortality (RR 1.12, 95% CI 0.99-1.26) but was confirmed only by univariable analysis. In 7/11 carriers developing CRAB infections, pre-LT and post-LT strains appeared closely related by pulsed-field gel electrophoresis analysis [46]. The second study reported pre-transplant CRAB colonization in 28 out of 762 (4%) LTR with occurrence of CRAB SSIs in 31 (10%) patients. The rates of CRAB SSIs were significantly higher among CRAB carriers versus noncarriers (P=0.001) [14].

Question 3.2: Should PAP be adapted in patients colonized with CRAB before surgery?

Recommendation

There is insufficient evidence for or against targeted PAP for patients who are colonized with CRAB before surgery at the time of writing and therefore no recommendation can be issued.

Review of the evidence

Targeted PAP in CRAB carriers

Freire *et al*. performed routine PAP with ampicillin plus cefotaxime in 18 out of 22 CRAB carriers receiving LT and targeted PAP (by addition of polymyxins to ampicillin plus cefotaxime) only in 4 patients; 2 out of 4 LTR receiving targeted PAP acquired postoperative CRAB infections with polymyxin MIC >16 mg/dL, while no outcome data were reported for the others [46]. Since data were retrieved from 4 patients, no conclusions could be drawn on targeted PAP in CRAB colonized patients.

Antimicrobial stewardship considerations

Although there is no evidence for recommending targeted PAP for CRAB carriers, the knowledge of CRAB colonization in high-risk patients such as those receiving transplant surgery is relevant not only for infection control purposes but also for the adaption of post-surgical empirical treatment, for example in case of sepsis or severe infections [44].

Research and conditional use in restricted trials

Due to the limited evidence that CRAB colonization prior to surgery increases the risk of postoperative CRAB infections, the panel suggests designing clinical trials comparing the incidence risk of CRAB infections in carriers versus noncarriers, especially for patients undergoing high-risk surgery. The efficacy of targeted versus routine PAP in CRAB carriers should be also investigated in clinical trials.

4. Timing for preoperative MDR-GNB screening

Question 4. When should we perform the screening for MDR-GNB before surgery?

Recommendation

For MDR-GNB screening, cultures performed within 3 weeks before surgery may be considered (ungraded good practice statement).

Review of the evidence

There were no studies evaluating the incidence of SSIs or other clinical outcomes according to the timing of preoperative screening. In the retrieved studies, rectal screening to detect MDR-GNB carriage was usually performed starting from 2 to 3 weeks before surgery until the day of surgery, while some reports did not specify the timing for preoperative screening (Table 2). Colonization remains a dynamic process with long-term persistence of MDR-GNB carriage status that may occur in patients discharged by hospitals and those undergoing surgery, including SOT [47, 48]. Data favoring targeted PAP based on the results of cultures taken more than 3 weeks before surgery were not retrieved.

Research and conditional use in restricted trials

Studies analyzing the optimal timing for preoperative screening should be performed. Further research should evaluate the benefits of additional screening before surgery in case of recent antibiotic treatment.

5. Duration of PAP in MDR-GNB carriers

Question 5. Should the duration of PAP change in patients colonized with MDR-GNB before surgery?

Recommendation

PAP should be discontinued within 24 hours after surgery in patients colonized with MDR-GNB (strong recommendation, moderate certainty of evidence).

In transplant surgery other than renal transplant, the extension of PAP duration to 48-72 hours may be considered according to the type of transplant (ungraded good practice statement).

Review of the evidence

Since PAP aims to achieve adequate tissue levels prior and during surgery to minimize SSIs, a single dose of preoperative PAP is recommended for most surgical procedures [13]. In colonized patients, we either reported no clear evidence for changing the usual PAP (Table 1) or provided conditional recommendation to administer PAP regimens (that are already established according to international guidelines) according to the results of preoperative cultures (Table 3). Therefore, the duration of targeted PAP should align with current recommendations by the Infectious Diseases Society of America, American Society of Health-System Pharmacists, Surgical Infection Society, and Society for Healthcare Epidemiology of America (IDSA/ASHP/SIS/SHEA) as well as other international societies that consistently give indication for PAP discontinuation within 24 hours after surgery [3, 5, 49-54]. No additional dosing is usually recommended for intravascular lines and devices, surgical drains, or stent placement [5, 59,60]. The certainty of evidence supporting the benefits of limiting the duration of PAP to 24 hours is moderate mainly because of the high heterogeneity of studies performed in different types of surgery. The use of prolonged PAP (> 24-48 hours post-incision) has been associated with an increased risk of antibiotic resistance, acute kidney injury, and *C. difficile* infection in observational studies [55, 56] while conferring no apparent decrease in SSIs, as shown by a meta-analysis including only RCTs and by a recent cluster randomized trial in clean orthopedic surgery [55-58]. A meta-analysis on the optimal duration of antibiotic prophylaxis in cardiac surgery showed that PAP > 24 hours may be more efficacious in preventing sternal SSIs than shorter PAP, however the conclusions were hampered by the high heterogeneity of the PAP used and the studies' risk of bias [61].

In transplant surgery there is currently no formal consensus on PAP duration due to a lack of comparative trials; despite the lack of evidence, recommendations based on expert opinion suggest the administration of PAP for ≤24 hours in kidney, 24-48 hours in liver, heart, pancreas, and for 48-72 hours in intestinal/multivisceral and lung transplantation [5, 18, 62]. Exceptions are represented by

procedures that may require prolonged treatment (e.g., lung recipients with respiratory colonization or infection and intestinal or multivisceral transplant with infected mesh or fistulas) [18, 62].

Since the optimal duration of targeted PAP in MDR-GNB carriers should follow the same principles of PAP to minimize the risks associated with prolonged antibiotic administration, the recommendation is based on the abovementioned studies that do not specifically report the carrier status.

Research and conditional use in restricted trials

Further research should be performed to investigate the clinical impact of shorter versus longer PAP in patients undergoing transplant surgery.

6. Specific aspects of MDR-GNB carriage in SOT recipients

SOT recipients are exposed to MDR-GNB infections due to prolonged hospitalization, invasive procedures, ICU admission, and broad-spectrum antibiotic treatment [63, 64]. SSIs are a common issue and may occur in 3% to 53% of SOT recipients, with highest rates observed for intestinal, liver, and pancreas transplantation [62]. LTR can develop intra-abdominal infections especially in the early post-LT period. In this group, the risk of ESCR-E and CRKP infections range from 6% to 13% and 3% and 10%, respectively, depending on the geographic area [65, 66]. ESCR-E infections are common, accounting for up to 75% of MDR-GNB isolates in SOT recipients [67]. Among nonfermenters, rates of CRAB and MDR PA up to 63% and 52%, respectively, were reported in bloodstream infections (BSIs) [65, 68, 69]. Post-SOT infections caused by MDR-GNB are associated with higher mortality compared with their susceptible counterpart [62, 65, 70-73].

The American Society of Transplantation (AST) recommendations for MDR-GNB management and the Spanish Transplantation Infection Study Group (GESITRA) guidelines acknowledge that early detection of MDR-GNB carriers is useful to inform contact precaution in SOT candidates and may be taken into consideration when treating postoperative infections [44, 74]. Nevertheless, in asymptomatic SOT patients, non-outbreak settings, or in regions of endemicity the benefits of ESCR-E active surveillance are questioned [18, 74]. New emerging evidence, however, showed increased rates of post-LT infections among ESCR-E, CRE, and CRAB carriers before SOT [13, 14, 34, 40, 41, 46]. Kidney transplant recipients (KTR) who were ESCR-E carriers had more frequently post-KT urinary tract infections (UTIs) versus noncarriers [75]. Limited data are available for XDRPA colonization and occurrence of post-SOT infections. One prospective study in LTR showed that, out of 69 (38%) who were MDR-GNB carriers, 27% XDRPA carriers compared with 2% noncarriers developed postoperative XDRPA infections; however, most patients included in the study became colonized after LT [42]. Colonization of non-GI sites, such as respiratory colonization by XDRPA in lung recipients, CRAB skin or multisite colonization in LT, or pretransplant bacteriuria in KTR may be relevant to target PAP, but data remain limited [18, 42, 44, 45, 62, 76].

PAP regimens and duration vary across transplant centers and are often customized to suit unique SSIs risks factors and surgical scenarios [18, 62, 77]. A worldwide survey involving lung transplant specialists reported that 67% of prescribers performed targeted PAP based on pre-transplant MDR-GNB sputum colonization [76]. The AST guidelines for SSIs prevention recommend different PAP according to the type of SOT (with broader coverage for intestinal/multivisceral transplantation, lung transplantation, and delayed chest closure) and to adjust PAP in case of ongoing infections, with most recommendations being weak, with low quality evidence [18]. Targeted PAP in ESCR-E or CRE SOT carriers remains undefined, and recipient screening is recommended for lung transplant [74]. Although GESITRA recommended that ESCR-E colonized patients receive targeted PAP, no indication was given for a preferred regimen among beta-lactamase inhibitors, quinolones, aminoglycosides, or carbapenems [44]. Ertapenem was mentioned as an acceptable alternative in selected ESCR-E carriers, with a recommendation was made to limit carbapenem-based PAP due to the risk of carbapenemases production. For CRE carriers, targeted PAP was not recommended except for centers reporting a high incidence of CRE SSIs, however a cut-off was not provided [44]. Data comparing PAP regimens in SOT remain scarce. A study including 819 KTR found a significant reduction in SSIs when amikacin was used in PAP instead of a cephalosporin [78]. Although this result could be explained by the predominance of ESCR-E SSIs, data on preoperative carriage status were not provided [78]. As previously reported, two recent retrospective studies with moderate and high risk of bias showed conflicting results on the benefit of targeted PAP in CRE carriers undergoing SOT [14, 43].

Recommendations and future research

Recommendations for SOT recipients who are carriers of MDR-GNB before surgery are summarized in Table 1. Indications for future trials in ESCR-E, CRE, and CRAB carriers undergoing SOT are reported in the related sections. Moreover, future research is recommended for XDRPA screening to assess the risk of post-SOT infections among carriers. MDR-GNB multisite screening vs. rectal screening only should also be considered in SOT recipients before surgery to evaluate the impact on post-SOT infections according to the type of organ transplanted. Although these guidelines did not address postoperative colonization, the association between post-transplant MDR-GNB colonization and infections has often been documented, suggesting that culture surveillance should be considered also after SOT, according to the local epidemiology and individual risk factors [14, 41, 44, 48, 70, 79].

7. Urologic surgery

Targeted PAP has been predominantly studied in transrectal ultrasound-guided prostate biopsy (TRUSPB) among fluoroquinolone-resistant (FQR)-E carriers due to the type of surgical approach (that involves entering the gastrointestinal tract) and the increased rates of FQR-E colonization reported before TRUSPB.

Question 7.1 Should patients be screened for FQR-E prior to TRUSPB?

Recommendation

We suggest rectal screening to identify FQR-E carriers before TRUSPB (conditional recommendation, moderate certainty of evidence).

Question 7.2 Should PAP be modified for patients colonized with FQR-E before TRUSPB?

Recommendation

We suggest the use of targeted PAP for patients who are colonized with FQR-E before TRUSPB (conditional recommendation, moderate certainty of evidence).

Regimens that may be used for targeted PAP in FQR-E carriers are listed in Table 3.

Review of the evidence

Fluoroquinolone-resistant (FQR)-E in TRUSPB

Infectious complications (e.g., UTIs, acute prostatitis, BSIs, sepsis) following TRUSPB occur in 1% to 5% of patients [80, 81]. FQ are broadly prescribed for PAP due to the IV/oral administration and the high penetration into prostate tissues [82]. FQR-E rectal carriage has increased, showing rates exceeding 20% in certain areas, and was associated with alarming rates of post-TRUSPB infectious complications [83-87]. Bratzler et al. suggest that local resistance patterns to fluoroquinolones, particularly with *E. coli*, should be evaluated to help guiding PAP selection [5].

The retrieved studies reporting infectious complications and PAP in FQR-GNB carriers receiving TRUSPB are reported in Appendix S2. The use of ertapenem, cefoxitin, and fosfomycin in PAP was associated to reduced incidence of BSIs in FQR-E carriers undergoing TRUSPB [86, 88, 89]. Data on TRUSPB PAP, however, are limited by a high variability in the regimens used and the short follow-up to assess infectious complications. Two single-center observational studies performed in the US and Korea favored targeted vs. routine PAP [90, 91]. Suwantarat *et al*. included 44 FQR *E. coli* carriers (22% of screened patients); of these, 43% among those receiving an oral cephalosporin plus ciprofloxacin developed post-TRUSBP infections compared to none receiving targeted PAP (61% with cotrimoxazole) [90]. Dai *et al*. included 314 patients and 12% FQR-GNB carriers; of these, 36 (11%) received targeted PAP (69% cotrimoxazole, 56% in combination with intramuscular gentamicin) versus oral ciprofloxacin [91]. Targeted PAP was associated with decreased odds of post-TRUSBP infections (OR 0.70; 95% CI 0.20-2.50). Bloomfield *et al*. used ertapenem-based PAP in 326 patients; of these, 6% and 9% were colonized with ESCR-E and FQR-E, respectively [92]. Three (1%) episodes of post-TRUSPB sepsis were reported [92]. Although we excluded single articles referring exclusively to ambulatory TRUSBP, data from comprehensive systematic review and meta-analyses were reviewed.

Cussans *et al*. included 9 observational studies and 4571 patients (23% colonized by FQR-GNB) comparing FQ-based with targeted PAP; post-TRUSPB infections were 4.6% versus 0.7%, respectively [93]. The NNT to prevent one post-TRUSPB infection was 27. Scott *et al*. performed a meta-analysis of 15 articles up to March 2017 including 2 controlled trials and 13320 patients [94]. Post-TRUSPB infections were 3.4% versus 0.8% with an estimated risk difference (RD) of 2.6% for FQ-based versus targeted PAP. The NNT to prevent one post-TRUS infection was 39. No optimal targeted PAP for carriers was identified.

To date, the superiority of prolonged (e.g., 48-72 hours) or multiple-dose treatment versus short-course (24 hours) or single-dose PAP has not been demonstrated [82]. Some studies showed that PAP with ≥ 2 antibiotics caused the reduction of post-TRUSPB UTIs, but these results were not confirmed in clinical trials using targeted PAP [95, 96]. Other studies reported no benefits in the addition of aminoglycosides to FQ [97, 98].

A recently published (therefore not formally included in the evidence review) randomized, non-blinded, multicenter trial including 1288 patients undergoing TRUSBP (15.8% FQR carriers) and comparing ciprofloxacin PAP versus culture-based PAP showed a risk reduction of -1.8% (95% CI -0.004 to 0.040) in the 7-day post-TRUSPB infection rate. FQR carriers had a 6.2-fold higher risk of early post-biopsy infection compared to noncarriers [99].

The European Association of Urology (EAU) guidelines pose a weak recommendation for the use of targeted PAP in TRUSPB, indicating fosfomycin trometamol, cephalosporin, and aminoglycoside as alternatives to FQ without addressing specific MDR-GNB [100]. The EAU strongly recommends considering the transperineal approach for prostate biopsy due to the lower risk of infectious complications. Furthermore, a recent RCT performed in Norway enrolling 792 patients performing transperineal prostate biopsy reported that PAP may be omitted in this population since infections were not significantly higher in patients receiving and not receiving PAP [101].

Research and conditional use in restricted trials

Further studies are recommended to understand the impact of colonization with MDR-GNB other than FQR-E on post-TRUSPB infections. High-quality trials are suggested to assess the efficacy of specific PAP regimens in FQR-E carriers undergoing TRUSPB. A recommendation for research is made to design trials of targeted PAP in ESCR-E carriers, especially in areas with increased ESCR-E burden. Future trials should include adequate monitoring of infectious complications and development of antibiotic resistance following surgery.

Other urologic surgery

Question 7.3 Should screening be performed and PAP modified for patients colonized with MDR-GNB before urologic surgery?

Recommendation

Insufficient evidence is available at this time to recommend for or against screening to inform targeted PAP for patients who are colonized with MDR-GNB before urologic surgery (no recommendation).

Review of the evidence

There is limited evidence on the impact of targeted PAP on infectious complications following urologic surgery in MDR-GNB carriers. Rectal colonization may not be informative, while urinary cultures are often obtained to treat asymptomatic bacteriuria before surgery, as recommended by clinical practice guidelines [51, 102]. The 2019 American Urological Association (AUA) best practice guidelines report a high variability in prescribing PAP patterns for most urologic interventions [51]. Although targeted PAP is not routinely recommended, the AUA guidelines suggest that, if PAP is required and a known history of MDR organisms is reported, an expanded antimicrobial coverage should be warranted [51]. The EAU guidelines suggest that the identification of asymptomatic bacteriuria through urine culture prior to surgery aims to reduce the risk of infectious complications and to optimize antimicrobial coverage prior to invasive urological procedures, but does not provide recommendations on targeted PAP due to the high geographic variability in type of bacteria, susceptibility patterns, and availability of antibiotics [96].

Higher rates of postoperative infections were reported among patients with urinary colonization compared with noncolonized ones, and patients undergoing urologic surgery often have risk factors for MDR-GNB acquisition (e.g., previous surgical procedures, permanent bladder catheters, double J stents, etc.) [103, 104]. Nevertheless, studies comparing postoperative infections in MDR-GNB urinary carriers versus noncarriers are lacking. A small, prospective single-center study included 75 patients undergoing urologic surgery and receiving PAP based on the results of urine cultures (from day 2 before surgery until withdrawal of bladder catheter or until day 7) [105]. Sixteen (22%) ESCR-E carriers received targeted PAP mainly with aminoglycosides (63%), cefoxitin (19%), and imipenem (13%). Eleven (15%) postoperative infections, mainly SSIs, were detected in patients receiving targeted PAP compared with 5% in noncolonized ones (P=0.028). A total of 31% ESCR-E carriers developed postoperative infections; 80% of these were caused by the same colonizing strain compared to 9% in noncarriers [105].

Research and conditional use in restricted trials.

In urologic surgery other than TRUSBP, further research is needed to identify the impact of MDR-GNB colonization and targeted PAP based on preoperative cultures, including urinary cultures, on

postoperative infections. Furthermore, the optimal targeted PAP for different MDR-GNB should be investigated according to the type of urological procedure and the local rates of antibiotic resistance.

Limitations of the evidence and research needs

Our review has identified important knowledge gaps and limitations, including retrospective study designs, small sample sizes, lack of assessment of key outcomes, and a wide heterogeneity of surgical settings, types of PAP, and timing of assessment of postoperative infections from surgery. Most questions were addressed by observational studies with high risk of bias (Table 2 and Supplementary tables 1 and 2). Well-done RCTs are highly needed to fill in existing gaps and to improve patients' outcomes.

For ESCR-E and CRE carriers, increased evidence recently highlighted the association between rectal colonization and postoperative infections, supporting surveillance screening for MDR-GNB, especially in areas with high burden and for high-risk surgery, suggesting that targeted PAP may be effective in reducing SSIs. No RCT, however, was performed comparing targeted with routine PAP in MDR-GNB carriers. Furthermore, routine prophylaxis may vary according to local protocols and different geographic areas, potentially impacting SSIs. One prospective multinational study showed a potential benefit for ertapenem use in ESCR-E carriers undergoing colorectal surgery [38]. Previously, ertapenem-based PAP was used in studies not reporting colonization data, showing SSIs reduction in a retrospective study including 615 cancer patients undergoing abdominal surgery [106], while a RCT including 499 patients undergoing elective colorectal surgery reported similar efficacy for ertapenem versus routine PAP [107]. Because of the limited options currently available to effectively treat MDR-GNB, well-designed studies exploring optimal PAP are needed. These trials should investigate the impact of targeted PAP on microbiological, epidemiological, and clinical outcomes as well as development of resistance to the antibiotics used for targeted regimens. Antibiotic dosing should be chosen according to PK/PD principles and considering the cost-effectiveness of the intervention. Few studies have explored the impact of carrier status for MDR-GNB other than ESCR-E, CRE, and CRAB. XDRPA as well as PDR-GNB colonization effects on SSIs need further attention, as colonization rates by these bacteria are likely to increase in the future. If PAP including antibiotic combinations (e.g., two or more antibiotics with *in vitro* efficacy against MDR-GNB) are investigated, efforts should be made to analyze their potential for resistance selection and side effects.

Other antibiotic-based interventions for reducing postsurgical infections (e.g., decolonization, SDD) and targeting MDR-GNB carriers before surgery have not been explored in clinical trials. The ENTHERE study group performed an open-label, multicenter RCT treating 53 SOT recipients who were MDR-GNB carriers with oral colistin plus neomycin, while 52 did not receive the decontamination protocol. No significant difference in infections due to MDR Enterobacterales was observed between groups, however patients enrolled were colonized not only before (58%) but also after SOT (42%)

[108]. SDD with oral colistin, tobramycin, and amphotericin B was performed in a RCT in colorectal surgery showing a reduction of postoperative infections in the SDD arm compared to controls, nevertheless carrier status was not tested [109]. Since recent trials in colorectal surgery showed that the use of oral antibiotics (with or without mechanical bowel preparation) may reduce the risk of SSIs, protocols exploring the use of oral therapy with activity on MDR-GNB should be considered [110, 111]. While coordinated actions (e.g., decolonization, active surveillance, and stewardship measures) seemed to contribute to SSIs reduction for MDR Gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus*, no bundles complementing PAP in MDR-GNB carriers undergoing surgery were found [112]. Metagenomic studies assessing the effect of antibiotic treatment on the microbiota composition and on patients' colonization dynamics over time should be investigated within new protocols or bundled interventions targeting MDR-GNB.

The reduction of SSIs requires a comprehensive approach in terms of antibiotic-based interventions and best surgical practices (e.g., minimization of surgical operative time, regulation of glucose and temperature, optimization of sterile techniques, and management of patient comorbidities) [49, 59, 113]. The optimization of antibiotic-based interventions should focus not only on targeted PAP but also on heightening stewardship initiatives to monitor and contain the consequences of new prescription patterns, enhance surveillance protocols, improve local adherence to guidelines, and promote a multidisciplinary approach to target SSIs [114].

Transparency declaration

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Updating

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Authors' contributions

E.R. wrote the study protocol, supervised the work of the panel, selected and voted for PICO questions and for other relevant decision, performed literature search, drafted and approved the manuscript. N.T.M. wrote the study protocol, selected and voted for PICO questions and for other relevant decision, performed literature search, critically revised and approved the manuscript. X.G., M.D.T., C.E., A.W.F., M.G., J.K., E.P., G.S., C.T. selected and voted for PICO questions and for other relevant decisions, reviewed the literature, critically revised and approved the manuscript. E.LA.C, E.C., A.V., voted for PICO questions, performed literature search and data extraction, and approved the manuscript. E.T. chaired the panel, supervised the work of the panel, selected and voted for PICO questions and for other relevant decisions, drafted and approved the manuscript.

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Table 1. Summary of recommendations

Recommendation	Strength of recommendation	Level of evidence
Extended-spectrum cephalosporin-resistant Enterobacterales (ESCR-E)		
Recommendation on screening for ESCR-E colonization		
We suggest rectal screening to identify ESCR-E carriers before colorectal and liver transplant surgery according to the local epidemiology	Conditional	Low
It might be good clinical practice to screen all solid organ transplant recipients for ESCR-E before surgery according to the local epidemiology	Ungraded good practice statement	Expert opinion
Recommendation on targeted perioperative antibiotic prophylaxis (PAP) for patients who are colonized with ESCR-E before surgery		
We conditionally recommend targeted PAP in patients colonized with ESCR-E undergoing colorectal surgery	Conditional	Low
We conditionally recommend targeted PAP in patients colonized with ESCR-E undergoing liver transplant surgery	Conditional	Very low
It might be good clinical practice to consider targeted PAP for all solid organ transplant recipients who are colonized with ESCR-E before surgery	Ungraded good practice statement	Expert opinion
Carbapenem-resistant Enterobacterales (CRE)		
Recommendation on screening for CRE colonization		
We suggest implementing rectal screening to identify CRE carriers before liver transplant surgery according to the local epidemiology	Conditional	Low
It might be good clinical practice to screen, according to the local epidemiology, all solid organ transplant recipients for CRE before surgery	Ungraded good practice statement	Expert opinion
Recommendation on targeted PAP for patients who are colonized with CRE before surgery		

There is insufficient evidence for or against targeted PAP for patients who are colonized with CRE before surgery at the time of writing and therefore no recommendation can be issued	No recommendation	
Carbapenem-resistant *Acinetobacter baumannii* (CRAB)		
Recommendation on screening for CRAB colonization		
We conditionally recommend implementing rectal screening to identify CRAB carriers before liver transplant surgery according to the local epidemiology	Conditional	Low
It might be good clinical practice to screen, according to the local epidemiology, all solid organ transplant recipients for CRAB before surgery	Ungraded good practice statement	Expert opinion
Recommendation on targeted PAP for patients who are colonized with CRAB before surgery		
There is insufficient evidence for or against targeted PAP for patients who are colonized with CRAB before surgery at the time of writing and therefore no recommendation can be issued	No recommendation	
Fluoroquinolone-resistant Enterobacterales (FQR-E)		
Recommendation on screening for FQR-E colonization in transrectal ultrasound-guided prostate biopsy (TRUSPB)		
We suggest rectal screening to identify FQR-E carriers before TRUSPB	Conditional	Moderate
Recommendation on targeted PAP for patients who are colonized with FQR-E before TRUSPB		
We suggest the use of targeted PAP for patients who are colonized with FQR-E before TRUSPB	Conditional	Moderate
Recommendation on screening for MDR-GNB colonization and targeted PAP in other urologic surgery		
Insufficient evidence is available at this time to recommend for or against screening to inform targeted PAP for patients who are colonized with MDR-GNB before urologic surgery	No recommendation	
MDR-GNB (ESCR-E, CRE, CRAB) colonization before surgery		
Recommendation on timing for preoperative MDR-GNB screening		
For MDR-GNB screening, cultures performed within 3 weeks before surgery may be considered	Ungraded good practice statement	Expert opinion

Recommendation on duration of PAP in patients colonized with MDR-GNB before surgery		
PAP should be discontinued within 24 hours after surgery in patients colonized with MDR-GNB	Strong	Moderate
In transplant surgery other than renal transplant, the extension of PAP duration to 48-72 hours may be considered according to the type of transplant	Ungraded good practice statement	Expert opinion

Abbreviations: MDR-GNB= multidrug-resistant Gram-negative bacteria, ESCR-E= extended-spectrum cephalosporin-resistant Enterobacterales, PAP= perioperative antibiotic prophylaxis, CRE= carbapenem-resistant Enterobacterales, CRAB= carbapenem-resistant *Acinetobacter baumannii*, FQR-E= fluoroquinolone-resistant Enterobacterales, TRUSPB= transrectal ultrasound-guided prostate biopsy

Table 2. Characteristics of studies comparing postsurgical infectious complications in MDR-GNB carriers versus noncarriers

Author, year	Type of study	Country	Study Period	Type of surgery	Target bacteria	Carrier % (screened patients)	Time between sampling and surgery	Prophylaxis used	Postoperative infections (%); Post-surgical follow-up time
Bert, 2012 [a]	Prospective cohort study	France	2001 – 2010	LT	ESCR-E	4 (710)	On the day of LT	Cefoxitin	13/29 (45) carriers vs. 26/681 (4) noncarriers (p<0.0001); 120 d
Bert, 2014 [a]	Prospective cohort study	France	2009 – 2011	LT	ESCR-E	16 (317)	On the day of LT	Cefoxitin	24/50 (48) carriers vs. 18/267 (7) noncarriers (P < 0.001); 120 d
Golzarri, 2019	Prospective cohort study	Mexico	2014 – 2015	GI and GYN	ESCR-E	18 (171)	On the day of admission	Cefuroxime (23%), metronidazole (12%), ceftriaxone (10%), ciprofloxacin (5%), clindamycin (4%), cephalothin (1%)	SSIs: 10/37 (27) carriers (results includes also 7 post-surgical carriers) vs.15/34 (11) noncarriers (P=0.016); ESCR-E SSIs 11% carriers vs. 4% noncarriers; 30 d
Dubinsky-Pertzov, 2019	Prospective cohort study	Israel, Switzerland Serbia	2012 – 2017	Colorectal	ESCR-E	14 (3600)	14 days to 1 hour prior to surgery	Cephalosporin + metronidazole	SSIs: 55/220 (25) carriers vs. 49/440 (11) noncarriers, P < 0.001; ESCR-E SSIs 7% carriers vs. 2% noncarriers; 30 d
Apisarnthanarak, 2019 [b]	Prospective cohort study	Thailand	2017 – 2019	Abdominal	ESCR-E	36 (360)	Within 1 day before surgery	2G Ceph (48%), 3G Ceph (25%), BLBLI (14%), carbapenems (12%)	SSIs: 40/129 (31) carriers vs. 11/231 noncarriers (5); ESCR-E SSIs 6% carriers vs. 0% noncarriers; 28 d
De Pastena, 2021	Prospective, nonrandomized interventional study	Italy	2015 – 2018	Pancreatic	ESCR-E	11 (679)	Within 3 weeks prior to surgery	Ampicillin/sulbactam (56%), piperacillin/tazobactam (44%)	41/76 (54) carriers vs. 221/603 (37) noncarriers; SSIs: 32/76 (42) vs. 171/603 (28); NA
Logre, 2021	Retrospective cohort study	France	2010 – 2016	LT	ESCR-E	13 (749)	During follow-up before LT (NA) and at the time of transplant	ESCR inactive (16%) and active (84%: cefoxitin 40%, carbapenem 31%, piperacillin/tazobactam 29%)	ESCR-E infections 45/100 (45) carriers (39% same ESCR-E strain) vs. 23/649 (4) noncarriers; 30 and 90 d
Giannella, 2015	Prospective cohort study	Italy	2010 – 2013	LT	CRE (CRKP)	4 (237)	Multiple times before LT [c]	Ampicillin/sulbactam	CRKP infections: 18% carriers vs. 2% noncarriers (P<0.001); 180 d
Mazza, 2017	Retrospective cohort study	Italy	2012 – 2015	LT	CRE (CRKP)	3 (310)	On the day of LT	Ampicillin/sulbactam	CRKP infections: 3/10 (30) carriers vs. none in noncarriers (5/10 in post-LT carriers); ND
Giannella, 2019	Prospective cohort study	Italy	2010 – 2017	LT	CRE (CRKP)	7 (553)	Multiple times before LT [d]	Ampicillin/sulbactam	CRKP infections: 14/38 carriers (37) vs. 6/406 (2) noncarriers; 1 year
Freire, 2021	Retrospective cohort study	Brazil	2010 – 2018	LT	CRE CRAB	13 (762) 4 (762)	On admission for LT	Ampicillin + cefotaxime (61), ampicillin + amikacin (39)	CRE SSIs: 22/98 (22) carriers vs. 5% noncarriers, P=0.001; 30 d CRAB: 8/28 (29) carriers vs. 3% noncarriers, P=0.001; 30 d
Freire, 2016	Prospective cohort study	Brazil	2009 – 2011	LT	CRAB	12 (196)	On the day of LT	Ampicillin + cefotaxime; 4 (16) added polymyxin	CRAB infections: 11/24 (46) carriers vs. 45/172 (26) noncarriers; (carriers: 20% CRAB vs. 8% nonCRAB infections, P=0.002); 120 d

If not reported as SSIs (surgical site infections), infections are intended as any postoperative infection. Risk of bias reported in Supplementary Material (Appendix 2). Sampling was performed by rectal swab (RS) for all studies reported except Freire 2016 (also throat and axilla swabs obtained).

[a] Bert 2012 and 2014: partial data overlap possible during 01/2009-04/2010; [b] Apisarnthanarak included swabs until day 5 after surgery; [c] Giannella 2015: RS performed monthly while on a waiting list; colonization detected from day 40 until transplant day; [d] Giannella 2019: RS positivity at a median time of 12 d pre-LT (IQR 0.75-40).

Abbreviations: ESCR-E= extended-spectrum cephalosporin-resistant Enterobacterales; CRE= carbapenem-resistant Enterobacteriaceae; CRKP= carbapenem-resistant *K. pneumoniae*; CRAB= carbapenem resistant *A. baumannii*; 2G Ceph= second generation cephalosporins; 3G Ceph= third generation cephalosporins; GI= gastrointestinal; GYN= gynecological; LT= liver transplant; NA= not available; d= days.

Table 3. Options for perioperative antibiotic prophylaxis regimens for targeted prophylaxis in MDR-GNB carriers

MDR-GNB colonization type	Regimen for culture-based approach[a]	Intraoperative dosing[b]	WHO AWaRe class [33,34]	Comments and Clinical Use[c]
ESCR-E	Ampicillin/sulbactam 3 g IV [5,18]	Every 2-4 hours [5,18]	Access	• Use alternatives in penicillin allergic • Postoperative dosing every 6-8 hours • Amoxicillin/clavulanate IV alternative [5] • For ESCR-E treatment, ESCMID guidelines conditionally recommend amoxicillin/clavulanate for low-risk, non-severe infections (moderate certainty of evidence) and for stepdown targeted therapy (good practice statement) [37]; not enough evidence for ampicillin/sulbactam recommendations
	Gentamicin 5 mg/kg IV [5,18]	–	Access	• Used in case of penicillin allergy [5,18] • Amikacin alternative [5] • Consider avoiding aminoglycosides in combination with other nephrotoxic drugs or in case of renal dysfunction [5] • Administer in addition to anaerobic coverage (according to the type of surgery and allergic status) [5] • For ESCR-E treatment, ESCMID guidelines conditionally recommended aminoglycosides for short treatments in non-severe infections (e.g., UTIs; moderate certainty of evidence) [37]
	Ciprofloxacin 400 mg IV [5,18]	–	Watch	• Levofloxacin IV alternative [5,18] • Administered in addition to anaerobic coverage (according to the type of surgery and allergic status) • Postoperative dosing every 12 hours • For ESCR-E treatment, ESCMID guidelines conditionally recommend quinolones for low-risk, non-severe infections (moderate certainty of evidence) and for stepdown targeted therapy (good practice statement) [37]
	Ertapenem 1 g IV [5]	–	Watch	• Due to antimicrobial stewardship considerations, limit carbapenem use if alternatives available [5,67] • Preferred to meropenem/imipenem due to 1. single administration, 2. reserve other carbapenems for severe infections [37] • Caution in suspect immediate hypersensitivity to beta-lactams • For ESCR-E treatment, ESCMID guidelines recommends carbapenems as preferred regimen for severe infections; for BSIs without septic shock ertapenem may be preferred to imipenem or meropenem (conditional recommendation, moderate certainty of evidence) [37]
	Piperacillin/tazobactam 3.375-4.5 g IV [5,18]	Every 2-4 hours [5,18]	Watch	• Use alternatives in penicillin allergic • Postoperative dosing every 6-8 hours • Ongoing RCT (not targeted on carrier status) vs. cefoxitin in pancreatic surgery (NCT03269994) • For ESCR-E treatment, ESCMID guidelines conditionally recommend piperacillin/tazobactam for low-risk, non-severe infections (moderate certainty of evidence) and stepdown targeted therapy (good practice statement) [37]
	Other alternatives	According to the regimen used	According to the regimen used	• Other antibiotics may be considered if susceptibility confirmed by susceptibility tests (e.g., IV trimethoprim-sulfamethoxazole, fosfomycin)

				• For ESCR-E treatment, ESCMID guidelines recommend trimethoprim-sulfamethoxazole for non-severe cUTIs or stepdown targeted therapy (good practice statement); no evidence for cephamycins and cefepime therefore not recommended for use; fosfomycin recommended for cUTIs (strong recommendation, high certainty of evidence) [37]
FQR-GNB (TRUSPB)	Cotrimoxazole 160/800 mg PO [5]	Every 12 h	Access	• PO or IV administration • Prolonged (> 72 h) postoperative duration should be avoided
	Gentamicin 3-5 mg/kg IV [99]	–	Access	• Used in case of penicillin allergy [5] • Amikacin alternative [5] • Consider avoiding aminoglycosides in combination with other nephrotoxic drugs or in case of renal dysfunction [5] • Unclear prostate penetration by aminoglycosides and conflicting results on efficacy; further studies required for establishing the efficacy
	Cephalosporins [5,99]	Every 2-4 hours	Watch	• Susceptibility should be confirmed by susceptibility test (e.g., cefazolin, cefoxitin, cefuroxime)
	Fosfomycin 3 g PO [99]	–	Watch	• Susceptibility should be confirmed by susceptibility test • Limit to single dose or to 24 h post biopsy
	Other alternatives	According to the regimen used	According to the regimen used	• Other agents such as aztreonam (Reserve WHO AWaRe class), amoxicillin/clavulanate, piperacillin/tazobactam, ertapenem may be used according to preoperative cultures • Avoid broad-spectrum antibiotics if other options are available

The table reports antibiotic regimens with dosing recommended by previous guidelines on perioperative surgical prophylaxis (including guidelines that do not specifically address MDR-GNB colonization before surgery) [5,18]. For culture-based approach, susceptibility should be confirmed by susceptibility test.
Antibiotic regimens are reported in alphabetical order and according to the WHO AWaRe class (Access, Watch, and Reserve) [35,36]
Dosing reported for adults > 40 Kg with normal renal function. Obesity and renal impairment may require dose adjustments [5]
PAP should be administered within 60 minutes before the incision (for fluoroquinolones and vancomycin the infusion should be started 120 minutes prior to incision) [5]

[a]For culture-based approach, local stewardship protocols should be considered if multiple alternatives are available
[b]Intraoperatively redosing may be necessary depending on the duration of the procedure, the half-life of the antibiotics employed and should be considered in patients who have significant blood loss during surgery [5]
[c] Clinical use: ESCMID recommendations for the use of the indicated regimens in the treatment of ESCR-E are reported [37].

ESCR-E= extended-spectrum cephalosporin-resistant Enterobacterales; BSIs= bloodstream infections; UTIs= urinary tract infections; PK= pharmacokinetics; FQR= fluoroquinolone resistant; IV= intravenous; PAP= perioperative antibiotic prophylaxis; PO= oral; TRUSPB= transrectal ultrasound-guided prostate biopsy