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Screening for Intestinal Carriage of Extended-spectrum Beta-lactamase–producing Enterobacteriaceae in Critically Ill Patients: Expected Benefits and Evidence-based Controversies

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The rising burden of intensive care unit (ICU)-acquired infections due to extended-spectrum beta-lactamase–producing Enterobacteriaceae (ESBL-E) strengthens the requirement for efficient prevention strategies. The detection of intestinal carriage of ESBL-E through active surveillance cultures (ASC) and the implementation of contact precautions (CP) in carriers are currently advocated in most high-income countries, to prevent cross-transmission and subsequent ESBL-E infections in critically-ill patients. Yet, recent studies have challenged the benefit of ASC and CP in controlling the spread of ESBL-E in ICUs with high compliance to standard hygiene precautions and no ongoing outbreak of ESBL-producing *Klebsiella pneumoniae* or *Enterobacter* spp. Besides, given their debated performance to positively predict which patients are at risk of ESBL-E infections, ASC results appear of limited value to rationalize the empirical use of carbapenems in the ICU, emphasizing the urgent need for novel anticipatory and diagnostic approaches. This Viewpoint article summarizes the available evidence on these issues.

Keywords. extended-spectrum beta-lactamase; contact precautions; critical care; carbapenem; ventilator-associated pneumonia.

The rising prevalence of intensive care unit (ICU)-acquired infections due to extended-spectrum beta-lactamase–producing Enterobacteriaceae (ESBL-E) and the human and economic costs that they induce intensify the necessity for efficient prevention strategies [1]. Since the gut microbiome stands as the main reservoir of invasive ESBL-E strains, a search-and-isolate strategy, based on screening for intestinal carriage through active surveillance cultures (ASC) and the implementation of contact precautions (CP) in identified carriers, is currently advocated by international guidelines for ICUs facing ESBL-E endemicity or ongoing outbreaks [2, 3]. This policy primarily aims at preventing the cross-transmission of strains and/or ESBL-encoding plasmids and, thereby, subsequent ESBL-E infections in patients not colonized at admission. In addition, since prior colonization acts as a strong risk factor for ESBL-E infection, ASC results could assist the fine-tuning of empirical antibiotic therapy in critically-ill patients with sepsis by inciting intensivists to opt for carbapenems rather than other broad-spectrum beta-lactams in documented ESBL-E carriers [1, 4]. However, the benefit of ASC for controlling the spread of ESBL-E and rationalizing the use of carbapenems in the ICU has been increasingly challenged by the recent literature. In this short narrative review, we sought to summarize the available evidence on these issues.

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ACTIVE SURVEILLANCE CULTURES AND CONTACT PRECAUTIONS IN THE CRITICAL CARE ENVIRONMENT

ESBL-E—notably, CTX-M–producing *Escherichia coli*—have globally disseminated in the community, with estimated carriage prevalences ranging from 2 to 12% in Europe, 5 to 47% in Africa, 7 to 44% in Southeast Asia, and 29 to 63% in the West Pacific area [5]. This pandemic drives a continuous influx of ESBL-E into the hospital system that adds to the pool of inpatients colonized with healthcare-associated lineages. Thus, carriage prevalence at ICU admission is rapidly increasing, and now commonly reaches 10–15% in Europe and up to 40% in certain Asian countries [6], although marked fluctuations are observed depending on the hospital location and case mix (Supplementary Table S1). Of note, the prevalence of imported

carriage in a given ICU has been linked to the likelihood of ESBL-E acquisition among patients not colonized at admission, a phenomenon referred as to colonization pressure [7, 8]. This, along with variations in infection control policies, may explain why the average in-ICU acquisition rates remain quite limited in Europe and the Americas (ie, 3–4%) while exceeding 20% in high-prevalence areas [9] (Supplementary Table S1).

In addition to hand hygiene (HH) and other standard precautions, the concept of CP implies the utilization of single-bed rooms; patient-dedicated equipment; single-use gloves and gowns for healthcare workers during contacts with carriers or contaminated environments; and the signalization of carriage to ensure compliance [3]. Historically, CP have proven efficiency to control ICU outbreaks of hospital-associated ESBL-E clones, especially ESBL-producing *Klebsiella pneumoniae* and *Enterobacter* spp, both being associated with a more pronounced ability for patient-to-patient spreading than ESBL-producing *E. coli* [10, 11]. The determinants of this observation are manifold. One may suggest that patients colonized with ESBL-producing *K. pneumoniae* or *Enterobacter* spp. differ from those carrying ESBL-producing *E. coli* in terms of comorbidities and prior contacts with the healthcare system [12, 13]. This could reflect more requirements for nursing care and invasive procedures, as well as more frequent antimicrobial exposure (that is, a more severe intestinal dysbiosis, with a higher faecal relative abundance of ESBL-E), resulting in an increase in the probability of cross-transmission events. Also, prolonged environmental contamination is probably less of an issue with ESBL-producing *E. coli* than with other ESBL-E.

Yet, apart from epidemic situations, controversies have emerged on whether a systematic ASC and CP policy may help in preventing ESBL-E cross-transmission in hospital units applying current hygiene standards. Studies conducted in wards notably failed to demonstrate a superiority of CP to contain the spread of ESBL-producing *E. coli*, when compared to standard precautions [14]. It has also been shown that ESBL-E cross-transmission occurs rarely—even in double-bed rooms—in wards with a high level of compliance to standard precautions [10, 15]. Similar results have been increasingly reported in the critical care setting over the recent years. In the European multi-ICU MOSAR trial, universal screening for the carriage of multidrug-resistant (MDR) Enterobacteriaceae (mostly non–*E. coli* ESBL-E) and the implementation of CP in carriers had no measurable added value on acquisition rates after a first educational phase that increased HH compliance from 52 to 77% and included daily chlorhexidine body-washing [16]. The MOSAR investigators confirmed afterwards that the transmissibility of ESBL-E between ICU patients was actually weak, and was even 3 times lower for ESBL-producing *E. coli* when compared to other ESBL-E (number of secondary cases per index carrier: 0.047 and 0.17, respectively) [17]. These findings corroborate those of several single-center studies based on molecular methods (strain and/or ESBL typing) that reported very low rates of cross-transmission from documented ESBL-E carriers, including in units without single-bed rooms, suggesting other potential sources of acquisition, such as healthcare workers, contaminated environmental reservoirs, or patient transports outside the ICU [18, 19].

Contact isolation measures have been associated with a variety of deleterious side-effects, including patients' psychological distress and an increased hazard of adverse events or medical errors [20, 21]. Another key issue is the relatively high frequency of false-negative ASC samples—up to 25%—due to incorrect rectal swabbing procedures or colonization densities of ESBL-E below the detection thresholds [10]. Next, a policy of universal ASC generates both a massive workload for laboratory staffs and substantial expenditures for the hospital system, although its health-economic benefit has not been re-appraised in the contemporary epidemiological context. However, in a dynamic model of ESBL-E dissemination in a 10-bed ICU with an assumed baseline acquisition rate of 15%, improving HH compliance before and after each contact with patients from 60% to 80% was more effective and cost saving than routine carriage screening and CP isolation [22].

The targeted screening of patients with pre-specified risk factors for ESBL-E carriage (ie, recent antimicrobial exposure and/or transfer from long-term care facilities, wards, or other ICUs, especially if abroad) appears as a potentially cost-saving alternative to extended ASC [23]. In 2 before-and-after studies conducted in French ICUs with rates of imported ESBL-E carriage in the range of those usually reported in Northern European countries (that is, 6–7%), switching from universal to targeted ASC had no impact on the incidence of ICU-acquired ESBL-E infections [24, 25]. Of note, patients admitted directly from home through the emergency department and without known predisposing factors for ESBL-E carriage may be colonized by community-acquired ESBL-producing *E. coli*. These patients would be missed by a policy of targeted screening; nonetheless, and as discussed above, the hazard of cross-transmission from such unidentified carriers of ESBL-producing *E. coli* is probably negligible, provided that standard precautions are strictly applied. More pragmatically, in 2 recent studies conducted in ICUs with a relatively low prevalence of ESBL-E, high compliance to standard precautions, and only single-bed rooms, no change was observed in the incidence densities of ICU-acquired ESBL-E colonization and infection following the complete discontinuation of ASC and CP [26, 27], further raising doubt regarding the relevance of these measures in the absence of an outbreak. Still, ASC may be warranted for transferred or repatriated patients at high risk of carriage of carbapenemase-producing Enterobacteriaceae or other extensively drug-resistant Gram-negative bacteria (GNB), such as pan-resistant *Acinetobacter* spp.

ACTIVE SURVEILLANCE CULTURES DATA AND EMPIRICAL ANTIMICROBIAL THERAPY

ASC may provide relevant ecological insights at both individual and ICU levels for the steering of empirical therapy in critically-ill patients. Yet, the relative risk of ICU-acquired ESBL-E infection is up to 50-fold higher in patients with a previously-documented ESBL-E carriage than in those without [9]. Considering that the impaired outcome associated with ESBL-E infections mainly ensues from ineffective first-line coverage [28], the colonization status is understandably seen as a decisional tool to optimize the likelihood of adequate empirical therapy in patients with suspected nosocomial sepsis [1]. Nevertheless, this approach fosters a massive over-consumption of carbapenems in carriers not infected with ESBL-E [4], which may then enhance the spread of non-fermenting GNB exhibiting intrinsic (eg, *Stenotrophomonas maltophilia*) or acquired (eg, *Pseudomonas aeruginosa* mutants with modified OprD porin) resistance to this antimicrobial class [29]. This excess use of carbapenems could also contribute to the ongoing pandemic of carbapenemase-producing Enterobacteriaceae [30], although definite evidence is still lacking to confirm this hypothesis.

Overall, ESBL-E infections occur during ICU stays in only 10 to 25% of critically-ill patients with intestinal colonization [4, 6, 26, 31]. In those receiving mechanical ventilation, ESBL-E are responsible for ~40% of ventilator-associated pneumonia (VAP) [6, 32], while accounting for merely 7% of infection-related ventilator-associated complications [33]. Therefore, in an era of growing prevalence of colonization, identifying those carriers at risk for infection constitutes a pivotal challenge for carbapenem sparing in the ICU. Studies that focused on this issue yielded conflicting results on the predictive role of clinical parameters, such as prior length of the ICU stay, previous exposure to non-carbapenem antimicrobials (including beta-lactam/beta-lactamase inhibitor combinations, third-generation cephalosporins, or fluoroquinolones), or imported versus ICU-acquired carriage [6, 31, 33]. Patients colonized with ESBL-producing *K. pneumoniae* or *Enterobacter* spp. are seemingly at higher risk of infection than those colonized with ESBL-producing *E. coli* [6, 11], an association that might depend on clinical features of the carriers rather than on differences in invasiveness between species. To date, except for the protective effect of a recent exposure to carbapenems, no reliable predictor of ESBL-E infection may help limiting their empirical use in documented carriers [33]. Moreover, if the absence of documented colonization has a >90% negative predictive value for ESBL-E infections [34], it does not definitively rule out the involvement of such pathogens, due to the aforementioned possibility of a false-negative ASC or, more anecdotally, an acquisition of carriage between the last available ASC sample and the occurrence of infection. Also, a negative ASC sample for ESBL-E does not exclude an infection caused by other carbapenem-requiring GNB (eg, ceftazidime-resistant *P. aeruginosa* or MDR *Acinetobacter baumannii*). It is especially noteworthy that roughly half of culture-positive VAP episodes in ESBL-E carriers implicate non-fermenting GNB (including carbapenem-resistant isolates), alone or in combination with ESBL-E [6, 32, 33]. Hence, a policy of routine screening for intestinal carriage of ESBL-E appears of limited value to rationalize the use of carbapenems in ICU patients.

DEALING WITH THE EXTENDED-SPECTRUM BETA-LACTAMASE–PRODUCING ENTEROBACTERIACEAE PANDEMIC: PERSPECTIVES FOR INTENSIVISTS

The prevalence of ESBL-E carriage at ICU admission and the resulting colonization pressure are expected to increase steadily in the years to come, unless strong counter-measures are taken. In this global endemic situation, universal interventions could more effectively prevent cross-transmission than a carrier-centred approach. Sustained efforts to ensure a high level of compliance to HH (that is, above 80%) and other standard measures (eg, environmental disinfection and handling of excreta) are of paramount importance [35]. Overall, routine ASC and the implementation of CP should now be focused on highly-resistant pathogens, such as vancomycin-resistant enterococci or carbapenemase-producing GNB.

Antimicrobial stewardship initiatives are equally essential, since avoiding agents that degrade the normal gut microbiome and the colonization resistance that it confers might protect against ESBL-E acquisition [1, 35]. It has notably been reported that prior exposure to beta-lactam/beta-lactamase inhibitor combinations, third-generation cephalosporins (3GC), fluoroquinolones, and even carbapenems may predispose patients to in-ICU acquisition of ESBL-E carriage [8, 9]. Along this line, comparative metagenomic-based studies are warranted to better appraise the impact of antimicrobials on the gut ecosystem, including for agents without activity against Enterobacteriaceae but with a potent anti-anaerobe effect (eg, metronidazole) [36]. Antimicrobial adsorption in the intestinal lumen represents another promising track to reduce their ecological side effects [37].

New algorithms to restrain the empirical use of carbapenems in patients at risk for ESBL-E infection should be considered, given the poor specificity of qualitative ASC. Features of ESBL-E strains (especially virulence determinants) and those of the carrier's gut microbiome (namely, richness and diversity) could putatively impact the hazard of infection [36]. Next-generation sequencing technologies may yield new insights on the virulome and invasiveness of a given ESBL-E strain—as well as its potential for patient-to-patient dissemination—although such markers will not be shortly available at a bedside [38]. Also, the faecal relative abundance of MDR pathogens—including ESBL-E—correlates with the likelihood of infection in non-ICU patients [39–41], suggesting a potential role for quantitative ASC in critically-ill carriers. Then, in mechanically-ventilated patients, oropharyngeal and lower respiratory tract surveillance cultures have been shown

to usefully predict the pathogens responsible for subsequent VAP [42, 43]; however, this point remains to be specifically addressed for ESBL-E VAP. Next, recently-released beta-lactam/beta-lactamase inhibitor combinations (ie, ceftolozane-tazobactam and ceftazidime-avibactam) exhibit activity against multidrug-resistant *P. aeruginosa* (including carbapenem-resistant isolates), as well as certain ESBL-E strains (particularly ESBL-producing *E. coli*) [44], and could theoretically be considered as empirical regimen when both pathogens are suspected. However, clinical and ecological data remain somewhat scarce in critically-ill patients [45], leaving space for further studies to define their potential role as first-line drugs.

On a short-term basis, rapid diagnostic tools stand as the most pragmatic option to detect or exclude an ESBL-E in clinical samples and customize the empirical regimen of ICU patients when an infectious event arises, or to allow earlier de-escalation in those initially treated with a carbapenem. These tests may first be based on chromogenic assays that rapidly detect 3GC-hydrolyzing enzymes (including ESBL) on clinical specimens or early cultures. Direct antimicrobial susceptibility testing (AST) on clinical samples (eg, broncho-alveolar lavage fluid for patients with suspected VAP) is another relevant approach, as it provides susceptibility data from 24 to 48 hours earlier than conventional, subculture-based AST. Moreover, several molecular assays, allowing the detection of ESBL-encoding genes on clinical samples, have been recently released. Although their accuracy still requires in-depth and multi-center appraisal in ICU patients, these tools raise major hopes for the improvement of antibiotic stewardship practices in this specific population. Table 1 summarizes the available evidence on the diagnostic performances and potential applications for these tests.

CONCLUSIONS

In an era of global ESBL-E dissemination and a massive influx of colonized patients in the ICU setting, we believe that infection prevention strategies should focus on universal measures—with the aim of ensuring a high level of compliance to HH and other standard precautions—and not on a search-and-isolate policy based on the detection of all ESBL-E carriers through intestinal ASC (Table 2). Targeted screening and CP remain a conceivable

Table 1. Selection of Commercially Available or Homemade Diagnostic Tests for Earlier Detection of Extended-spectrum Beta-lactamase–producing Enterobacteriaceae in Clinical Samples

Diagnostic Tests	Clinical Samples	Performance for ESBL-E Detection (Available Published Data)	Time From Sampling to Results	Selected References
β-Lacta Test[a] (Bio-Rad, France), **chromogenic tests** for the detection of 3GC-hydrolyzing enzymes (including ESBL)	Urine with GNB on DE; tracheal aspirate (MV patients) with GNB on DE and/or culture ≥ 10.4 cfu/mL; blood culture positive for GNB	Se 87–100%, Sp 100%; Se 100%, Sp 100%, PPV 100%, NPV 100%; Se 100%, Sp 96%, PPV 90%, NPV 100%	60–120 min (test, 15 min); 60–120 min (test, 15 min); variable[b] (culture + 3-hour subculture + 15-min test)	[46] [47] [48]
Rapid ESBL NP Test[c] (homemade), chromogenic tests for the detection of 3GC-hydrolyzing enzymes (including ESBL)	Urine with GNB on DE; blood culture positive for GNB	Se 100%, Sp 99%, PPV 98%, NPV 99%; Se 100%, Sp 100%, PPV 100%, NPV 100%	60–120 min (test, 15 min) Variable[b] (test, 30–45 min)	[49] [50, 51]
Direct AST on respiratory sample without sub-culture (homemade)	Broncho-alveolar lavage (MV patients) with GNB on DE	Se 100%, Sp 95%, PPV 94%, NPV 100% (values are for 3GC resistance in Enterobacteriaceae: ESBL and other mechanisms)	18–24 hours	[52]
Verigene BC-GN (Luminex), automated multiplex PCR for pathogen identification and detection of bla_{CTX-M} genes	Blood culture positive for GNB	Se 80–93%, Sp 99–100%, NPV 93–99%, PPV 97–100% (values are for *Escherichia coli* and *Klebsiella pneumonia* only)	Variable[b] (test, 2.5 hours)	[53, 54]
Unyvero (Curetis, Germany) Automated multiplex PCR for pathogen identification and detection of bla_{CTX-M} genes	Tacheal aspirate and broncho-alveolar lavage (HPN cartridge); blood culture (BCU cartridge); urine (UTI cartridge)	Se 100%, Sp 85–95%, NPV 100%, PPV 20–40% (values are for *E. coli* and *K. pneumonia* only); not published; not published	4–5 hours; 4–5 hours; 4–5 hours	[55] … …
Accelerate pheno system (Accelerate Diagnostics) Automated FISH (pathogen identification) and AST	Positive blood culture	Agreement with culture-based AST for ceftriaxone resistance in Enterobacteriaceae, 95–97%	Variable[b] (test, 6–7 hours)	[56, 57]

Abbreviations: 3GC, third-generation cephalosporins; AST, antimicrobial susceptibility testing; DE, direct examination; ESBL, extended-spectrum beta-lactamase; ESBL-E, ESBL-producing Enterobacteriaceae; FISH, fluorescence in situ hybridization; GNB, Gram-negative bacteria; MV, mechanical ventilation; NPV, negative predictive value; PCR, polymerase chain reaction; PPV, positive predictive value; Se, sensibility; Sp, specificity.

[a]The β-Lacta Test detects all cephalosporin-hydrolyzing enzymes, including ESBL; chromosomal and plasmid-borne AmpC cephalosporinases; and carbapenemases, which may decrease the specificity of this test for the detection of ESBL in settings where other cephalosporine-hydrolyzing beta-lactamases are prevalent.

[b]Depending on the time to positivity of blood cultures (usually 6 to 12 hours for bloodstream infections, due to Enterobacteriaceae).

[c]The Rapid ESBL NP Test only detects ESBL.

Table 2. Key Messages

- Rates of imported ESBL-E carriage are rapidly increasing in most ICUs worldwide, owing to the successful spread of these pathogens (especially CTX-M–producing *E. coli*) in both community and hospital ecosystems.
- Universal screening for intestinal carriage of ESBL-E through ASC and the implementation of contact precautions in identified carriers appears of limited added value to prevent cross-transmission events in those ICUs with high compliance to standard precautions and no ongoing outbreak of ESBL-producing *K. pneumoniae* or *Enterobacter* spp.
- The results of qualitative ASC for ESBL-E carriage are neither sufficient nor efficient to rationalize the empirical use of carbapenems in ICU patients.
- Novel predictive and diagnostic approaches (including phenotypic or molecular rapid diagnostic tools on clinical samples) are needed to customize the empirical antimicrobial therapy in critically-ill patients at risk for ICU-acquired ESBL-E infections.

Abbreviations: ASC, active surveillance cultures; ESBL, extended-spectrum beta-lactamase; ESBL-E, ESBL-producing Enterobacteriaceae; ICU, intensive care unit.

approach in critical-care environments with uncontrolled endemicity or outbreaks of ESBL-producing *K. pneumoniae* or *Enterobacter* spp., while the available evidence argues against the usefulness of such interventions in ICUs where ESBL-producing *E. coli* predominate. Given the rising incidence of healthcare-associated infections due to carbapenem-resistant GNB, a paradigm shift from ACS-based empirical regimen to new diagnostic approaches is urgently needed to restrain the overconsumption of carbapenems in patients at risk for ICU-acquired ESBL-E infections. The use of clinical algorithms, including rapid diagnostic tests, which are able to rule out the involvement of ESBL-E based on high negative predictive values, will probably help ICU physicians to choose the best therapeutic options in patients with suspected healthcare-associated infections.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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