Contact Precautions for Preventing Nosocomial Transmission of Extended-Spectrum β Lactamase–Producing Escherichia coli: A Point/Counterpoint Review

Sarah Tschudin-Sutter,¹ Jean-Christophe Lucet,² Nico T. Mutters,³ Evelina Tacconelli,⁴ Jean Ralph Zahar,⁵ and Stephan Harbarth⁶

¹Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Switzerland; ²Infection Control Program, Bichat University Hospital, Paris, France; ³Heidelberg University Hospital, Department of Infectious Diseases, and ⁴Division of Infectious Diseases, Department of Internal Medicine I, German Center for Infection Research (DZIF), Tübingen University Hospital, Germany; ⁵Infection Control Unit, Microbiology Department, Avicenne Hospital, Paris-Nord University (UHR SMBH), Bobigny, France; and ⁶Infection Control Programme, Geneva University Hospitals and Medical School, Switzerland

Contact precautions have been recommended for hospitalized patients colonized or infected with extended-spectrum β-lactamase–producing Escherichia coli (ESBL-EC). Despite such recommendations, a steady, worldwide increase of ESBL-EC has been reported. We discuss arguments in favor of and against contact precautions for ESBL-EC carriers. Healthcare settings with high ESBL-EC colonization pressure, extended hospital stay, and close contact between patients may serve as amplification platforms, further accelerating transmission. However, the evidence base for justifying the implementation of contact precautions for all ESBL-EC carriers remains weak. Until more high-level evidence is available, we support the attitude that hospitals and countries should carefully evaluate their decision on whether to implement contact precautions for ESBL-EC carriers. It is likely that a majority of patients and wards do not need to rely on contact precautions for preventing nosocomial ESBL-EC transmission in nonepidemic settings, without harming patient safety, providing sufficient compliance with standard precautions and ongoing surveillance.

Keywords. ESBL-producing Escherichia coli; ESBL-EC; contact precautions; nosocomial transmission.

Contact precautions have been recommended for hospitalized patients colonized or infected with extended-spectrum β-lactamase (ESBL)–producing Escherichia coli (ESBL-EC) to prevent further nosocomial spread [1, 2]. Despite the implementation of such recommendations, a steady increase of ESBL-EC related to both healthcare- and community-associated infections has been reported globally [3]. This trend is of particular concern, as ESBL-producing Enterobacteriaceae show reduced rates of response to antimicrobial treatment [4, 5], resulting in an increased use of carbapenems, thus fostering the emergence of carbapenem-resistant bacteria. Transmission of ESBL producers is further complicated by ESBL genes being encoded on self-transmissible plasmids, which can be exchanged among the same and different species of Enterobacteriaceae [6].

Contact precautions comprise a bundle of different infection control measures, such as allocation to single rooms or adequate spatial separation between beds in shared rooms, wearing gloves and gowns for all interactions with both the patient or the patient’s direct environment, and enhanced cleaning and disinfection of the patient’s environment, all aimed at avoiding spread by direct or indirect contact. While the rationale to introduce such measures is obvious, drawbacks include associated costs, concerns regarding patient safety, and disputable benefits regarding their effect on halting the rapidly expanding ESBL-EC epidemic, calling for a careful evaluation of their effectiveness and cost-benefit ratio.

The objective of this article is to discuss arguments in favor of and against contact precautions for patients colonized or infected by ESBL-EC in the healthcare setting. This review is intended as a general overview of complementing and antagonizing perspectives on this controversial issue, rather than a systematic review of the literature with evaluation of the evidence base.

**POINT: TRANSMISSION OF ESBL-EC IS A POTENTIAL RISK IN HEALTHCARE SETTINGS Requiring Implementation of Contact Precautions**

Transmission of ESBL-EC is Relevant in Healthcare Settings, Which Represent an Underrecognized Epidemiological Reservoir of ESBL-EC

The main reservoir of ESBL-EC is the digestive tract of colonized patients. The prevalence of ESBL-EC in the general population varies according to continents, with high prevalence in Southeast Asia, Africa, and Central America, and lower prevalence in Europe [7]. The prevalence of ESBL-EC in Western European populations can, however, reach 10%, including countries with low hospital prevalence (eg, the Netherlands or Scandinavian countries) [8].

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Correspondence: S. Harbarth, Hôpitaux Universitaires de Genève, Service Prévention et Contrôle de l’Infection, CH-1211 Genève 14, Switzerland (stephan.harbarth@hcuge.ch).

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Unsurprisingly, the prevalence of ESBLs in the hospital setting is higher than in the community. For example, the prevalence of ESBL producers at hospital admission to acute care and rehabilitation varied between 12.8% and 26.4% in recent multicenter studies [9, 10]. The transmission rate has repeatedly been estimated to be at least 2-fold higher from patients colonized with ESBL Klebsiella pneumoniae (ESBL-KP) than from those colonized with ESBL-EC, suggesting that it is less transmissible than ESBL-KP [11–13]. The low transmission rates of ESBL-EC, at 2.6% in contact patents sharing the same room, was confirmed in acute care, but it reached 8.6% in a geriatric rehabilitation hospital, with the probability of transmission increasing with the duration of room sharing [14]. If we consider that transmission of mobile genetic elements is possible between E. coli from the same species or between different species of Enterobacteriaceae, transmission rates might, however, be even higher.

The burden of transmission has to be considered in addition to the transmission rate. A recent study in 14 large Dutch centers showed a higher transmission rate in ESBL Enterobacter cloacae and K. pneumoniae (10% and 11%) than in E. coli (4.4%). However, 61% of all ESBL transmissions were attributable to E. coli, against 27.8% and 11.1% for K. pneumoniae and E. cloacae, respectively [15].

Such data provide the rationale to suggest that contact precautions may be a valuable tool to decrease the likelihood of ESBL-EC transmission, independent of other basic control measures.

ESBL-EC Has the Potential to Cause Outbreaks and Serious Health Economic Adverse Outcomes

ESBL-EC is increasingly reported to cause outbreaks and severe infections in both healthcare [16] and community settings [17], with serious health economic adverse outcomes such as increased in-hospital mortality, high rates of clinical failure, prolonged length of stay, and increased direct and indirect costs [3, 18–20]. Although the low incidence density of transmission, ranging from 0.4 to 4.2 per 1000 exposure-days [12, 21], does not enable the microorganism to cause sustained outbreaks, it does not limit its ability to be responsible for short-term outbreaks in clinical settings [21–23]. The attack rate or clinical manifestation index, the number/percentage of colonized patients developing an infection with ESBL-EC within a certain time frame, varies from 1% to 39% [23–28], with the majority of studies reporting that up to one-third of all ESBL-colonized patients develop an infection due to a strain genetically close to the colonizing one [27]. Importantly, outbreaks due to ESBL-EC may originate from different sources, including food, water, and endogenous colonization [29]. Following the emergence of presumably highly virulent and transmissible strains of ESBL-EC, such as the sequence type 131 (ST131) H30 lineage, large-scale nosocomial outbreaks have been reported, suggesting that standard precautions may not suffice to control epidemics due to specific clones [30, 31]. A recent meta-analysis concluded, however, that current epidemiologic data do not sufficiently support or reject the hyperendemicity of specific clones [32].

The added burden of diseases due to ESBL-EC is important. A recent meta-analysis showed that ESBL production in Enterobacteriaceae is associated with a higher mortality compared with bacteremia due to ESBL-negative Enterobacteriaceae, although the estimate of this association is partly affected by adjustments [33]. Mortality of healthcare-associated infections was significantly higher than that of community-acquired infections (31% vs 11%) [34, 35]. Infections with ESBL-EC have also been associated with increased healthcare costs by 25%–48% compared to those due to non-ESBL producers [18, 19] due to prolonged infection-related length of stay (11.6 vs 7.5 days) and indirect care costs for enhanced infection control measures [18, 19]. A large pan-European cohort study of >600000 inpatients from 10 hospitals recently confirmed these estimates: Bacteremia due to ESBL producers significantly increased the hazard of death (1.63; 95% confidence interval [CI], 1.13–2.35), length of stay (4.9 days; 95% CI, 1.1–8.7 days), and cost compared with susceptible strains [3].

ESBL-EC May Cause Relevant Environmental Contamination in Healthcare Settings

Contamination of the environment and patient’s surroundings appears to be of limited importance in transmission of ESBL-EC in healthcare settings [36]. However, there may be relevant environmental contamination of surfaces or materials by E. coli, as illustrated by a few outbreak reports [37–39]. Escherichia coli can easily colonize perianal and inguinal regions, thus, frequently used surfaces (eg, toilet seats) could serve as reservoirs for further transmission [40]. Studies in the field of environmental and veterinary microbiology have shown that E. coli contamination and shedding can be important from various innate or alive E. coli sources [41]. This has also been suggested by experimental studies performed in neonatal care settings [42]. Thus, certain types of patients and hospital wards are prone to ESBL-EC transmission via the environment or hidden superspreaders, suggesting that contact precautions for specific ESBL-EC carriers may add benefit to standard precautions.

ESBL-EC May Serve as a Reservoir of Mobile Genetic Resistance Elements for Other Enterobacteriaceae

ESBLs in the 1980s were associated with hospital outbreaks due to K. pneumoniae carrying ESBLs derived from the SHV and TEM β-lactamases. In the early 2000s, the emergence of ESBL CTX-M clones was only observed in E. coli, with rapid community worldwide dissemination, especially the presumably more invasive and superspreading E. coli ST131 CTX-M15 [32]. Other Enterobacteriaceae were not found carrying the
CTX-M β-lactamase. Nowadays, both flows are tightly interlinked. Specifically, hospital ESBL-KP and ESBL-producing Enterobacter species mostly carry CTX-M enzymes, showing that species of Enterobacteriaceae can easily share enzymes. Molecular analysis from 5 European rehabilitation units showed that 27 of the 28 clones of ESBL-KP harbored at least 1 CTX-M enzyme [43]. The same figure was observed in ESBL-producing E. cloacae [44]. It is therefore likely that ESBL-EC may serve as a reservoir of mobile genetic elements for other species of Enterobacteriaceae. There are strong arguments supporting a higher frequency of conjugation between species of Enterobacteriaceae in the digestive flora with large concentration of ESBLs, a frequent situation in hospitalized patients receiving antibiotic treatment [45, 46]. Possible sharing of mobile genetic elements between Enterobacteriaceae, especially from E. coli to those with higher ability for spreading, suggests that patients with any ESBL-producing Enterobacteriaceae should be placed under contact precautions.

Evidence-Based Guidelines Supporting Contact Precaution Measures for ESBL-EC in Nonepidemic Settings

The 2015 European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines provided strong recommendation, although with moderate evidence, to implement contact precautions to reduce the spread of ESBL-producing Enterobacteriaceae in nonepidemic hospital settings [1]. After their publication more evidence became available. In the Mastering Hospital Antimicrobial Resistance in Intensive Care Units (MOSAR-ICU) study, in-hospital transmission rates were 3 times higher for ESBL than for vancomycin-resistant enterococci or methicillin-resistant Staphylococcus aureus (MRSA) [9]. It is also important to underline that the guidelines focused only on the evidence available in hospitalized patients whereas other health systems such as long-term-care facilities (LTCFs) or rehabilitation centers were excluded. In these settings, ESBL-EC intra- and interfacility transmission has been recently demonstrated. In 9 nursing homes including 567 individuals followed for 2 years with repeated sampling, ESBL-EC strains from residents living in adjacent rooms were found to be closely genetically related [47]. In a cross-sectional survey in 2 Canadian LTCFs, approximately one-fourth of residents carried ST131 E. coli resembling ST131 clinical isolates, and molecular analyses proved cross-transmission [48].

The availability of new data on E. coli transmission questions the cessation of contact precautions to contain the spread of ESBL-EC, in particular in immunocompromised and elderly patients. Until new evidence is available, implementation of contact precautions in these populations should be warranted to reduce morbidity and mortality of severe infections due to ESBL-EC. Furthermore, contact precautions should be considered to control presumably hyperendemic and highly pathogenic clones, such as the ST131 H30-Rx E. coli strain [31].

COUNTERPOINT: TRANSMISSION OF ESBL-EC IS LOW IN HEALTHCARE SETTINGS NOT REQUIRING IMPLEMENTATION OF CONTACT PRECAUTION MEASURES

The Epidemiologic Reservoir of ESBL-EC is Not the Hospital but the Community

A growing body of evidence points to community reservoirs as the most important driver for the emergence and spread of ESBL-EC. Transmission in households has been shown to outweigh nosocomial transmission [11]. High rates of ESBL carriage have been identified in healthy individuals, especially in returning travelers [49], and an abundance of ESBL genes have been recovered from the food chain, with >90% of chicken meat [50, 51] and almost 20% of pork being contaminated with ESBL-EC [52]. While the relevance of transmission of ESBL-producing strains from food sources to humans has been questioned, transmission of distinct plasmids may contribute to dissemination of ESBL genes between different reservoirs [33].

Transmission models aiming to predict the effect of contact precautions on rates of ESBL-producing Enterobacteriaceae revealed limited impact of such interventions, if most of the incidence originates from sporadic sources, as encountered during community-associated acquisition [54]. Similarly, an uncontrolled intervention study assessing the impact of a hospital-wide screening strategy for ESBL producers and consecutive implementation of contact precautions for patients found to be colonized or infected revealed no reduction in nosocomial incidence rates [55]. In conclusion, if community acquisition outweighs healthcare-related acquisition, the overall, population-based incidence rates are unlikely to be influenced by contact precautions in hospitals.

Transmission Rates of ESBL-EC Are Low in Acute Care Settings, and ESBL-EC Has Low Potential to Cause Outbreaks

At a tertiary care center, exposure to patients colonized or infected with ESBL-EC resulted in transmission in 1.5% of cases [13]. This low rate of transmission in acute care settings has been supported by similar single-center studies performed in different institutions supporting its generalizability [11, 21]. In line with these findings, a reduction of nosocomial ESBL-EC or ESBL-KP rates was not achieved by universal screening strategies and consecutive implementation of contact precautions [55]. Transmission of ESBL-EC may increase with prolonged contact time [14], supporting the observation that transmission in household settings outweighs transmission in acute care settings. In contrast to ESBL-KP, nosocomial outbreaks with ESBL-EC are less frequently reported when querying both the outbreak (www.outbreak-database.com) and the Medline (National Library of Medicine Bethesda, Maryland) databases (based on the number of hits related to the respective search terms), supporting lower transmission rates for ESBL-EC compared with other ESBL producers. We acknowledge, however, that quantification of hits related to search terms may lead to
biased estimates regarding the true extent of the number of nosocomial outbreaks.

ESBL-EC Has Low Potential to Survive in the Hospital Environment

The ability of a pathogen to sustain itself in the hospital environment is one of the key requirements for its successful nosocomial spread. In rooms occupied by patients colonized or infected with ESBL-producing Enterobacteriaceae, 4% of all environmental samples yielded ESBL producers. Whereas Klebsiella species accounted for 89% of all positive samples, E. coli was only identified in 10.5% and colonization or infection with ESBL-KP was the only independent risk factor related to surface contamination [56]. Strikingly similar figures were identified in a second study performed at a different institution assessing hospital environmental contamination with ESBL producers, underscoring the reproducibility of these findings [57]. While admission to an intensive care unit (ICU) room previously occupied by a patient with multidrug-resistant Pseudomonas aeruginosa or Acinetobacter baumannii has been identified as an independent risk factor for respective acquisition by subsequent room occupants, such a relationship could not be identified for ESBL-producing Enterobacteriaceae [36]. Overall, these studies suggest that ESBL-EC may be less successful than other gram-negative bacteria in surviving for extended periods on environmental surfaces, thus limiting the possible impact contact precautions may have on further spread.

No Evidence Supporting Contact Precaution Measures for ESBL-EC in Nonepidemic Settings

As contact precaution measures are almost always implemented as part of a bundle of different infection control strategies, their isolated effect on controlling multidrug-resistant organisms (MDROs) can hardly be estimated. Although isolation measures were conducted during outbreak situations [58, 59], little is known about their efficacy in an endemic setting. Currently, there is no published randomized trial (although several controlled clinical trials are still ongoing) suggesting the effectiveness of contact isolation to control the spread of ESBL-EC. In a quasi-experimental study, authors found that contact precautions contributed to outbreak prevention but had no impact on nosocomial ESBL incidence [60]. More recently, an observational study comparing 2 hospitals with different control policies suggested that contact isolation measures were inefficient to limit the spread of ESBL-EC [61]. Moreover, in a recent multicenter randomized trial conducted in 13 European ICUs, active surveillance and contact isolation were ineffective to control the spread of MDROs [9]. Several hypotheses might explain the lack of efficiency of contact isolation for controlling ESBL-EC. First, contact isolation might be poorly beneficial in a context of high hand hygiene compliance. Second, according to different culture methods, active surveillance may fail to detect a large reservoir of carriers, and so underestimate the colonization pressure, as direct culture has been shown to fail to identify up to 26% of rectal carriers of ESBL-producing Enterobacteriaceae [62]. Finally, as selective pressure seems to play a key role in acquisition [63] and spreading [64], hygiene measures alone without an antimicrobial stewardship program may be insufficient.

CONSENSUS AND FUTURE RESEARCH QUESTIONS

Settings with high ESBL-EC colonization pressure, extended hospital stay, and close contact between vulnerable patients may serve as amplification platforms to further accelerate transmission of ESBL-EC. Furthermore, the contribution of transmission of plasmids rather than strains to ongoing ESBL transmission is currently elusive. Such considerations may favor contact precautions for patients colonized or infected with ESBL-EC. The potential benefits of such a strategy, however, need to be carefully balanced against its drawbacks, such as impediment of patient care and safety, socioeconomic burden, competing infection control priorities, and possibly low impact on overall incidence. Low transmission rates in healthcare settings, poor potential for survival in the hospital environment, and community transmission dominating nosocomial transmission may outweigh the potential benefits of contact precautions for controlling ESBL-EC, providing the considerations and circumstances detailed below.

Although more research on the value of contact precautions for hospitalized ESBL-EC carriers is needed to validate this control measure and a number of important clinical trials are currently under way, the evidence base for justifying the implementation of contact precautions for all identified ESBL-EC carriers is rather weak. Several powerful arguments highlighted by the “Con” section of this review support this attitude. However, clinicians and hospital epidemiologists should be aware that specific settings and patient populations could still benefit from contact precautions; for instance, carriers of specific ESBL-EC ST131 clones in high-risk settings or LTCFs may still warrant contact precautions to prevent ongoing cross-transmission and outbreaks. In settings in which ESBL colonization is associated with high co-colonization rates for other pathogenic MDROs, such as MRSA or carbapenemase-producing Klebsiella species [65], introducing pathogen-specific isolation strategies for ESBL-EC may be cumbersome. When abandoning contact precautions for ESBL-EC carriers, a few prerequisites need to be fulfilled: (1) high compliance with standard precautions including hand hygiene, (2) ongoing surveillance and early detection of nosocomial ESBL-EC outbreaks, and (3) if possible, sporadic molecular typing of ESBL-EC infection isolates to exclude ongoing nosocomial transmission of virulent and presumably highly transmissible ESBL-EC ST131 clones, such as the H30-Rx subclone. While we acknowledge that achieving such conditions may not be convertible for all
institutions, especially when access to molecular typing and further identification of underlying resistance mechanisms is limited, we support the opinion that achieving high compliance with standard precautions and hand hygiene is achievable even in low-resource settings [66]. We further recognize that introducing pathogen-specific isolation policies (i.e., delineating infection control strategies for ESBL-EC from those for other gram-negative MDROs) requires solid understanding, comprehensive staff education, and sophisticated alert systems, as well as strong support by the infection control team.

If resources are limited, especially regarding single rooms, priority should be given to place carriers of non–E. coli ESBL producers into contact precautions, as they may cause a higher rate of cross-transmission. Until more high-level evidence is available, we support the attitude that hospitals and countries should individualize their decision on whether to implement contact precautions for ESBL-EC carriers in their setting. However, it is likely that a large majority of patients and wards do not need to rely on contact precautions for controlling nosocomial ESBL-EC transmission, with no harm to patient safety.

Notes

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