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Important note: Knowledge and practices regarding the most effective measures to control the spread of ESBL-producing enterobacteria are constantly evolving. It should therefore be noted that the recommendations contained in this document reflect the state of knowledge at the time of original printing in 2008.

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INTRODUCTION

Most international recommendations for the prevention of the nosocomial transmission of microorganisms resistant to antibiotics target methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE).

In light of the continuing increase in antibiotic resistance in Gram-negative bacteria and in particular the emergence of extended spectrum ß-lactamase (ESBL) producing enterobacteria, it seemed necessary to create specific recommendations for these multiresistant organisms.

The objective of this booklet is to optimize the detection of ESBL-producing bacteria in the laboratory and to offer practical advice on the prevention, surveillance and control of the cross-transmission of these organisms.

However, in contrast to MRSA, there is little scientific consensus on the most effective measures to control the spread of ESBL-producing enterobacteria in hospitals. The literature on the subject often offers expert opinions that are contradictory, depending on the type of situation (an endemic situation or a nosocomial epidemic), the affected patient population (intensive care or other hospital departments), the bacterial species or the type of ESBL involved.

Similarly, the literature is contradictory on the question of which groups are at risk and would therefore benefit from screening.

Considering the general lack of conclusive evidence in the literature, we have chosen to present this booklet in the form of a series of Questions & Answers. The questions deal with practical subjects, from diagnosis to the surveillance, prevention and control of ESBL-producing enterobacteria in the hospital setting.

We are aware that many of the recommendations in this document may be open to discussion and must in any case be reassessed in the coming years as to their applicability as well as their beneficial impact on the control of the nosocomial transmission of ESBL-producing resistant organisms.

Belgian Working Party of the
Belgian Infection Control Society (BICS)

Table of Contents

MICROBIOLOGY

1 WHAT IS AN ESBL?

- ESBLs are defined as ß-lactamases that contain serine in their active site and belong to class A or D of the Ambler classification and to group 2be of the Bush-Jacoby classification. They are capable of hydrolyzing penicillins, all cephalosporins (including third and fourth generations, C3G and C4G) and aztreonam.

They do not hydrolyze carbapenems nor temocillin and are inhibited in vitro by ß-lactamase inhibitors (clavulanic acid, tazobactam and sulbactam).

The structural genes are carried by mobile genetic elements such as plasmids, integrons and transposons. These elements are transferable between strains of the same species and between species. In contrast to type *Amp*C cephalosporinases (not inhibited by ß-lactamase inhibitors), ESBLs do not hydrolyze cephamycins such as cefoxitin, but can inactivate fourth-generation cephalosporins (cefepime and cefpirome).

2 ARE ESBLs A NEW PHENOMENON?

- The production of ß-lactamases is not a new phenomenon, since the mechanism exists in nature. The first enzymes were discovered well before the clinical use of penicillin. However, during a period of heavy use of ß-lactams, particularly since the introduction of broad-spectrum cephalosporins in the early '80s, bacterial ß-lactamases evolved greatly–towards more diversification, enlargement of their spectrum of activity and spread among numerous species of enterobacteria and nonfermentative bacilli such as *Pseudomonas* spp. and *Acinetobacter* spp.

The majority of ESBLs are derived from single mutations in the genetic sequence of the active site of the first-known ß-lactamases (TEM-1, TEM-2 and SHV-1). Other more recent enzymes (CTX-M) have their origin in the cephalosporinases forming certain plant bacterial species (*Kluyvera* spp.) that inserted into transposable genetic elements. Currently there are more than 350 different ESBLs, and numerous unrelated enzymes have been described (OXA, CTX-M, PER, VEB, GES, BES, TLA, SFO and IBC).

RISK FACTORS

3 WHAT ARE THE RISK FACTORS FOR COLONIZATION OR INFECTION BY AN ESBL-PRODUCING STRAIN?

- Many studies have analyzed the risk factors for hospitalized patients to acquire an ESBL-producing strain (by colonization or infection). Most of these studies have been set in intensive care units. The majority of these have been case-control studies and numerous differences exist between them, in terms of the selected populations, the sample size, and the selection of cases and controls. In general, it is mainly severely ill patients who acquire ESBL-producing bacterial infections, following prolonged hospitalization and after exposure to invasive procedures (intravenous catheters, vesical catheters or endotracheal tubes). Other risk factors include malnutrition, hemodialysis, total parenteral nutrition, admission to intensive care or prior hospitalization.

Factors related to antibiotic therapy have frequently been associated with risk: prior exposure to third-generation cephalosporins (and also to fluoroquinolones, aminoglycosides and cotrimoxazole), the number of antibiotics administered and the length of treatment.

A stay in a long-term care center has also been considered to be a risk factor in certain countries. These centers can become reservoirs of multiresistant *E. coli* and *Klebsiella* strains. Oral treatment with antibiotics such as cotrimoxazole and fluoroquinolones facilitates the colonization by this type of strain in long-term care center residents. The spread of ESBL-producing bacteria in this context is associated with the difficulty in applying hygiene measures such as wearing gloves or disinfecting hands. Advanced age, repeated urinary infections, diabetes and fluoroquinolone treatment are recognized as risk factors in nonhospitalized patients.

This explains why in a great number of cases, ESBLs are found in patients hospitalized in geriatrics, rehabilitation, hematology-oncology, intensive care or pneumology departments. It is important to emphasize that the majority of studies investigating these risk factors were performed in the context of nosocomial epidemics caused by old ESBL forms, such as TEM and/or SHV.

There is currently little known about the risk factors associated with new ESBLs (CTX-M). In many cases, no link can be established with a hospital or any other healthcare facility (rest home or nursing home), nor with prior patient exposure to antibiotics.

An animal source has been suggested because CTX-M ESBLs are largely found in the intestinal microflora of farm animals, in particular in bacterial species which can be transmitted to man via the food chain (e.g. *Salmonella* spp., *E. coli*).

ESBL TESTING SITES

4 WHAT COLLECTION METHODS SHOULD BE USED FOR ESBL SCREENING?

- The preferred collection methods for ESBL screening are:
  - rectal swab or stool sample
  - urine (in the presence of a urinary catheter)

The following additional collection sites could also be used (though the value of testing these additional sites has not been demonstrated):

- endotracheal or bronchial expectorations and secretions (patients in ICU with assisted respiration)
- wounds
- umbilicus, armpit or inguinal fold (in neonatology)

5 IS A SINGLE COLLECTION SITE SUFFICIENT FOR ESBL SCREENING?

- **Yes**

In contrast to MRSA testing, no convincing data has shown any added value of collecting samples from several sites rather than just one. If a single sample is collected, a stool sample or rectal swab are preferred, as ESBL-producing bacterial are generally found in the intestinal flora. Under no circumstances should an inguinal or perineal smear be used as an alternative to a rectal swab.

6 CAN I COLLECT SAMPLES FROM THE SAME SITES FOR ESBL AND MRSA SCREENING ?

- **No**

This is not appropriate since the best methods for detecting these microorganisms are very different.

A nasal, throat, axillary or inguinal swab are the preferred methods for MRSA screening but are not effective for ESBL screening.

When screening, it is important to specify on the laboratory test form the methods used and the types of bacteria to be detected (MRSA or ESBL-producing enterobacteria).

HOW TO TEST FOR ESBLs IN THE LABORATORY

7 SHOULD AN ENRICHMENT MEDIUM BE USED FOR ESBL SCREENING?

- Contrary to MRSA screening, there is no proven benefit to using an enrichment medium to test for ESBL-producing organisms in patients.

It is possible that detection sensitivity could be increased, but the use of enrichment broths also extends the length of the procedure by at least 24 hours.

8 SHOULD ALL ENTEROBACTERIAL ISOLATES IN THE LABORATORY BE CONSISTENTLY TESTED FOR ESBLs?

- **Yes**

Several European and American studies have shown that a large number of participating laboratories (30 to 50 percent) did not correctly identify ESBLs.

Failure to detect or late identification of an ESBL isolate could lead to therapeutic failure due, for example, to the administration of broad-spectrum cephalosporins (third or fourth generation), which, in a great number of cases, could seem to be effective when tested using conventional methods.

Furthermore, certain ESBL-producing organisms are capable of creating outbreaks and can spread quickly among patients and across hospital units and hospitals when requisite control measures are not applied.

In addition to the species in which they were initially found (*E. coli*, *K. oxytoca* and *K. pneumoniae*), ESBLs are now present in the majority of Enterobacteriaceae species, such as *Enterobacter* spp., Citrobacter spp., Serratia spp., *Salmonella* spp., *Proteus mirabilis*– and many others.

Because ESBL genes are located on mobile genetic elements (plasmids, transposons, integrons), these enzymes have the ability to spread rapidly in and across species and genera, not only in hospitals but also in the community.

That is why it is strongly recommended that ESBL detection is carried out systematically for all enterobacteria. Nevertheless, it must be emphasized that current detection and interpretation procedures are limited to a small number of organisms (*E. coli*, *Klebsiella* spp., *Proteus mirabilis*). Consequently, species identification is essential to correctly interpret the results.

9 IS IT POSSIBLE TO DETECT ESBLs USING ONLY ONE ANTIBIOTIC SUBSTRATE?

- **No**

Screening accuracy depends on the cephalosporin(s) used as a first-line "indicator," the bacterial species and the type of ESBL.

To improve the accuracy of ESBL detection, it is advisable to use a combination of at least two indicator cephalosporins.

The antimicrobial agents most often used as indicators in screening tests are ceftazidime, cefotaxime, ceftriaxone and aztreonam.

In inducible enterobacterial species (*Enterobacter* spp., *Citrobacter freundii*, *Serratia marcescens*, *Providencia* spp.), screening tests are unable to distinguish ESBLs from hyperproduced *Amp*C chromosomal cephalosporinases.

In *K. oxytoca*, resistance to certain indicator substrates (aztreonam, ceftriaxone and cefotaxime) more often indicates the presence of a hyperproduced chromosomal K1 ß-lactamase than that of an ESBL. In all of these examples, complementary tests are necessary to confirm the presence of an ESBL.

10 IS IT POSSIBLE TO DETECT AN ESBL USING ONLY ONE METHOD?

- **No**

Enterobacterial isolates resistant to one of the first-line indicator cephalosporins should be confirmed by phenotypic tests. The confirmation of ESBL production depends on the determination of a synergy between a ß-lactamase inhibitor (clavulanic acid), and the cephalosporin(s) to which the isolate was initially resistant.

Different methods can be routinely used for confirmation: double disk tests, combination disk methods, ESBL Etest®. For *E. coli*, *Proteus mirabilis* and *K. pneumoniae*, the use of ceftazidime and cefotaxime are recommended as confirmation agents. For organisms with hyperproduced *Amp*C chromosomal cephalosporinases (for example, *Enterobacter* spp.), cefepime or cefpirome are recommended.

In ESBL detection, it is always strongly recommended to use a combination of two methods:

1. A screening test that detects resistance or decreased sensitivity to ceftazidime, cefotaxime, ceftriaxone and aztreonam. Since no "indicator" cephalosporin alone is able to detect all types of ESBL, testing several cephalosporins (at least two) is recommended as a first-line procedure.

2. A second confirmatory test, based on the synergy between a cephalosporin (cefotaxime or ceftazidime) and a ß-lactamase inhibitor (clavulanic acid), should then be carried out. This test could be a double disk test, combination disk method or ESBL Etest®.

11 IS MANUAL DETECTION PREFERABLE TO AN AUTOMATED METHOD?

● **No**

Currently there is no ideal method for ESBL detection. The most routinely used automated systems for bacterial identification and for antibiotic susceptibility testing (VITEK® 2, bioMérieux; Phoenix, BD) include ESBL detection. These systems have shown a sensitivity comparable to that of manual ESBL detection tests for *E. coli* and *Klebsiella* spp.

Nevertheless, certain problems remain for ESBL detection:

- the large number of enzymes with different substrate affinities,
- the varying level of expression of enzyme activity (ESBL-producing strains often show Minimum Inhibitory Concentrations (MICs) below the resistance threshold or critical values),
- the presence of other co-expressed resistance mechanisms (cephalosporinases in inducible bacteria such as *Enterobacter* spp., or reduction of permeability by porin modification) that can mask the inhibitory effect of clavulanic acid and interfere with synergy tests for detection.

Automated methods are generally based on the Clinical Laboratory Standard Institute (CLSI®) criteria and currently only include ESBL detection for *E. coli*, *Klebsiella* spp. and *P. mirabilis*. Phenotypic confirmation methods can also produce false-positive results (for example, hyperproduction of chromosomal K1 penicillinase in *K. oxytoca*) and false negatives (ESBL masked by the hyperproduction of cephalosporinases in *E. aerogenes*).

Despite the development of different tests for ESBL detection, the optimal detection of this mechanism in inducible bacteria, such as *Enterobacter* spp., is still being studied.

Currently, it seems insufficient to rely solely on the use of automated tests. Confirmation based on a combination of several methods (automated and manual) is essential and significantly improves result specificity.

12 IS IT IMPORTANT TO CONSISTENTLY REPORT THE PRESENCE OF ESBLs AND INTERPRET THE RESULTS FOR ALL ENTEROBACTERIA?

● Studies carried out in different countries show that a considerable number of laboratories (20 to 40 percent) do not report and/or do not interpret the presence of detected ESBLs.

However, it is important to consistently report the presence of ESBLs detected in bacteria isolated from clinical samples for several reasons:

1. The relatively high number of strains falsely reported to be susceptible (without interpretation or therapeutic correction).

2. The increased risk of therapeutic failure.

3. The increased potential risk of cross-transmission.

A large proportion of ESBL-producing strains are sometimes falsely reported to be susceptible to cephalosporins of the third (cefotaxime, ceftriaxone, ceftazidime) or fourth (cefepime) generations, or to aztreonam, in particular when the bacterial inoculum size is weak or when the susceptibility test incubation period is short (automated systems). These strains often prove to be resistant when the inoculum is stronger and/or the incubation period prolonged.

Several studies have shown that ESBLs can have a major clinical impact in terms of complications and associated mortality, and these outcomes are most frequently observed in cases of inappropriate treatment.

The CLSI® currently recommends considering ESBL-producing strains of *E. coli*, *Klebsiella* spp. and *Proteus mirabilis* as resistant to all penicillins, cephalosporins (including third and fourth generations) and aztreonam. A brief note should therefore be included in the lab

report explaining that the presence of ESBLs in these bacteria can be associated with treatment failure if these antibiotics are used, and that therapeutic alternatives (for example, carbapenems) should be used in cases of severe infection (strain isolation by hemoculture or any other deep testing site).

Given the possible implication of ESBLs in nosocomial outbreaks, it seems necessary to report their presence each time they are detected in the laboratory, in order to limit further spread within healthcare facilities.

OUTBREAK DETECTION

13 HOW CAN AN OUTBREAK OF ESBL-PRODUCING ENTEROBACTERIA BE DETECTED?

- As for the detection of all outbreaks or clusters of cases caused by multiresistant bacteria, initial information will be based on laboratory data.

An outbreak can be defined as the appearance of cases of nosocomial infections or colonizations at an incidence level significantly higher during a risk period compared to the incidence level of the preceding period. This phenomenon is presumably linked to the onset or increase in the frequency of nosocomial transmission.

A minimum operational threshold for intervention could be the observation of a cluster of two or more new cases of the same species with the same susceptibility profile within a one-month period in the same treatment unit in clinical samples taken outside of a screening program.

14 HOW SHOULD AN ESBL OUTBREAK BE INVESTIGATED/CONFIRMED?

- The steps to follow for the investigation and control of outbreaks caused by ESBL-producing bacteria include the definition of cases, the identification of infected and colonized patients (including by active surveillance of patient colonization), an estimate of the clinical impact (number of cases of severe infection and mortality), the use of molecular tests to investigate the clonal and/or plasmidic character of the outbreak, and the initiation of additional contact precautions to be used above all in cases of clonal spread.

A statistical verification of the outbreak can be carried out using the monthly incidence level of the nosocomial acquisition of a defined phenotype (species, ESBL type, resistance profile). The outbreak curve showing the number of new cases by unit of time should be calculated on a weekly, or at most monthly basis in order to follow the trend over time, depending on the mean exposure/incubation period.

If these measures fail, other possible measures are the determination of the transmission mode, including testing for environmental contamination source, identifying risk factors such as antibiotic use, or exposure to enteral nutrition and invasive procedures. The search for specific environmental reservoirs can be adjusted according to the identification of the bacterial species.

For more information, go to www.outbreak-database.com.

SURVEILLANCE

15 SHOULD THE PRESENCE OF ESBL-PRODUCING ENTEROBACTERIA BE TESTED IN THE ENVIRONMENT?

- **No**

Such testing is only useful in certain outbreak situations.

In the majority of cases, cross-transmission is due to contact with the hands of healthcare workers (HCW). Nevertheless, some isolated cases of contamination have occasionally involved the environment (for example, stethoscopes, thermometers, endoscopes, ultrasound equipment, bathtubs, bath gels, shampoo, artificial nails, as well as insects such as cockroaches).

The search for an environmental contamination source can be considered when the usual outbreak control measures have failed.

In such cases, molecular typing of ESBL-producing isolates from infected or colonized patients is important to determine the clonal distribution and identify clusters of cross-transmission or clusters linked to an environmental source.

16 WHEN AND WHY SHOULD STRAINS BE SUBMITTED FOR MOLECULAR TYPING?

● Typing strains using a high-resolution genotypic method is necessary to confirm the hypothesis of clonal transmission. For enterobacteria, the Pulsed-Field Gel Electrophoresis (PFGE) technique after macrorestriction is recommended as the most reliable. Typing by arbitrary/repeat element PCR (AP-PCR, rep-PCR) can also be useful if the system's accuracy and reproducibility have been validated.

To detect the transfer of plasmids, analyses and plasmid typing, even the conjugative transfer of the resistance phenotype, are necessary and require the resources of a reference laboratory.

Ideally, strain typing should confirm an outbreak and is particularly useful at the beginning of an outbreak. Molecular typing is probably of less use in an endemic scenario.

17 SHOULD ESBLs BE MONITORED IN HOSPITALS?

● **Yes**

Hospitals are advised to monitor the resistance level and incidence (number) of new nosocomial cases on a monthly basis for each department.

Ideally, this data should be used to make a monthly report to department heads and should include a graph showing indicator trends as well as a list of cases.

It is also advisable for hospitals to participate in a national Surveillance Network.

At the hospital level, ESBL surveillance has the following objectives:

- Comparison of incidence and resistance levels with those of other hospitals
- Validation (in terms of accuracy) of the laboratory data (ESBL identification)
- Typing of endemic strains.
  The typing of strains in the context of an epidemic is part of another strategy (see question 16).

18 SHOULD PATIENTS BE SCREENED FOR ESBL-PRODUCING BACTERIA ON ADMISSION TO HOSPITAL?

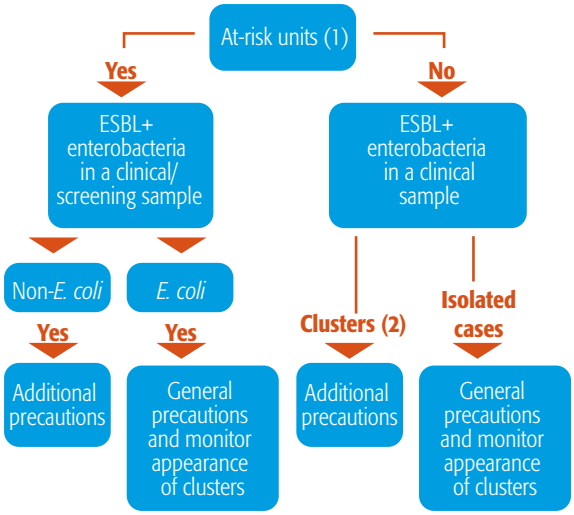
● Given the lack of data in the literature on non-outbreak situations and considering the units where outbreaks have been observed, it seems prudent to recommend screening on admission and then regularly during a stay in an "at-risk" unit.

At-risk units include: intensive care, burn, oncology-hematology, hemodialysis and organ transplant units. However, this list is not exhaustive and screening measures should be determined by infection control specialists according to local epidemiology.

ADDITIONAL PRECAUTIONS

19 WHEN SHOULD ADDITIONAL PRECAUTIONS BE USED?

● All enterobacteria capable of secreting ESBLs do not have the same outbreak potential. It has been shown that cross-transmission is not the principal mode of transmission for ESBL+ *E. coli* since its genotype often shows polyclonality.



(1) Intensive care, hematology-oncology, hemodialysis and burn units
(2) See the question concerning outbreaks for the definition of clusters.

Additional precautions should be applied:

- Routinely for ESBL-producing enterobacteria except *E. coli* in at-risk units.
- For all ESBL-producing bacteria regardless of the unit if there is an outbreak.

20 WHAT MINIMUM PRECAUTIONS SHOULD BE TAKEN FOR ALL PATIENTS? A REMINDER OF GENERAL PRECAUTIONS.

● The goal of the general precautions is to prevent the transmission and spread of microorganisms. These precautions should be observed by all staff in contact with patients. Respecting these measures reduces the risk of transmission between patients of multi-drug resistant organisms (MDRO) as well as all other infections, such as MRSA, for example. In addition, healthcare workers can protect themselves from infection from patients with these measures.

The general precautions, which have been outlined by the American Centers for Disease Control and Prevention (CDC), can be summarized as follows:

- General precautions required all healthcare workers to disinfect their hands with an alcohol-based hand cleanser before and after each contact with a patient.
- If hands are visibly soiled, wash them first with soap and water and dry them before rubbing them with an alcohol-based handrub solution.
- If contact with a patient's blood or body fluids is likely, precautions should be taken to avoid direct contact with them. Gloves, and if necessary a gown or mask, should be worn.
- After removing the gloves, hands should be disinfected with an alcohol-based handrub solution.
- All measures should be taken to avoid needle sticks or cuts.

This strategy should also be used in a larger context, for example when handling laundry, disposing of medical waste and during the daily cleaning of frequently touched surfaces in patients' rooms.

21 WHAT PERSONAL PROTECTIVE EQUIPMENT SHOULD BE ADOPTED?

● Personal protective equipment (PPE) against ESBL+ enterobacteria includes:

- Non-sterile gloves used during patient care and in case of possible contact with the patient's environment.
- When administering multiple treatments to a single patient, depending on the sequence of treatments, gloves should be changed and hands disinfected each time the gloves are removed.
- A protective gown with long sleeves to be worn over work clothes.

This gown should ideally be disposable and be changed for each patient. If using a cotton gown, it should be changed as soon as it is soiled.

The protective gown should be located at the entrance to the patient's room and should therefore be put on before entering the room if a HCW's work clothes may come into contact with the patient or the patient's environment.

When leaving the room, the way and above all the sequence of removing PPE is very important to avoid contamination of hands or work clothes.

For more information:

http://www.cdc.gov/ncidod/dhqp/ppe.html
http://www.cdc.gov/ncidod/dhqp/pdf/ppe/ppeposter148.pdf

If a gown is not disposable, it should be hung on a coat rack, taking care not to contaminate the side of the gown in direct contact with the work clothes. Try to adopt the best practice possible to avoid contamination according to the facilities and means available at local level.

Removal of the gown and gloves should be followed by hand disinfection with an alcohol-based handrub solution.

When cohorting patients (placing several ESBL+ patients in the same room), the same gown can be used for several patients (as long as it is not soiled or wet). However, gloves should be changed between patients and hands disinfected each time gloves are removed. Hands must be disinfected before taking a new pair of gloves from the box.

All of these measures should also be adopted by people who may not be directly linked to patient care but who are in contact with many patients (volunteers, religious ministers, dieticians, social workers, etc.).

In Practice

Personal protective equipment (PPE) to be used for all physical contact with the patient or the patient's environment:

- Non-sterile gloves
- Long-sleeved gown

Before and after wearing gloves, hands must be disinfected with an alcohol-based handrub solution.

22 SHOULD I WEAR A MASK WHEN TREATING AN ESBL+ PATIENT FOR WHOM "CONTACT" PRECAUTIONS ARE BEING APPLIED?

● **No**

A mask is not routinely recommended to prevent the transfer of enterobacteria.

However, during procedures that could create spattering of body fluids or during treatment of patients who have had procedures such as a tracheotomy or bronchoscopy, a mask should be used, as outlined in the general precautions.

23 SHOULD I WEAR A MASK IF THE PATIENT'S RESPIRATORY TRACT IS INFECTED AND THE PATIENT COUGHS?

● **No**

Even if the patient's respiratory tract is infected and the patient coughs, a mask is unnecessary.

Use masks as outlined in general precautions. However, if there is a risk of the projection of secretions due to heavy coughing, the healthcare worker should wear a mask. The presence of a carrier of ESBL-producing Gram-negative bacteria in the respiratory tract is not an indication for wearing a mask. The transfer of the bacteria occurs mainly through direct contact. It is therefore important to take precautionary measures and above all to observe good hand hygiene.

24 SHOULD I TAKE CONTACT PRECAUTIONS IF I ENTER A PATIENT'S ROOM TO DELIVER A FOOD TRAY?

● **No**

As long as no other activity is carried out in the room (helping the patient get settled to eat, for example, or positioning the tray table). Hands must be disinfected with an alcohol-based handrub solution afterwards.

25 SHOULD CLEANING STAFF ALSO TAKE CONTACT PRECAUTIONS?

● Cleaning staff are not in direct contact with patients, but they are in contact with the patient's potentially contaminated environment. Furthermore, they move from room to room.

That is why:

- The room of an ESBL+ patient should be cleaned last (as for all multiresistant bacteria).
- Wearing nonsterile gloves is recommended.
- Wearing a protective gown is recommended.
- Hands should be disinfected after glove removal, on leaving the room.

26 BESIDES TAKING CONTACT PRECAUTIONS, SHOULD THE PATIENT BE ISOLATED?

● Ideally yes, because even patients carrying an infection solely in the digestive tract contaminate their environment.

Cohorting patients is possible but difficult to manage because other species could emerge in a single patient because of antibiotic selection pressure.

If isolation is impossible, it is reasonable to think that certain situations contaminate the environment more than others. The infection control team and the treatment staff should decide together which measures would be best to put in place.

27 CAN TWO PATIENTS CARRYING DIFFERENT SPECIES OF ESBL+ ENTEROBACTERIA STAY IN THE SAME ROOM?

- **No**

The outbreak potential of different ESBL-producing species is highly variable. For example, *Klebsiella pneumoniae* can survive longer on the hands and in the environment than other enterobacteria, facilitating horizontal transmission.

In addition, the ESBL plasmid can carry genes for resistance to other antibiotics (quinolones, aminoglycosides), which could compromise the effectiveness of antibiotic therapy in the event of infection. Finally, certain organisms produce multiple ESBLs, reducing the effectiveness of ß-lactams/ß-lactamase inhibitor combinations.

Therefore, placing patients carrying different ESBL+ enterobacteria in the same room is not recommended.

28 CAN TWO PATIENTS CARRYING ESBL+ ENTEROBACTERIA, ONE OF WHOM IS ALSO CARRYING MRSA, STAY IN THE SAME ROOM?

- **No**

Because sharing the room of a patient carrying MRSA is a known risk factor for colonization by MRSA.

Therefore, placing two patients carrying ESBL in the same room if one of them is also carrying MRSA is not recommended.

29 HOW SHOULD PATIENTS' ROOMS BE CLEANED DURING AND AFTER THEIR STAY?

- The focus should be put on good daily disinfection of frequently touched objects (by the patients and/or the healthcare workers), such as call systems, bed frames, night tables, etc. Floor disinfection is less important.

An observational assessment of room cleaning (during the patient's stay and after departure) may be useful. Certain studies show that cleaning and disinfection guidelines are not always respected. An assessment should perhaps be considered before deciding whether to use a combination product (a disinfectant-cleanser), or to disinfect the entire room after having cleaned it.

Enterobacteria such as *Klebsiella* spp. and *E. coli* have a survival time that varies from several hours to several days, and even weeks, depending on the environment.

30 SHOULD SHARED EQUIPMENT BE DISINFECTED BEFORE USE BY THE FOLLOWING PATIENT?

- **Yes**

See the section on general precautions (Question 20).

31 HOW SHOULD FOOD TRAYS BE HANDLED AFTER A MEAL?

- Food trays should be immediately placed on the meal cart and follow the usual thermal disinfection procedures used for dishes.

Do not to collect used trays while distributing clean meal trays.

32 HOW SHOULD LAUNDRY BE HANDLED?

- Laundry should be collected in plastic bags with minimum handling.

33 HOW SHOULD WASTE BE DISPOSED OF?

- Since the risk to public health is minimal, a patient's ESBL status should not determine how waste is handled. The disposal of solid waste created during patient care must respect local legislation.

34 SHOULD CERTAIN EQUIPMENT BE PATIENT-SPECIFIC?

- Equipment such as stethoscopes, thermometers, tourniquets, sphygmomanometers, etc., should be patient-specific and should under no circumstances circulate from room to room. Equipment that must be shared by several patients should be disinfected with a product approved for the disinfection of medical instruments before being used for another patient.

35 WHAT SHOULD BE DONE WITH DISPOSABLE SUPPLIES STORED IN A PATIENT'S ROOM ONCE THE PATIENT LEAVES THE HOSPITAL?

● Storing supplies in the room of a patient carrying ESBL+ enterobacteria should be avoided, to limit unnecessary waste of material that cannot be disinfected (for example, packs of compresses).

In addition, anything in packaging that is not intact (soiled, ripped, crumpled, heavily handled) should be discarded.

36 SHOULD THERE BE AN ALERT SYSTEM FOR ESBL+ PATIENTS ?

● **Yes**

1. Hospital Computer System Alerts

Automatic alerts for ESBL-carrying patients, created by the infection control team, can be very useful, if the hospital's computer system is equipped with this function. The main advantage of this type of alert is that it follows patients throughout their hospital stay, no matter what unit they are in. In addition, if the patient is hospitalized again, the alert will still be active (unless deactivated by hospital staff), allowing proper precautions to be taken immediately. These patient-"tagged" alerts can also warn radiologists or doctors who see these patients on an in-patient or outpatient basis to take the proper precautions.

2. Poster Alerts

Posters should at least contain a logo recognizable by everyone at the facility.

The problem with this minimalist attitude is that employees in technical services, porters, etc., may not be familiar with this pictogram. On the other hand, posters are particularly useful when proper precautionary measures for healthcare workers are added to the logo (wearing of gloves and gowns, hand hygiene). This information helps regular staff as well as personnel who may have only occasional contact with these patients (radiology technicians, physical therapists, porters, etc.) A second poster on the bed of the ESBL-carrying patient can also help transmit information so that proper precautions can be taken when the patient leaves the room for an examination (e.g. radiology, consultation, etc.).

3. In-hospital Communication

A patient's ESBL status should be mentioned clearly in hospital reports and any time the patient is transferred from one ward to another.
A telephone call prior to transfer allows the receiving ward to take the necessary measures before the patient's arrival.

37 HOW AND TO WHOM SHOULD THE PATIENT'S STATUS BE COMMUNICATED?

● A patient's ESBL status should be communicated to the doctor who ordered the lab test, the head nurse of the unit where the patient has been hospitalized and the contact person (doctor or nurse) in the infection control department, if there is one.

The means to communicate this information are multiple:

- Ideally by visiting a member of the infection control team on the unit.
- By an internal alert system, if the hospital's computer system is equipped.
- By internal memo (in the form of an alert or a monitoring sheet).
- By telephone: in this case, to ensure the information has been correctly understood, a memo should also be sent as a back-up.

In all circumstances, the information sent should include the following points:

- The patient's contact information.
- The date and type of test that allowed the ESBL identification.
- A detailed list of precautions.
- How long the precautions must be observed.
- If applicable, the fact that the patient has been tagged with an alert.

38 HOW SHOULD A PATIENT'S STATUS BE COMMUNICATED TO ANOTHER HEALTHCARE FACILITY?

● The period of colonization by an ESBL-producing species is currently not well known, but is probably prolonged. Communicating ESBL status when a patient is transferred to another facility (a nursing home or another hospital) is therefore essential. If empiric antibiotic therapy has been started, then the presence of an ESBL will be known and necessary precautions can be taken.

A transfer document mentioning the type of bacteria, the site(s) where it has been detected, as well as the dates of positive tests

should accompany the patient (See an example of a transfer document at the end of this booklet.).

Close collaboration with social services will allow the optimal use of this type of document.

39 WHAT ADVICE SHOULD BE GIVEN TO MEDICO-TECHNICAL UNITS FOR THE CARE OF THESE PATIENTS?

● When transferring a patient from a treatment unit to a medico-technical unit, or for an examination, the unit should be informed of the patient's infectious status.

The patient's hospital gown should be clean and hands disinfected before leaving the room.

Different situations should be treated differently:

- **ESBL in wounds:** cover the contaminated wounds with an airtight bandage before transporting the patient. The bandage should be clean.
- **ESBL in urine:** in case of urinary incontinence, change the protective pads.
- **ESBL in the respiratory tract:** if the patient has a productive cough, provide disposable paper tissues and ask the patient to cover their mouth when coughing. A box of tissues and a garbage bag/kidney-shaped bedpan should be taken to the examination.

Preventive measures in medico-technical units:

- The additional precautions recommended for the treatment units should be applied: gloves in case of direct contact with the patient and the patient's mode of transport, gown in case of risk of contact with work clothes.
- The environment should be disinfected between patients no matter what their microbiological status.

40 WHAT PRECAUTIONS SHOULD BE TAKEN IF AN ESBL-CARRYING OUTPATIENT IS TREATED IN A MEDICO-TECHNICAL UNIT (INCLUDING DIALYSIS UNIT)?

● In all cases: patients should be asked to disinfect their hands with an alcohol-based cleanser upon arrival.

- The additional precautions recommended for the treatment units should be applied: gloves in case of direct contact with the patient and the patient's mode of transport, gown in case of risk of contact with work clothes.
- The equipment and environment should be disinfected between patients regardless of their microbiological status.

41 WHAT PRECAUTIONS SHOULD BE TAKEN IF THE PATIENT IS TREATED AS AN OUTPATIENT?

- The additional precautions recommended for the treatment units should be applied: gloves in case of direct contact with the patient and the patient's mode of transport, gown in case of risk of contact with work clothes.
- The equipment and environment should be disinfected between patients regardless of their microbiological status.

42 CAN THE PATIENT BE TREATED IN THE HYDROTHERAPY POOL?

● **No**

Patients for whom the additional precautions are applied should not be treated in hydrotherapy.

43 WHAT PRECAUTIONS SHOULD BE TAKEN WHEN A PATIENT GOES FOR AN EXAMINATION?

● Patients can leave their rooms under the following conditions:
The hospital gown must be clean and hands disinfected.

Different situations should be treated differently:

- **ESBL in wounds:** cover the contaminated wounds with a clean, airtight bandage before transporting the patient.
- **ESBL in urine:** in case of urinary incontinence, change the protective pads.
- **ESBL in the respiratory tract:** if the patient has a productive cough, provide disposable paper tissues and ask the patient to cover their mouth when coughing. A box of tissues and a garbage bag/kidney-shaped bedpan should be taken to the examination.

44 SHOULD SPECIAL PRECAUTIONS BE TAKEN IN THE OPERATING ROOM?

- Recommendations for the transfer to another unit or in case of an examination in a medico-technical unit should also be applied for patients undergoing surgery. Whenever possible, surgery on ESBL-carrying patients should be carried out after other surgeries have been completed. In the operating room, general precautions are sufficient for avoiding ESBL transmission. It is essential that these precautions are also applied in the recovery room.

The use of negative pressure in the operating room is not justified, as the principal mode of transmission of ESBL is by direct or indirect contact with the patient and not through the air. It is nevertheless important to make sure that operating room doors remain closed during the entire length of the operation. In addition, the number of people in the operating room should be limited to those who are absolutely necessary. Comings and goings of nursing staff and anesthesiologists should also be limited during the operation. The use of disposable overshoes does not prevent the transmission of ESBL.

45 CAN THE PATIENT BE TREATED IN REHABILITATION?

- **Yes**

See the preceding questions. Particular attention should be paid to equipment the patient touches during the session.

46 CAN THE PATIENT BE TREATED IN OCCUPATIONAL THERAPY?

- During an outbreak period, occupational therapy activities should be limited to equipment that can be easily disinfected or reserved for individual patient use.

47 CAN A PHYSICAL THERAPIST GO OUT INTO THE HALLWAY WITH THE PATIENT?

- ESBL carriers may participate in physical therapy outside of their rooms.

Measures to be taken for the patient: see above.
Measures to be taken by the physical therapist: gloves and a gown should be worn, if risk of contact of work clothes with the patient.

48 WHAT PRECAUTIONS SHOULD VISITORS (FAMILY, FRIENDS) TAKE?

- It is recommended that visitors disinfect their hands with an alcohol-based handrub solution before leaving the room.

49 WHAT PRECAUTIONS SHOULD BE TAKEN BY THE FAMILY WHEN THE PATIENT RETURNS HOME?

- The presence of the organism should not affect the family at home. Usual personal hygiene and household cleaning is sufficient, and there are no restrictions to activities or visitors. Towels, clothes, bedsheets etc. can be washed in a domestic washing machine. All eating utensils and dishes can be washed as normal.

50 WHAT PRECAUTIONS SHOULD BE TAKEN WHEN TRANSPORTING A PATIENT WHO CANNOT WALK?

- During transport in a hospital bed, hand cleansing before and after transporting the patient is essential.

If transporting the patient in a wheelchair, the chair should be covered with a mattress pad and any places the patient's hands touch should be disinfected.

51 WHAT PRECAUTIONS SHOULD BE TAKEN IF THE PATIENT WOULD LIKE TO GO TO THE CAFETERIA, VISIT THE CHAPEL OR BUY A NEWSPAPER?

- Outings should be limited, considering the lack of control on these activities and possible contact with other patients.

If an outing is authorized, the patient should disinfect their hands before leaving their room.

DECONTAMINATION OF CARRIERS

52 SHOULD CARRIERS BE DECONTAMINATED IN NON-OUTBREAK SITUATIONS?

- In the context of preventing transmission, decontamination of patients carrying ESBLs in their digestive system is not recommended, as there is little available data and the use of antibiotics carries a risk, including that of the emergence of resistance.

As for preventing infection, even though gastrointestinal carriage of ESBL+ *Klebsiella pneumoniae* is an independent risk factor for clinical infection, there is no recommendation concerning the decolonization of the digestive tract of ESBL carriers.

53 SHOULD CARRIERS BE DECONTAMINATED DURING AN OUTBREAK?

- Selective decontamination of the digestive tract has been shown to control outbreaks of ESBL infection when usual control measures have not been effective. This measure should be reserved for uncontrolled outbreaks and always in consultation with an infectious disease specialist or the person in charge of antibiotic therapy.

CONTROLLING OUTBREAKS

54 WHAT IS AN ESBL OUTBREAK?

- Definition of an outbreak:

Number of nosocomial cases (colonization/infection) in excess of the expected level in a given geographic area and during a specific time period.

How to define the expected level: this level will vary according to sector (intensive care unit, geriatrics, etc.).

To define the expected level, it is necessary to:

- Have sufficient historical surveillance data.
- Take into account all changes in policy and testing methods.
- Use a surveillance system that is sensitive enough to identify an increase in the incidence of nosocomial infection.

55 WHAT MEASURES SHOULD BE APPLIED WHEN AN OUTBREAK IS SUSPECTED?

- Necessity to evaluate the clinical impact of the infections
  ➔ Evaluation of morbidity/mortality

First-Line Approaches

1. Analysis of available data

Description of cases; outbreak curve, including a retrospective analysis.

2. Inform the personnel, ensure general precautions are applied and implement additional precautions, if not already initiated.

- Meet with the relevant healthcare workers, and pay particular attention to factors that could limit control measures (lack of personnel or replacement personnel, etc.) and to recent changes in the organization of care.
- Analysis of cases to find out what they have in common (a colonization or infection site, a particular exam or treatment).

Second-Line Approaches

1. Periodic screening of all patients on the relevant unit and of all new admissions if there is no systematic screening, in order to:

- Establish the real extent of the problem.
- Apply the measures to all of the colonized patients.

2. Contact the person in charge of antibiotic therapy.

Restrict the use of antibiotics and adapt empiric antibiotic therapy to the antibiotic phenotype of the epidemic species in order to avoid selection pressure.

3. Reinforce cleaning and disinfection procedures on the unit: equipment, surfaces used during treatment, full disinfection of rooms during cleaning.

4. Meet regularly with the healthcare workers to check control measures are respected and assess the clinical impact of the outbreak (morbidity, mortality).

Third-Line Approaches

If new cases arise despite the application of second-line measures:

1. Screen all patients on the concerned unit regularly (frequency will vary according to the unit) and all new admissions.

2. Isolate carriers, or place them on one unit or one part of a unit.

3. Cohort the nursing staff ➔ important change in working habits.

4. If there is a major clinical impact on the unit, stop new admissions until the outbreak has been controlled.

5. Conduct an analytical investigation into the risk factors and source of contamination: conduct a cohort or case-control study.

Fourth-Line Approaches

Completely close the unit to new admissions until the last colonized patient is discharged.

56 WHEN CAN CONTACT PRECAUTIONS BE LIFTED?

● On "at-risk" wards , given the presence of risk factors linked to the patient and selection pressure created by antibiotics, it is recommended that additional precautions are kept in place until the patient leaves the unit. If the patient is transferred to a unit where there is no risk and there are no other cases of infection on the unit, general precautions should be applied while monitoring the appearance of any new cases of infection. According to current knowledge, there is no need for regular follow-up of former colonization sites or of the digestive tract.

57 WHAT STEPS SHOULD BE TAKEN WHEN A KNOWN CARRIER IS HOSPITALIZED?

● **Should the patient be tested?**

If the patient is entering an at-risk unit, they should be tested.

Should contact precautions be observed while awaiting the result?

On an at-risk unit: **Yes**

Given the lack of current data, a single set of tests should be sufficient. If the result is negative, additional precautions may be lifted.

Recommended set of tests: sites that formerly tested positive and the digestive tract.

58 SHOULD THE STAFF BE TESTED DURING AN OUTBREAK?

● **No**

There is no proof that staff are a reservoir for nosocomial ESBL+ bacteria (except in rare cases -> carrying the infection on the hands in cases of chronic skin lesions or wearing false nails).

However, screening staff's hands could play an education role.

59 SHOULD THE ENVIRONMENT BE TESTED?

● Not outside of outbreak periods.

During an outbreak, even if the environment is not the main source of nosocomial ESBLs (with exceptions), such tests could prove useful if:

- The acquisition of the infection seems linked to one or several rooms, to a particular exam, etc.
- Properly implemented control measures do not seem to be effective.

Above all, environmental testing can educate staff about the importance of hand hygiene.

60 SHOULD THE ANTIBIOTICS POLICY OR ANTIBIOTICS PRESCRIPTION HABITS ON A WARD BE CHANGED WHERE THERE IS AN OUTBREAK?

● During an outbreak, it is best to make contact with the person in charge of antibiotic therapy. The use of antibiotics should be restricted, in particular for antibiotics whose use had increased before the outbreak or whose use is associated as an individual risk factor for being colonized/infected by the epidemic strain. The empiric antibiotic therapy should be adapted to the antibiotic phenotype of the epidemic species in order to avoid selection pressure.

Given the connection between antibiotic pressure and resistance ecology, it is advisable to review the antibiotic policy of the unit in order to prevent an outbreak in the future.

EXAMPLE OF A TRANSFER DOCUMENT

PATIENT INFORMATION

Transfer document to a rest home or nursing home

Date … /… /…
Your patient was hospitalized in our facility on … /… /…

The patient tested positive for a bacteria, which required taking additional precautions during his/her stay.

This bacteria is

	Date of the first test	Origin [1]
○ MRSA (*S. aureus* resistant to oxacillin)	… /… /…	
…….		
○ *Clostridium difficile*	… /… /…	……
○ ESBL+ enterobacteria	… /… /…	……
○ Other	… /… /…	……

[1] 1 on admission; 2 acquired in the hospital

If an Antibiotic Susceptibility profile is available, it should be attached.

Site(s) that tested positive at least once during the hospital stay

- ○ Nose
- ○ Perineum
- ○ Throat
- ○ Surgical wound
- ○ Bedsore
- ○ Other wound
- ○ Sputum and related
- ○ Urine
- ○ Stool
- ○ Gastrostomy
- ○ Blood cultures……
- ○ Other……
- ○ Other……

Decolonizing treatment administered

- ○ No. Why ……
- ○ Yes. Why ……

Start date: ……

End date: ……

Site(s) still positive on patient discharge

- ○ Nose
- ○ Perineum
- ○ Throat
- ○ Surgical wound
- ○ Bedsore
- ○ Other wound
- ○ Sputum and related
- ○ Urine
- ○ Stool
- ○ Gastrostomy
- ○ Other……
- ○ Other……

Follow-up treatment

- ○ No
- ○ Yes. As follows ……

Other remarks: ……
……

If you have any questions, for example about the necessity of performing follow-up tests, do not hesitate to contact our infection control team:

- Dr.……

Infection control practitioner

- tel.: ……

Infection control nurse

- tel.: ……

Please also inform the relevant unit if the patient is still carrying the causative microorganism and if he/she must be rehospitalized, or if the patient will visit one of our units as an outpatient (consultation, radiology, etc.).

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