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Nosocomial Infections Caused by ESBL

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Review Article

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Abstract

Nosocomial infection is infection that is acquired in a hospital or other health care facility also called a health care-associated infection (HAI or HCAI), these infections can be caused by many bacteria, nowadays ESBL (Extended spectrum beta-lactamases) appear as a very important cause of nosocomial infections. These are enzymes produced by certain bacteria, are able to hydrolyze beta-lactam antibiotics.

Keywords: ESBL; B Lactamases; Nosocomial

Introduction

In Gram-negative pathogens, β-lactamases production remains the most important contributing factor to β-lactam resistance. B- lactamases are bacterial enzymes which inactivate β-lactam antibiotics by hydrolysis, result in ineffective compounds. One group of β-lactamases, extended-spectrum β lactamases (ESBLs), has the ability to hydrolyse and cause resistance to various types of the newer β-lactam antibiotics, including the expanded-spectrum (or third-generation) cephalosporins (eg, cefotaxime, ceftriaxone, ceftazidime) and monobactams (eg, aztreonam), but not the cephamycins (eg, cefoxitin and cefotetan) and carbapenems (eg, imipenem, meropenem and ertapenem) they become important and widespread cause of nosocomial infection due to many factors [1-3].

Risk Factors for Colonization and Infection with ESBL Producers

Patients at high risk for developing colonization or infection with ESBL-producing organisms are often seriously ill patients with prolonged hospital stays and in whom invasive medical devices are present (urinary catheters, endotracheal tubes, central venous lines) for a prolonged duration. The median length of hospital stay prior to isolation of an ESBL producer has ranged from 11 to 67 days, depending on the study [4].

Heavy antibiotic use is also a risk factor for acquisition of an ESBL-producing organism. Several studies have found a relationship between third-generation cephalosporin use and acquisition of an ESBL-producing strain. Furthermore, a tight correlation has existed between ceftazidime use in individual wards within a hospital and prevalence of ceftazidime-resistant strains in those wards. In a survey of 15 different hospitals, an association existed between cephalosporin and aztreonam usage at each hospital and the isolation rate of ESBL-producing organisms at each hospital [5].

The use of a variety of other antibiotic classes has been found to be associated with subsequent infections due to ESBL-producing organisms. These include quinolones, trimethoprim-sulfamethoxazole, aminoglycosides and

metronidazole. Conversely, prior use of ß-lactam/ß-lactamase inhibitor combinations, penicillins, or carbapenems seems not to be associated with frequent infections with ESBL-producing organisms [6].

Modes of Spread of ESBL-Producing Organisms within Hospitals

A common environmental source of ESBL-producing organisms has occasionally been discovered. Examples have included contamination of ultrasonography coupling gel, bronchoscopes, blood pressure cuffs and glass thermometers (used in axillary measurement of temperature). Cockroaches have been implicated as possible vectors of infection; in one study, ESBL-producing *Klebsiella pneumoniae* isolated from cockroaches was indistinguishable from those infecting patients. ESBL-producing organisms have been isolated from patients' soap, sink basins and babies' baths, but the contribution of this environmental contamination to infection was impossible to determine [7].

Present evidence suggests that transient carriage on the hands of health care workers is a more important means of transfer from patient to patient. Hand carriage has been documented by most but not all investigators who have sought it. In these instances, the hand isolates were genotypically identical to isolates which caused infection in patients. Hand carriage by health care workers is usually eliminated by washing with chlorhexidine or alcohol-based antiseptics. However, prolonged, persistent skin carriage in a nurse with chronic dermatitis was documented. The use of artificial nails may also promote long-term carriage and has been associated with at least one outbreak [8].

The hands of health care workers are presumably colonized by contact with the skin of patients whose skin is colonized with the organism. It is important to recognize that many patients may have asymptomatic colonization with ESBL-producing organisms without signs of overt infection. These patients represent an important reservoir of organisms. For every patient with clinically significant infection with an ESBL-producing organism, at least another patient exists in the same unit with gastrointestinal tract colonization with an ESBL-producer. In some hyperendemic intensive care units and transplants units, 30 to 70% of patients have gastrointestinal tract colonization with ESBL- producers at any one time [9].

Primary gastrointestinal carriage of ESBL-producing *Klebsiella pneumoniae* is an independent variable associated with infection with ESBL-producing *Klebsiella pneumoniae*. At least 80% of patients with infection with ESBL-producing *Klebsiella pneumoniae* can be documented to have prior gastrointestinal tract carriage. Patients who develop infection usually do so within weeks of acquiring gastrointestinal tract colonization (range= 0 to 90 days) [10].

Infection Control Interventions to Overcome ESBL-Producing Organisms

Nosocomial bacterial infections are a major focus of concern for infection control programs. Such infections may occur as an outbreak (or epidemic) or may become established as a regular occurrence (endemic). Control of endemic ESBL producers is difficult, and may only be possible after significant nursing and medical reorganization, at substantial financial cost [11].

Therefore, control of the initial outbreak of ESBL-producing organisms in a hospital or specialized unit of a hospital is of critical importance .The initial stages of the infection control program in a hospital or unit which has not previously been affected by ESBLs should therefore include (i) performance of rectal swabs to delineate patients colonized (but not infected) with ESBL producers, (ii) evaluation for the presence of a common environmental source of infection, (iii) a campaign to improve hand hygiene, and (iv) introduction of contact isolation for those patients found to be colonized or infected [12].

Contact isolation implies use of gloves and gowns when contacting the patient. Several studies have documented that this practice alone can lead to reduction in horizontal spread of ESBL-producing organisms. However, compliance with these precautions needs to be high in order to maximize the effectiveness of these precautions [12].

In Marcadé G, et al. [13] were forced to close a ward temporarily in order to adequately control an outbreak which had been unresponsive to conventional measures.

A number of groups have previously attempted selective digestive tract decontamination as a means of interrupting transmission of ESBL-producing organisms. Erythromycin-based therapies have not been effective. However, three groups successfully used selective digestive tract decontamination with polymyxin, neomycin, and nalidixic acid, colistin and tobramycin, or norfloxacin to interrupt outbreaks of infection with ESBL-producing organisms that had not been completely

controlled using traditional infection control measures. It should be noted that in many hospitals at least 15 to 30% of ESBL-producing organisms are quinolone resistant and therefore unlikely to be suppressed by use of norfloxacin prophylaxis. Additionally, multidrug-resistant isolates are unlikely to respond to selective digestive decontamination using aminoglycosides [14].

An alternative approach to digestive tract decolonization has been decolonization of the nasopharynx. A study has utilized a nasal spray with povidone-iodine as a means of decolonizing the upper respiratory tract. In this study (performed in a neurologic rehabilitation unit), only 1 of 10 patients had gastrointestinal carriage with an ESBL-producing organism but all had nasotracheal colonization [15].

Although infection control procedures continue to play a central role, changes in antibiotic policy may play an even greater role in this setting. It was suggested that use of ß-lactam/ß-lactamase inhibitor combinations, rather than cephalosporins, as empirical therapy for infections suspected as being due to gram-negative bacilli, may facilitate control of ESBL producers. The mechanism by which these drugs may reduce infections with ESBL producers is not certain. It should be noted, however, that many organisms produce multiple ß-lactamases, which may reduce the effectiveness of ß-lactam/ß-lactamase inhibitor combinations [16].

Typing of ESBL Producers

It is important to be able to determine whether nosocomial infections are caused by the same clone of organism (monoclonal or oligoclonal outbreaks) because this implies that the organisms are being passed horizontally by some means from patient to patient. This has important infection control implications in that some intervention should be introduced to prevent horizontal tranfer of organisms. Nosocomial infections with organisms of the same species which are not of the same clone (polyclonal outbreaks) may be due to selective pressure imposed by antibiotic use [17].

Before the advent of molecular biologic techniques to assess the genetic relationships between nosocomially acquired organisms, typing methods that assessed phenotypic differences between organisms were widely used. At least seven phenotypic methods could potentially be used to type *Klebsiella pneumoniae* isolates harbouring ESBLs. These include biotyping (assessing the potential clonal relationship between organisms by way of observing common biochemical reactions, colonial morphology, or environmental tolerances) and assessment of the antimicrobial susceptibility test pattern. Neither test has particularly good discriminatory power. Occasionally, stored isolates of organisms may lose transferrable genetic elements (for example, plasmids) which confer antibiotic resistance and appear to have a different antibiotic susceptibility pattern than when the isolate was examined fresh [18].

Serotyping is potentially useful in discriminating ESBL-producing klebsiella. The klebsiella typically express both lipopolysaccharide (O antigen) and capsule polysaccharide (K antigen) on the surface. Seventy-seven K antigen types form the basis of an internationally recognized capsule antigen scheme. The drawback of this method is the large number of serological cross-reactions that occur among the 77 capsule types. Thus, individual sera have to be absorbed with the cross-reacting K antigens. Moreover, the antisera are not commercially available and the typing procedure is difficult because of the time needed to perform the test. Finally the test is susceptible to subjectivity because of weak reactions that are not always easy to interpret. In contrast to the large number of capsular serotypes, only nine lipopolysaccharide O groups have been recognized. Since there are only nine O types compared with 77 K types, O typing is clearly less discriminatory than K typing. Furthermore, traditional methods of O typing are hampered by the heat stability of capsular polysaccharide. An inhibition enzyme-linked immunosorbent assay method has been developed which overcomes this technical problem. A combination of K and O typing is likely to be a very discriminatory non-molecular method of typing ESBL-producing klebsiellae [19].

Phage typing, bacteriocin typing, analytical isoelectric focusing, and multilocus enzyme electrophoresis are other methods which have been used to discriminate ESBL-producing strains [20].

Since the vast majority of ESBLs are plasmid mediated, plasmid profile analysis has been applied to the epidemiologic study of ESBL-producing organisms. A simple method is to determine the number and size of the plasmids carried by the organism by preparing a plasmid extract and subjecting it to routine agarose gel electrophoresis. The reproducibility and discriminatory power of plasmid analysis can be improved by first digesting the plasmids with restriction enzymes and then performing agarose gel electrophoresis. This procedure and the analysis of the size and number of the resulting

restriction fragments are referred to as restriction enzyme analysis of plasmids. A drawback in plasmid profile analysis is that plasmids may be lost after storage. It should be noted that plasmid extraction methods may yield different results if the efficiency of extraction is not optimal.

Most researchers use molecular methods to determine the relatedness of ESBL-producing organisms. Pulsed-field gel electrophoresis of chromosomal DNA is probably the most widely used method of genotyping ESBL-producing organisms [21].

Ribotyping, a southern blot analysis in which strains are characterized by the restriction fragment lengh polymorphisms associated with the ribosomal operons, is very useful in typing ESBL-producing organisms, especially when automated ribotyping systems are used [22].

Multiple variations of polymerase chain reaction (PCR) have been applied to the typing of ESBL-producing organisms. These are randomly amplified polymorphic DNA, which is also known as arbitrarily primed PCR, and PCR based on repetitive chromosomal sequences. Of these, use of arbitrarily primed PCR has been by far the most popular method used to evaluate the genetic relatedness of ESBL-producing strains. The randomly amplified polymorphic method is based on the observation that short primers (around 10 base pairs), whose sequence is not directed to any known genetic locus, will regardless hybridize at random chromosomal sites with sufficient affinity to permit the initiation of polymerization. If two such sites are located within a few kilobases of each other on opposite DNA strands and in the proper orientation, amplification of the intervening fragment will occur. The number and locations of these random sites (and therefore the number and sizes of fragments) will vary among different strains of the same species [23].

Restriction site insertion PCR is a technique that detects mutations of the SHV genes to identify ESBLs [24]. Ligase chain reaction is a technique also used to discriminate SHV variants [25].

Another described method marries the sensitivity of PCR with fluorescently labeled probes. Randegger CC, et al. [26] developed a technique using real-time PCR monitored with fluorescently labeled hybridization probes followed by melting curve analysis. Their technique was able to differentiate SHV variants in five well-characterized Escherichia coli strains and six clinical isolates, and to discriminate between non- ESBLs and ESBLs. It remains to be seen whether this technique, termed the SHV melting curve mutation detection method, will identify all SHV variants.

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