Treatment of ESBL producers

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Infections with ESBL-producing organisms can be life-threatening. In vitro studies would suggest that carbapenems or non-beta-lactam antibiotics should be optimal therapy for ESBL-producers since they are not hydrolyzed by ESBLs. The greatest clinical experience is with carbapenems, and these remain the gold standard of therapy for serious infections due to ESBL-producers. Co-production of ESBLs and carbapenem- hydrolyzing enzymes has been described and may threaten the utility of carbapenems in the future. For this reason, ongoing development of new antibiotics active against Gram negative bacilli is extremely important..

Key words: **Extended-spectrum beta-lactamases. Carbapenem. Non-beta-lactam antibiotics.**

Tratamiento de las infecciones por microorganismos productores de BLEE

Las infecciones por microorganismos productores de betalactamasas de espectro extendido (BLEE) son potencialmente mortales. Los estudios in vitro sugieren que los carbapenemes o los antibióticos no betalactámicos son las opciones óptimas para el tratamiento de las infecciones causadas por estos microorganismos, ya que no son hidrolizados por las BLEE. Se dispone de mayor experiencia clínica con los carbapenemes, que siguen siendo el estándar de referencia en el tratamiento de las infecciones graves por microorganismos productores de BLEE. Se ha descrito la producción simultánea de BLEE y enzimas hidrolizantes de los carbapenemes, lo que puede suponer una amenaza para la utilidad de éstas en el futuro. Por este motivo, es extremadamente importante el desarrollo continuado de nuevos antibióticos activos frente a los bacilos gramnegativos..

Palabras clave: **Betalactamasas de espectro extendido. Carbapenem. Antibióticos no betalactámicos.**

Introduction

Infections with extended-spectrum beta-lactamase (ESBL) producing Gram negative bacilli can be serious and life-threatening. Examples include bloodstream infection, meningitis, peritonitis and hospital-acquired pneumonia. Bloodstream infection with ESBL-producing Gram negative bacilli is typically associated with a portal of entry such as a central venous catheter, urinary tract infection, pneumonia or an intra-abdominal infection. Meningitis due to ESBL-producing organisms usually follows neurosurgical procedures. Documented cases of pneumonia due to ESBL-producing organisms are typically ventilator-associated, and may have an associated mortality rate of greater than 20%.

At the other extreme, ESBL-producing organisms may be associated with colonization rather than true infection. A common example is urinary tract colonization, especially associated with indwelling urinary catheters. Gram negative organisms may colonize the upper airways of hospitalized patients – the finding of an ESBL-producer in a sample such as an endotracheal aspirate may therefore be of dubious clinical significance if not associated with clinical and radiological signs of pneumonia. ESBL-producing organisms may colonize the skin of hospitalized patients and residents of nursing home facilities. Of course, colonization of any site does not require specific antimicrobial therapy.

Treatment options for ESBL producers

In vitro, the carbapenems (including imipenem, meropenem, doripenem and ertapenem) have the most consistent activity against ESBL producing organisms, given their stability to hydrolysis by ESBLs[1]. Cephamycins (for example, cefoxitin and cefotetan) are also stable to hydrolysis by ESBLs. Various other cephalosporins are sometimes partially stable to hydrolysis by certain ESBLs, but in general are not recommended for treatment of ESBL-producing organisms. More commentary on this issue follows. In vitro, beta-lactamase inhibitors are able to inactivate the ESBLs, but again the clinical utility of beta-lactam/beta-lactamase inhibitor combinations for the treatment of serious infections due to such organisms is debatable. Non-beta-lactam antibiotics such as fluoroquinolones, aminoglycosides, tigecycline and polymyxins round out the armamentarium against ESBL-producers and will be discussed individually.

Carbapenems

Carbapenems should be regarded as the drugs of choice for serious infections with ESBL producing organisms,

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on the basis of increasingly extensive positive clinical experience. In a sub-group analysis of patients in a randomized trial of cefepime versus imipenem for nosocomial pneumonia, clinical response for infections with ESBL producing organisms was seen in 100% (10/10) patients treated with imipenem but only 69% (9/13) patients treated with cefepime[2]. Prospective, observational studies have shown a significantly lower mortality from carbapenem treated bloodstream infections due to ESBL producing *K. pneumoniae*, compared to other antibiotic classes[3-6]. Although synergy has occasionally been exhibited between carbapenems and other antibiotic classes, there is no evidence that combination therapy involving a carbapenem is superior to use of a carbapenem alone.

The choice between the different carbapenems for serious infections with ESBL producers is difficult. Published clinical experience is greatest with imipenem and meropenem. Doripenem is not yet commercially available except in Japan. In general MICs are slightly lower for meropenem and doripenem than for imipenem and ertapenem, although the clinical significance of this in vitro superiority is not yet clear. Ertapenem shares the good in vitro activity of the other carbapenems, although resistance rates are slightly higher than with the other carbapenems[7]. The ability to use ertapenem once daily makes it potentially useful in serious infections with ESBL producers in nursing home residents or patients continuing parenteral therapy out of hospital.

The advent of carbapenem hydrolyzing beta-lactamases such as those of the KPC type and the metallo-beta-lactamases (MBLs, for example, IMP, VIM, SPM) threatens the long-term utility of the carbapenems[8,9]. Co-production of ESBLs and carbapenem-hydrolyzing beta-lactamases has been described[10]. Clearly, the discovery of carbapenem resistant Enterobacteriaceae is an infection Control urgency and should be dealt with aggressively to prevent spread of this antibiotic resistance phenotype.

Cephamycins

There are few published reports of the use of cephamycins (for example, cefoxitin and cephamycin) in the treatment of ESBL producers. In one of these reports, selection of porin resistant mutants occurred during therapy, resulting in cefoxitin resistance and relapse of infection[11]. In addition, combined cephamycin and carbapenem resistance in *K. pneumoniae* has been observed in the setting of widespread cephamycin use in response to an outbreak of infection with ESBL-producing organisms[12]. Therefore, cephamycins are not recommended as first-line therapy for ESBL producing organisms, despite their good in vitro activity.

Third generation cephalosporins

How frequently are ESBL producing organisms "susceptible" to third generation cephalosporins? The answer to this question depends on which breakpoints are used. Differences between different organizations are quite considerable. For example, the CLSI (Clinical and Laboratory Standards Institute) denotes third and fourth generation cephalosporin susceptibility as a minimal inhibitory concentration (MIC) ≤ 8 µg/mL whereas EUCAST denotes a cephalosporin MIC of ≤ 1. In a review of studies which have evaluated collections of ESBL producing organisms using standard CLSI disk diffusion or MIC breakpoints, 13-49% of isolates were cefotaxime "susceptible", 36-79% ceftriaxone "susceptible", 11-52% ceftazidime "susceptible" and 10-67% aztreonam "susceptible"[2,13]. Approximately 40% tested "susceptible" to at least one oxyimino β-lactam and 20% to all oxyimino β-lactams. The reasons for this apparent susceptibility to some cephalosporins is the result of varying degrees of hydrolysis of cephalosporins by different β-lactamases and enhanced penetration through the bacterial outer membrane of some cephalosporins compared to others. Regardless, extended-spectrum cephalosporin MICs of 2-8 µg/mL are 4-8 dilutions higher than those seen in the same strain producing only the parent TEM-1, TEM-2 or SHV-1 β-lactamase (0.03-0.25 µg/mL)[2].

It has been well recognized for some time that poor outcome occurs when patients with serious infections due to ESBL producing organisms are treated with third generation cephalosporins to which the organism is frankly resistant. The failure rate in such patients has ranged from 42 to 100%[1]. Similar failure rates exist when cephalosporins are used to treat patients with serious infections due to ESBL producers which have cephalosporin MICs in the intermediate range and even with some MICs in the susceptible range. The failure rate when third generation cephalosporins were used for serious infections with ESBL producing organisms with MICs for the treating cephalosporin of 4-8 µg/mL exceeds 90%[13]. The failure rate when MICs for the treating cephalosporin were ≤ 2 µg/mL is substantially lower[13].

Cefepime

Cefepime appears to have a higher intrinsic activity against many ESBL-producing organisms than the third-generation cephalosporins. However, some ESBL-producing organisms have a cefepime MIC of 8 µg/mL; stochastic modeling suggests that cefepime dosed at 1-2 grams every 12 hours may not have a high probability of achieving pharmacokinetic/pharmacodynamic targets which have previously been correlated with clinical success when such an MIC occurs[1]. Elevated cefepime MICs may be more frequent in strains which produce the CTX-M-type ESBLs or when ESBLs occur in *Enterobacter* strains[14,15].

As noted above, a randomized trial of cefepime versus imipenem for nosocomial pneumonia, showed a clinical response for infections with ESBL producing organisms was seen in 100% (10/10) patients treated with imipenem but only 69% (9/13) patients treated with cefepime[2]. It is highly debatable whether cefepime should be used as first-line therapy against ESBL producing organisms; if it is used it should be restricted to organisms with a cefepime MIC of < 2 µg/mL and should be used in high dosage (at least 2 grams twice a day).

Beta-lactam/beta-lactamase inhibitor combinations

By definition, ESBLs are inhibited by beta-lactamase inhibitors such as clavulanic acid. However, clinical isolates of ESBL-producing organisms are frequently resistant to beta-lactam/beta-lactamase inhibitor combinations. This may be due to hyperproduction of beta-lacta-

mases (including narrow spectrum beta-lactamases co-produced by ESBL-producing strains), co-production of inhibitor resistant beta-lactamases by ESBL-producing strains or the combination of β-lactamase production and porin loss. For example, CTX-M-15 producing *E. coli* isolates may be resistant to antibiotics such as piperacillin-tazobactam, not because of production of CTX-M-15 but because of co-production of OXA-1 beta-lactamases which are resistant to inhibition by clavulanic acid or tazobactam. Some animal studies have shown β-lactam/β-lactamase inhibitor combinations to be less effective than carbapenems against ESBL producing organisms. Published clinical experience with β-lactam/β-lactamase inhibitor combinations in the treatment of serious infections due to ESBL producers is limited and shows mixed results[1,16]. These drugs may be an option in treatment of urinary tract infections due to susceptible strains.

Non-beta-lactam antibiotics

Fluoroquinolones are obviously not affected by beta-lactamases, but co-existence of resistance mechanisms affecting the quinolones and ESBLs are frequent. Three observational clinical studies have assessed the relative merits of quinolones and carbapenems for serious infections due to ESBL producing organisms. Two of these studies found that carbapenems were superior to quinolones, whereas one of the studies found that they were equivalent in effectiveness[3,5,17]. It is possible that suboptimal dosing of quinolones in the presence of strains with elevated quinolone minimal inhibitory concentrations (yet remaining in the "susceptible" range) may account for these differences.

Aminoglycosides are renally excreted and may be potentially useful in the treatment of complicated urinary tract infections due to ESBL-producing organisms. However, they are not typically recommended as monotherapy for serious infections at other sites. Aminoglycosides are often used in combination with beta-lactam antibiotics for treating serious Gram negative infections. However, no data exists supporting routine use of beta-lactam/aminoglycoside combinations in the management of infections due to ESBL-producing organisms.

Nitrofurantoin or fosfomycin may retain activity against ESBL-producing organisms. These antibiotics are only useful in the treatment of urinary tract infection, and should not be used in the treatment of more serious infections.

Tigecycline is active against most ESBL-producing strains and is stable to the effects of carbapenem-hydrolyzing beta-lactamases, but caution needs to be exercised when using this antibiotic for bloodstream and urinary tract infections given the low drug concentrations at these sites[18]. Published clinical data on use of tigecycline for serious infections due to ESBL-producing organisms is lacking thus far.

Colistin and polymyxin B also have activity against most ESBL producing strains but dosing regimens are not well-established for these antibiotics, especially in critically ill individuals with renal failure. There are case reports of success with colistin or polymyxin B for treating serious infections with multiply resistant Gram negative infections.

Conclusions

ESBL-producing organisms have the capability to be associated with infections that have high underlying mortality. Inadequate treatment of such infections may increase the mortality still further. At the present time, carbapenems are regarded as the treatment of choice for serious infections due to ESBL producers. However, the spread of carbapenemase producing organisms (mainly as a result of poor infection control) threatens the long-term utility of this drug class. New antibiotic options need to be developed which have activity against ESBL-producing organisms.

References

1. Paterson DL, Bonomo RA. Extended-spectrum β-lactamases: a clinical update. Clinical Microbiology Reviews. 2005;18:657-86.
2. Zanetti G, Bally F, Greub G, Garbino J, Kinge T, Lew D, et al. Cefepime versus imipenem-cilastatin for treatment of nosocomial pneumonia in intensive care unit patients: a multicenter, evaluator-blind, prospective, randomized study. Antimicrobial Agents and Chemotherapy. 2003;47:3442-7.
3. Paterson DL, Ko WC, Von Gottberg A, Mohapatra S, Casellas JM, Goossens H, et al. Antibiotic therapy for *Klebsiella pneumoniae* bacteremia: implications of production of extended-spectrum beta-lactamases. Clinical Infectious Diseases. 2004;39:31-7.
4. Burgess DS, Hall RG, Lewis JS, Jorgensen JH, Patterson JE. Clinical and microbiologic analysis of a hospital's extended-spectrum beta-lactamase-producing isolates over a 2 year period. Pharmacotherapy. 2003;23:1232-7.
5. Endimiani A, Luzzaro F, Perilli M, Lombardi G, Coli A, Tamborini A, et al. Bacteremia due to *Klebsiella pneumoniae* isolates producing the TEM-52 extended-spectrum beta-lactamase: treatment outcomes on patients receiving imipenem or ciprofloxacin. Clinical Infectious Diseases. 2004;38:243-51.
6. Meyer KS, Urban C, Eagan JA, Berger BJ, Rahal JJ. Nosocomial outbreak of *Klebsiella* infection resistant to late-generation cephalosporins. Annals of Internal Medicine. 1993;119:353-8.
7. Elliott E, Brink AJ, van Greune J, Els Z, Woodford N, Turton J, et al. In vivo development of ertapenem resistance in a patient with pneumonia caused by *Klebsiella pneumoniae* with an extended-spectrum beta-lactamase. Clinical Infectious Diseases. 2006;42:e95-8.
8. Walsh TR, Toleman MA, Poirel L, Nordmann P. Metaalo-β-lactamases: the quiet before the storm? Clinical Microbiology Reviews. 2005;18:306-25.
9. Bratu S, Brooks S, Burney S, Kochar S, Gupta J, Landman D, et al. Detection and spread of *Escherichia coli* possessing the plasmid-borne carbapenemase KPC-2 in Brooklyn, New York. Clinical Infectious Diseases. 2007; 44:972-5.
10. Pope J, Adams J, Doi Y, Szabo D, Paterson DL. KPC-type beta-lactamase, rural Pennslyvania. Emerging Infectious Diseases. 2006;12:1613-4.
11. Pangon B, Bizet C, Bure A, Pichon F, Philippon A, Regnier B, et al. In vivo selection of a cephamycin-resistant, porin-deficient mutant of *Klebsiella pneumoniae* producing a TEM-3 beta-lactamase. Journal of Infectious Diseases. 1989;159:1005-6.
12. Bradford PA, Urban C, Mariano N, Projan SJ, Rahal JJ, Bush K. Imipenem resistance in *Klebsiella pneumoniae* is associated with the combination of ACT-1, a plasmid-mediated AmpC beta-lactamase, and the loss of an outer membrane protein. Antimicrobial Agents and Chemotherapy. 1997;41:563-9.
13. Paterson DL, Ko WC, Von Gottberg A, Casellas JM, Mulazimoglou L, Klugman KP, et al. Outcome of cephalosporin treatment for serious infections due to apparently susceptible organisms producing extended-spectrum beta-lactamases: implications for the clinical microbiology laboratory. Journal of Clinical Microbiology. 2001;39:2206-12.
14. Yu WL, Pfaller MA, Winokur PL, Jones RN. Cefepime MIC as a predictor of the extended-spectrum beta-lactamase type in *Klebsiella pneumoniae*, Taiwan. Emerging Infectious Diseases. 2002;8:522-4.
15. Szabo D, Bonomo RA, Silveira FD, Pasculle AW, Baxter C, Linden PK, et al. SHV-type extended-spectrum beta-lactamase production is associated with reduced cefepime susceptibility in Enterobacter cloacae. Journal of Clinical Microbiology. 2005;43:5058-64.
16. Gavin PJ, Suseno MT, Thomson RB, Gaydos JM, Pierson CL, Halstead DC, et al. Clinical correlation of the CLSI susceptibility breakpoint for piperacillin/tazobactam against extended-spectrum beta-lactamase producing *Escherichia coli* and *Klebsiella* species. Antimicrobial Agents and Chemotherapy. 2006;52:2244-7.

17. Kang CI, Kim SH, Park WB, Lee KD, Kim HB, Kim EC, et al. Bloodstream infections due to extended-spectrum beta-lactamase producing *Escherichia* coli and *Klebsiella pneumoniae*: risk factors for mortality and treatment outcome, with special emphasis on antimicrobial therapy. Antimicrobial Agents and Chemotherapy. 2004;48:4574-81.

18. Peleg AY, Potoski BA, Rea R, Adams J, Sethi J, Capitano B, et al. *Acinetobacter baumannii* bloodstream infection while receiving tigecycline: a cautionary report. Journal of Antimicrobial Chemotherapy. 2007;59:128-31.