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Special Article

ESBL- FROM PETRI DISH TO THE PATIENT

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Abstract

Treatment of extended spectrum beta-lactamase (ESBL) producing strains of *Enterobacteriaceae* has emerged as a major challenge in hospitalised as well as community based patients. Infections due to ESBL producers range from uncomplicated urinary tract infection to life threatening sepsis. Although several reviews have been published in the literature about the detection and identification of these pathogens in the laboratory, there is not much guidance in Indian literature about how these organisms should be treated in clinical settings. The present article tries to address the clinical questions in the management of ESBL producing organisms. The article emphasises on antibiotic choice, pharmaco-therapeutic considerations, non-antibiotic aspects of management, and testing of clinical samples in the initial screening of patients for resistant gram negative organisms.

Key words: *ESBL, pharmaco-therapy, non-antibiotic approach, OPAT, screening*

Extended spectrum beta-lactamase (ESBL) producing strains of *Enterobacteriaceae* have emerged as a major problem in hospitalised as well as community based patients.[1,2] These organisms are responsible for a variety of infections like urinary tract infection (UTI), septicaemia, hospital acquired pneumonia, intra-abdominal abscess, brain abscess and device related infections. Although recent reviews have addressed the laboratory aspects in detection and classification of ESBLs they do not offer significant guidance about how to deal with these organisms in a particular clinical scenario.[1,3] The present article aims at addressing the important clinical questions which are integral to the routine patient management.

Management decisions in the treatment of ESBL producers

The decision to treat ESBL producing organisms should not be based on microbiology reports alone. A holistic understanding of the patient's clinical condition and practical considerations such as cost, ease of antibiotic administration, patient compliance, adverse effects of antibiotics, antibiotic efficacy must form essential decision making tools in deciding the most suitable clinical intervention. The questions that need to be asked and answered in deciding the most appropriate therapy include:

- Do the bacteria isolated from the patient represent infection or colonisation?
- Can this infection be treated with antibiotics alone? Can the condition be treated without antibiotics?
- What is the most appropriate antibiotic(s) in this clinical setting? Monotherapy or combination therapy?
- Pharmacotherapeutic considerations: dose, duration, route, frequency, tissue penetration, oral bioavailability, therapeutic-drug level monitoring?
- Alternative antibiotics in case of allergy? (distinguish allergy from intolerance)
- Side effects, contraindications, dose adjustments? Issues related to pregnancy, lactation and paediatric patients.
- OPAT- out patient parenteral antibiotic therapy?
- Is it hospital acquired or community acquired?
- How to prevent the spread of ESBL in wards? Which antibiotics to avoid in ESBL positive patients?
- How to screen patients for the presence of multiresistant gram negative organisms?

Infection versus colonisation

This distinction can be made on the basis of some specific information like, a) Specimen type? (isolates from physiologically sterile sites like blood, broncho alveolar lavage, tissue biopsy are to be taken seriously; whereas isolates from non-sterile sites like chronic wound swabs, sputum are more likely to be colonisers; isolates from catheterised specimen of urine are more likely to represent

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colonisation than isolates from mid stream urine; however, isolates from intravascular catheters/lines represent colonisation as well as potential sources of systemic infections), b) inflammatory parameters of the patient- white cell count, C-reactive protein, erythrocyte sedimentation rate, serum (infection is likely to be associated with derangement of these parameters), c) general condition of the patient- temperature, blood pressure, pulse rate, arterial oxygen saturation, inotrope requirement, organ support requirement. These factors should be looked in combination rather than in isolation, and generally temporal trends in diagnostic parameters are more significant than a single value.

Can the infection/colonisation be treated without antibiotics

Non-antibiotic approach in the management of infections is a critical step in therapeutic decision making. Removal of the source of infection is crucial in management of most infections. ESBL is no exception. When the source of infection is a foreign body or a prosthetic device, removal or replacement of the device becomes all the more necessary. This is because infections associated with surgical implant and devices are associated with biofilm formation. Slow growth of microbes, together with restricted penetration of antibiotics inside biofilms makes eradication and treatment of device related infections difficult. The non-antibiotic approach in the management of ESBL related infections would include removal of a ESBL colonised intravascular line (central venous catheter, peripheral venous catheter), change of a colonised indwelling urinary catheter, drainage of an intra-abdominal or other intra-visceral abscesses, and removal of an infected prosthetic device- heart valve, prosthetic joint. It needs emphasis that in device related infections antibiotic therapy alone is unlikely to result in clinical improvement.[4]

Choice of antibiotic(s)

The factors which determine the choice of antibiotics and other management options include: a) site of infection, b) severity of infection, c) presence of a prosthetic device or implant, d) metabolic parameters- liver and renal function, e) patient related factors such as age, pregnancy, lactation. Blood stream infections should be managed by carbapenems (e.g. imipenem, meropenem), whereas non-bacteraemic urinary tract infections especially lower urinary tract infections can be managed with a variety of antibiotics depending on its susceptibility. These include oral antibiotics like trimethoprim, nitrofurantoin, co-amoxiclav, mecillinam, or intravenous agents like aminoglycoside (gentamicin, amikacin), piperacillin-tazobactam, besides carbapenems (e.g., ertapenem).[5]

In vitro studies have demonstrated no synergy, additivity or antagonism in combination therapy (carbapenem + aminoglycoside). However, the bactericidal activity of imipenem in combination with amikacin was greater than that of imipenem alone. This was due to the faster killing rates of amikacin.[6] It is in this background that in the treatment of life threatening infections like septicaemia, hospital acquired pneumonia, intra-visceral abscesses, carbapenems may be combined with a second agent (amikacin) for the first few days.

Meningitis (rare with ESBLs) and brain abscesses would require treatment with an agent which has good CSF penetration like meropenem (imipenem although efficacious, is better avoided in this setting as it is epileptogenic). The presence of an infected or colonised prosthesis complicates the management of ESBLs. Prosthesis removal should be the priority. However, if this were not done due to poor general condition of the patient, or physician's reluctance, long term combination therapy with a carbapenem and an aminoglycoside would be required.

Beta-lactam-beta-lactamase inhibitor combinations (co-amoxiclav, piperacillin-tazobactam, etc.) are not the optimal therapy for serious infections due to ESBL-producing organisms. Although the inhibitors have significant activity against ESBLs *in vitro*, their clinical effectiveness against serious infections due to ESBL-producing organisms is controversial. The majority of ESBL producing organisms produce more than one beta-lactamase, often in different amount. Hyperproducing strains may produce enough beta-lactamase to overcome the effect of the inhibitor. Moreover, infections with high organism burden (intra-abdominal collections, sepsis) may be associated with sufficient beta-lactamase production to overcome the effects of the beta-lactamase inhibitor. Finally, beta-lactams need to traverse outer membrane proteins through porin channels in order to reach the penicillin-binding proteins. Organisms such as *K. pneumoniae* may become deficient in these crucial outer membrane proteins, thereby rendering the beta-lactam beta-lactamase inhibitor combination clinically ineffective. However, they may be useful for less serious infections such as uncomplicated non-bacteraemic lower urinary tract infection because the infection is localised and the antibiotic is excreted in large amount through the urine.[7]

Pharmacotherapeutic considerations

The table addresses some of the pharmacotherapeutic considerations associated with the management of ESBL. The duration of therapy depends on the source of infection. In an uncomplicated non-bacteraemic urinary tract infection (UTI) 3 days of antibiotic therapy is considered sufficient.[8] Whereas, complicated UTI would necessitate 2 weeks of treatment. Bacteraemia would require a minimum of 10-14 days of treatment[9] apart from endocarditis and prosthetic joint infections, where 4-6 weeks of treatment is recommended. Tissue penetration of antibiotics is crucial in deciding therapy. For CNS infections aminoglycosides penetrate poorly through the blood brain barrier and should never be used in monotherapy. Similar logic applies to aminoglycosides in chest infections. Therapeutic antibiotic level monitoring is

Table: Antibiotics in the treatment of ESBL producing organisms

Antibiotic	Common adult dose, frequency, route*
Carbapenems	Antibiotics of choice; useful in empirical therapy
Imipenem	500 mg four times daily iv
Meropenem	1 gm three times daily iv
Ertapenem	1 gm once daily iv
Aminoglycosides	Antibiotic blood level monitoring recommended to prevent nephrotoxicity and ototoxicity
Gentamicin	5 mg/kg body weight once daily iv
Amikacin	15 mg/kg body weight divided into two equal doses iv
Beta-lactamase inhibitor combinations	Not recommended apart from uncomplicated non-bacteraemic UTI when other suitable alternatives are not available
Co-amoxiclav	625 mg-1.2 gm 3 times daily oral/iv
Piperacillin-tazobactam	4.5 gm 3 times daily iv
Others	May be used only after susceptibility test results in uncomplicated non-bacteraemic UTI
Mecillinam	Initially 400 mg then 200 mg every 8 hours oral
Trimethoprim	200 mg twice daily oral
Nitrofurantoin	50 mg four times daily oral

*Dose adjustment would be required for renal and hepatic impairment, drug interactions, extremes of body weight. Duration of treatment depends on source of infection.

essential in aminoglycoside therapy. Pre-dose level should be <1 mg/L for gentamicin (for once daily dosing at 5mg/kg), and < 10 mg/L for amikacin.

Allergy versus intolerance

Complain of "allergy" to various antibiotics are not uncommon. However, every effort must be made to distinguish true allergy, which is an IgE mediated type 1 hypersensitivity reaction from intolerance (which is non-immunological and usually non-life threatening). Failure to appreciate this distinction may result in unnecessary usage of expensive, less effective antibiotic causing accelerated medical cost and under treatment of potentially serious infections. Patients exhibiting true allergy to penicillins may show about 10% cross reactivity to carbapenems. In these situations therapy becomes difficult and probable choices in sensitive strains include aminoglycosides and quinolones (depending on antibiotic susceptibility).

Side effects and contraindications, dose adjustments in renal and hepatic impairment

No antibiotic is without side effect. However, some side effects are notable. These include allergic reactions and antibiotic associated colitis from carbapenems, seizures from imipenem, nephro- and oto-toxicity from aminoglycosides.

Drug interactions also need to be considered before prescribing. Common examples are aminoglycosides with cyclosporin (used as immunosuppressive in transplant recipients) where there is an enhancement of nephrotoxicity, carbapenems with oestrogens (reduction of efficacy of oral contraceptives). Pharmaceutical prescribing guides (e.g., Electronic Medicines Compendium, British National Formulary)[10,11] that include key information on the selection, prescribing, dispensing and administration of medicines should be used in case of any doubt especially with regards to the dosage adjustments, drug interactions, side effects and contraindications. While adjusting dosage, importance should be given to the creatinine clearance, which is dependent on age, lean body weight and serum creatinine level, and not just on urea or creatinine level. Some antibiotics are best avoided in pregancy and lactation, like, aminoglycosides (risk of ototoxicity), nitrofurantoin (neonatal haemolysis if used at term), trimethoprim in pregnancy (teratogenic). It is important to remember that some of the antibiotics used in the treatment of ESBL (especially carbapenems) are broad spectrum. Hence, utmost care must be taken in its selection. Injudicious and inappropriate usage may lead to selection of resistant organisms like MRSA, *Stenotrophomonas maltophilia*, metallo beta lactamase producing strains of *Pseudomonas aeruginosa* and *Acinetabacter baumanii*, and *Candida* spp. and development of antibiotic associated diarrhoea caused by *Clostridium difficile*.

Outpatient parenteral antibiotic therapy (OPAT)

It is clear from the above discussion that the treatment of ESBL producing organisms is a therapeutic challenge in view of the expense, use of broad-spectrum agents, frequent need of intravenous therapy, and infection control considerations. Management of systemically stable patients in hospital setting may give rise to cross infection, escalated cost and increased morbidity. Use of parenteral antimicrobial agents, which can effectively be administered in an outpatient setting, can minimise a lot of these problems and improve patient compliance and quality of life. The availability of intravenous antibiotics like ertapenem and aminoglycosides (such as gentamicin) which can be administered once daily has given greater options in an OPAT setting.[12]

The source of ESBL: Hospital or community

There was a time when virtually all ESBL isolates used to be reported from the hospital environment. However, with increasing use of broad spectrum antibiotics in the community setting and increasing number of ESBL positive patients who carry the organism from hospital to the community, more and more reports are emerging about community acquired outbreaks of ESBL infections.[2] The information about the probable origin of the ESBL in a patient is important for infection control and epidemiologic reasons. The hospital microbiologist, infection control team, and clinician responsible for care need to be notified for adequate precautions and appropriate antibiotic therapy.

Prevention of spread of ESBL positive organisms in the ward

Infection control precautions like barrier nursing, cohorting of patients and nurses, contact precautions through the use of disposable gloves, gowns, and strict attention to hand washing are essential to limit its spread. Development of an infection control policy and hospital antibiotic prescribing guide should follow next. Education of medical and nursing staffs, patients, visitors and medical students through handouts, posters and meetings could play an important part. ESBL producers are intrinsically resistant to all cephalosporins and aztreonam (even if they exhibit *invitro* susceptibility).[13] Interpretative comments can accompany microbiology reports to underline this fact. Co-resistance to quinolones and aminoglycosides are common.[14] Quinolone antibiotics are strong selectors of ESBL producers and their use should be restricted as far as possible.

Screening of patients for the presence of ESBLs

With ESBLs becoming an increasing problem in hospital and community setting, screening for the presence of these resistant pathogens (like MRSA screening) would ultimately become a necessity, especially in units with high antibiotic use. These would include high dependency units, post-operative wards, intensive care units, haematology, oncology, burn wards, orthopaedic and transplant centres. Screening for ESBL in large number of patients is a technical as well as financial challenge. A robust screening policy and an effective standard operating procedure would be crucial to minimise cost and confusion. Several specimens like rectal swabs, as well as urine, stool and sputum are tested in some centres to screen for resistant gram negative bacilli (GNB). The choice and number of specimens in an institutional setting may ultimately depend on several factors like patient profile and resource availability. The use of antibiotic (gentamicin, ciprofloxacin, cefpodoxime) incorporated agar[15] in microtitre plates may facilitate cost effective screening for resistant GNBs in laboratories with large sample load. Resistant isolates can then be subjected to confirmatory tests to identify the presence of ESBLs.

Future research prospects and conclusion

The development of evidence based guidelines for the management of ESBL positive infections would require the performance of double blinded randomised controlled trials (RCT). Meta-analyses, which are based on the results of several RCTs, provide the best level and grades of evidence. At present there does not seem to exist any significant evidence based recommendations about several aspects in the management of ESBL related infections such as: monotherapy versus combination therapy, optimal duration of therapy, best practice in preventing patient to patient spread in hospital settings.

The management of ESBL requires a multi-disciplinary approach. Co-ordinated participation of microbiologists, clinicians, nursing personnel, hospital infection control team is essential. Therapeutic decision making requires a sound appreciation of clinical perspective. Potential for screening exists but it must be tailored to the institutional need and patient profile. The petri-dish has long inspired our admiration for ESBL producers. It is time to extend our appreciation to the patients who are the ultimate sufferers.

References

1. Chaudhury U, Aggarwal R. Extended spectrum beta-lactamases (ESBL)- An emerging threat to clinical therapeutics. *Indian J Med Microbiol* 2004;**22**:75–80.

2. Rodriguez–Bano J, Navarro MD, Romero L, Martinez–Martinez L, Muniain MA, Perea EJ, et al. Epidemiology and clinical features of infections caused by extended–spectrum beta–lactamase–producing Escherichia coli in nonhospitalized patients. *J Clin Microbiol* 2004;**42**:1089–94.

3. Bradford PA. Extended–Spectrum –Lactamases in the 21st Century: Characterization, epidemiology, and detection of this important resistance threat. *Clin Microbiol Rev* 2001;**14**:933–51.

4. Darouiche RO. Treatment of infections associated with surgical implants. N Engl J Med 2004;**350**:1422–9.

5. Iannini PB. Hospital–acquired Urinary Tract Infections: Implications for Treatment and Prevention. *Curr Tr Op Infect Dis* 2002;**4**:15–20.

6. Pattharachayakul S, Neuhauser MM, Quinn JP, Pendland SL. Extended–spectrum beta–lactamase (ESBL)–producing Klebsiella pneumoniae:activity of single versus combination agents. *J Antimicrob Chemother* 2003;**51**:737–9.

7. Paterson DL. B–Lactamase inhibitors and new beta –lactamases. *Curr Treat Opt Infect Dis* 1999;**1**:85–87.

8. Lutters M, Vogt N. Antibiotic duration for treating uncomplicated, symptomatic lower urinary tract infections in elderly women (Cochrane Review). *In*: *The Cochrane Library*, Issue 3. Chichester, UK: John Wiley & Sons, Ltd; 2004. http://www.cochrane.org/cochrane/revabstr/ab001535.htm

9. Bloomfield P, Hodson EM, Craig JC. Antibiotics for acute pyelonephritis in children (Cochrane Review). In:*The Cochrane Library*, Issue 3. Chichester, UK:John Wiley & Sons, Ltd; 2004. http://www.cochrane.org/cochrane/revabstr/ab003772.htm

10. Electronic Medicines Compendium. www.medicines.org.uk

11. British National Formulary. http://www.bnf.org/bnf/

12. Tice AD. Ertapenem: a new opportunity for outpatient parenteral antimicrobial therapy. J Antimicrob Chemother 2004;53:83–6.

13. Paterson DL, Ko WC, Von Gottberg A, Casellas JM, Mulazimoglu L, Klugman KP, et al. Outcome of Cephalosporin Treatment for Serious Infections Due to Apparently Susceptible Organisms Producing Extended–Spectrum –Lactamases: Implications for the Clinical Microbiology Laboratory. *J Clin Microbiol* 2001;**39**:2206–12.

14. Mathai D, Rhomberg PR, Biedenbach DJ, Jones RN. India Antimicrobial Resistance Study Group. Evaluation of the in vitro activity of six broad–spectrum beta–lactam antimicrobial agents tested against recent clinical isolates from India: a survey of ten medical center laboratories. *Diagn Microbiol Infect Dis* 2002;**44**:367–77.

15. Fergusson J. On behalf of the AICA National Advisory Board. Aust Infect Con 2002;**7**;http://www.aica.org.au/docs/about/downloads/definition2.pdf