BETA-LACTAMASE THREAT IN RESPIRATORY TRACT INFECTIONS: FOCUS ON CEPHALOSPORIN-CLAVULINIC ACID

AP Misra, New Delhi

Beta-lactamases are a group of enzymes secreted by certain bacteria, mainly gram negative, which act upon beta-lactam antibiotics and render them ineffective. Beta lactam antibiotics include penicillins, cephalosporins and some carbapenems. These antibiotics have a four carbon atoms ring, called as Beta-lactam which is broken open by Beta-lactamases.

First Beta-lactamase, penicillinase was discovered in 1940. Till now a large number of Beta-lactamases have been discovered. Bacteria of family Enterobacteriaceae produce extended spectrum Beta-lactamases (ESBL). Beta-lactamases are divided into 4 functional groups. Group 1, 3 & 4 are not inhibited by clavulanic acid, only Group 2 which comprises of penicillinase, cephalosporinases or both are inhibited by clavulanic acid.2,3

Respiratory tract infections are broadly grouped into upper and lower respiratory tract infections. Upper respiratory tract infections include infections of nose, paranasal sinuses, pharynx, larynx, trachea and bronchi, while lower respiratory infections comprise those of bronchioles, alveoli and pleura. Upper respiratory infections are mostly caused by viruses; Group A Beta Haemolytic Streptococci (GABHS) is responsible for 5-15% of cases with acute pharyngitis. Among the lower respiratory tract infections, pneumonia cause immense morbidity and mortality and are a leading cause for hospitalization. In this chapter we shall primarily focus on pneumonia. Pneumonia has been divided into 4 major classes; Community Acquired Pneumonia, Health-care Associated Pneumonia, Hospital Acquired Pneumonia and Ventilator Associated Pneumonia.

Bacteria responsible for Community Acquired Pneumonia-
Streptococcus pneumoniae (Pneumococcus), Mycoplasma pneumoniae, Haemophilus influenzae and Chlamydia species

The likelihood of S pneumonia is increased by alcoholism, COP, immunoglobulin deficiency; HIV infection. M pneumonia and Chlamydia affect young healthy adults while CAP due to H influenzae usually occurs after upper respiratory tract infection.

Bacteria responsible for Healthcare Associated and Hospital Acquired Pneumonia-
Streptococcus pneumoniae, Staphylococcus aureus (MRSA), Pseudomonas aeruginosa, E. coli, Klebsiella pneumoniae, Enterobacter spp.

Bacteria responsible for Ventilator Associated Pneumonia (VAP)-
MRSA, P aeruginosa, Acinetobacter spp., K pneumoniae, E. coli, Enterobacter spp.

Streptococcus pneumoniae (Pneumococcus) is the most common cause of CAP and acute otitis media. Mortality and suppuration associated with pneumococcal infection dropped dramatically following the advent of Penicillin in 1940s. However the strains with reduced susceptibility to penicillin were identified in Australia and New Guinea in 1960s and in South Africa in 1970s. Till early 1980s drug resistant strains of Pneumococcus were rare in US, but during late 80s and 90s, there has been a rapid increase in drug resistant strains and in some states 35% of these strains are penicillin resistant. At times there is resistance to many drugs and some isolates have been found which are susceptible only
to vancomycin. Similar is the story in India, where resistance is reported from 9.52%-26.7%. Other common respiratory pathogens, Haemophilus influenzae and Moraxella catarrhalis have also been showing increasing resistance to antimicrobial agents. H. influenzae showed about 25-30% beta lactamase production which has remained stable in last decade. It shows resistance to penicillin, quinolone and cotrimoxazole in 33%, 51% and 10% respectively. M. catarrhalis shows resistance to penicillin and quinolones in 33% and 30% cases.

MRSA was discovered in 1961 in England. It made its first major appearance in the United States in 1981 among intravenous drug users. MRSA is often referred to in the press as a “superbug”. The number of MRSA infections in the US has been increasing significantly. A 2007 report, a publication of the Centers for Disease Control and Prevention (CDC), estimated the number of MRSA infections in hospitals doubled nationwide, from approximately 127,000 in 1999 to 278,000 in 2005, while at the same time annual deaths increased from 11,000 to more than 17,000. Another study led by the CDC estimated that MRSA was responsible for 94,360 serious infections and associated with 18,650 hospital stay-related deaths in the United States in 2005. These figures suggest that MRSA infections are responsible for more deaths in the U.S. each year than AIDS. In India an increasing trend in the prevalence of MRSA has been noted. Reported prevalence from different parts of country range from 30-85% and so far vancomycin resistance has not been reported barring a single report.

The CDC reported that Vancomycin Resistant Enterococci (VRE) in US hospitals had shot up from 0.3 percent of all Enterococci in 1989 to 7.9 percent in 1993. In some hospitals, the percentage was closer to 14 percent. By the mid-1990’s, the mortality rate for patients with VRE had climbed to more than 40 percent. In India VRE prevalence are reported as 8, 55 and 23% from Delhi, Chandigarh and Mumbai respectively.

Gram negative bacterial infections are the predominant isolates in hospitalized patients especially in IC Us. Many bacteria especially those belonging to family Enterobacteriaceae produce Extended Spectrum Beta Lactamase (ESBL) ESBL, first described in 1983 in Germany, are beta-lactamases that hydrolyze extended-spectrum cephalosporins with an oxyimino side chain. These cephalosporins include cefotaxime, ceftriaxone, and ceftazidime as well as the oxyimino-monobactam aztreonam. Thus ESBLs confer resistance to these antibiotics and related oxyimino-beta lactams. In typical circumstances, they derive from genes for TEM-1, TEM-2, or SHV-1 by mutations that alter the amino acid configuration around the active site of these beta-lactamases. This extends the spectrum of beta-lactam antibiotics susceptible to hydrolysis by these enzymes. An increasing number of ESBLs not of TEM or SHV lineage have recently been described. The ESBLs are frequently plasmid encoded. Plasmids responsible for ESBL production frequently carry genes encoding resistance to other drug classes (for example, aminoglycosides). Therefore, antibiotic options in the treatment of ESBL-producing organisms are extremely limited. Carbapenems are the treatment of choice for serious infections due to ESBL-producing organisms, yet carbapenem-resistant isolates have recently been reported. ESBL-producing organisms may appear susceptible to some extended-spectrum cephalosporins. However, treatment with such antibiotics has been associated with high failure rates.

The incidence of ESBL producing E. coli and K. pneumoniae has increased dramatically all over the country. A study from AIIMS New Delhi in 2002, reported that 68% of Enterobacteriaceae were ESBL producers, while other studies from Vellore and Chennai have reported 73.3% and 67.3% respectively. Further an Asian multi-centric study SMART reported community prevalence of ESBL producers 79% in E. coli and 70% in Klebsiella spp. Another study from Chennai showed 87% of K. pneumoniae strains, in children 0-5 yr producing ESBL. In 1996 the first isolate of K. pneumonia producing carbapenemase was discovered and since then it has spread to different parts of the world.

AmpC beta lactamases have emerged now, which are resistant to 3rd generation cephalosporins including Beta Lactam – Beta Lactamase Inhibitors (BL-BLI). These strains retained sensitivity to 4th generation cephalosporins. Strains with AmpC are often multi-drug resistant and may not respond to cephalosporins in spite of in-vitro susceptibility.

Pseudomonas aeruginosa (PA), rarely causes community acquired pneumonia, though it is the most frequent pathogen involved in acute exacerbation of chronic bronchitis. It has been shown that formation of biofilm could influence it’s ability to produce different beta lactamases. Study from different parts of country has shown threefold increase in PA in hospitalized patients. Carbapenem resistance from 31 to 64% has been shown from different areas in India. The more alarming is resistance to polymyxins which has been shown as 8% from a Delhi centre. Another finding which has been noted is that isolates from wards show less resistance vs. those from ICUs.

Acinetobacter baumannii is a pleomorphic, gram negative organism commonly isolated from hospitalized patients. Acinetobacter infections are uncommon but, when they occur, usually involve organ systems that have a high fluid content (e.g., respiratory tract, CSF, peritoneal fluid, urinary tract). It is an important organism causing ventilator associated pneumonia. The presence of Acinetobacter isolates in respiratory secretions in intubated patients nearly always represents colonization. Acinetobacter pneumonias occur in outbreaks and are usually associated with colonized respiratory-support equipment or fluids.
**A baumannii** is a multidrug resistant bacillus sensitive to relatively few antibiotics. Multidrug resistant *Acinetobacter* is not a new or emerging phenomenon, but *A. baumannii* has always been an organism inherently resistant to multiple antibiotics. Carbapenem resistance has been reported from 48-80% from different areas.

Both PA and *A. baumannii* can produce metallo beta lactamase and cause further havoc.

There are some emerging nosocomial gram negative pathogens e.g. *Burkholderia cepacia* and *Stenotrophomonas maltophilia*. These organisms are intrinsically resistant to many antibiotics.

**TREATMENT STRATEGIES**

Here we shall be discussing various strategies to combat these organisms. To simplify the issue we will take important organisms separately.

**Pneumococcus**

Therapy for upper respiratory infections (URIs) such as otitis media and sinusitis is usually empiric. *S. pneumoniae* is the leading cause of these syndromes and pneumococcal infections are less likely to resolve in the absence of antimicrobial therapy than are infections caused by other pathogens. Therefore, therapy effective against pneumococcus is paramount for success. Amoxicillin remains first line therapy for otitis media because antibiotic levels in the middle ear fluid generally exceed the MIC of susceptible and intermediately resistant strains and continued clinical effectiveness has been documented. Doubling the dose of amoxicillin to 60 to 80 mg/kg/d may further increase effectiveness against nonsusceptible pneumococcal infections. Several of the new oral cephalosporins widely promoted as therapy for URIs have poor activity against pneumococci and should be avoided if pneumococcal infection is suspected.

For empiric treatment of invasive pneumococcal infections, the addition of vancomycin should be reserved for patients who are critically ill or immune-compromised. Even in cases where *S. pneumoniae* are resistant to penicillin and ESCs, clinical response to therapy is often good. The choice of antibiotic therapy should be guided by the clinical response, susceptibility to other antibiotics, and the results of follow-up blood cultures.

**MRSA**

For HA-MRSA or CA-MRSA where patient is sick or necrotizing / cavitary infiltrates are present, empiric therapy containing vancomycin, linezolid and clindamycin is given for 7-21 days, pending the culture results. If empyema is present it must be drained.

**ENTEROCOCCUS**

They are usually resistant to cephemycins such as cefoxitin.

Initial resistance to third-generation cephalosporins (e.g., ceftriaxone, cefotaxime, cefazidime) and extended-spectrum penicillins (e.g., ticarcillin, azlocillin, pipiracillin) varies but can develop during treatment. The activity of the fourth-generation cephalosporins (e.g., ceftime) is fair, and the activity of the carbapenems (e.g., imipem, meropenem, ertapenem, doripenem) is excellent. However, resistance has been reported, even to these agents.

**K. PNEUMONIAE**

*Klebsiella* organisms are resistant to multiple antibiotics. This is thought to be a plasmid mediated property.

**Community-acquired pneumonia**

The mortality rate may be 50%, regardless of treatment.

Effective treatment for this rare condition consists of empirical coverage for gram-negative organisms, aggressive ventilation, and supportive care. Other measures include clinical and radiologic surveillance for surgically treatable entities such as pulmonary gangrene, lung abscess, and empyema.

Third-generation cephalosporins or quinolones provide coverage for community-acquired *K. pneumoniae* infection. In one study, combination therapy with aminoglycosides was shown to be superior; this benefit was not observed in other studies. Macrolides have no useful activity against *K. pneumoniae*.

Antibiotic therapy should be implemented for at least 14 days.

**Nosocomial *K pneumoniae* pneumonia**

Choose antibiotics with high intrinsic activity. A regimen that includes imipem, third-generation cephalosporins, quinolones, or aminoglycosides may be used alone or in combination. Always confirm susceptibility. Treatment should last at least 14 days.

A study from Manipal has shown the efficacy of cefoperazone-sulbactam in 70% of patients while piperacillin-tazobactam combination was effective in 60%. Sensitivity to ceftazidime (a surrogate marker for ESBL production) remained low at 35-40%. However as various studies from different parts of country show ESBL production around 60-70%, all sick patients should be treated as ESBL producer till proven otherwise.

Some strains which produce carbapenemase may show resistance to carbapenems.

If response is slow, chest tomography scans may be useful in helping exclude entities that are treatable with debridement or drainage.

In patients who rapidly respond to intravenous therapy, switching to an oral quinolone is regarded as safe so long as the isolate is susceptible.
E. COLI

E. coli pneumonia may respond to 3rd generation cephalosporins and quinolones. However as various reports from country show 68-80% ESBL producing E. coli, which may require carbapenems or polymyxins.

ACINETOBACTER, PSEUDOMONAS

These organisms are niche pathogens that primarily cause opportunistic healthcare-associated infections in patients who are critically ill or immune-compromised. Multidrug resistance is common and increasing among gram negative non-fermenters, and a number of strains have now been identified that exhibit resistance to essentially all commonly used antibiotics. The beta lactam-beta lactam inhibitors, cefoperazone-sulbactam and piperacillin-tazobactam remain the mainstay of treatment. Varying degree of resistance to carbapenem is shown all over the country. Polymyxins are the remaining antibiotic drug class with fairly consistent activity against multidrug-resistant strains of P aeruginosa, Acinetobacter spp.8,13,14

In our setting we are observing widespread ESBL producing gram negative bacteria, which are multi-drug resistant. MRSA has also increased but it is not to the extent as seen in western countries. This is probably due to widespread and empiric use of 2nd and 3rd generation cephalosporins in 1980s and 1990s. It is of paramount importance to use antibiotics judiciously, collect local data of resistance patterns, prescription auditing and following good infection control practices, as there are no new antibiotics in pipeline in near future.

REFERENCES

13. Abhilash KPP, Veeraragavan B, Abraham OC. Epidemiology and Outcome of Bacteremia caused by ESBL Producing E coli and Klebsiella spp. In a Tertiary Care Teaching Hospital in South India. JAPI 2010;58:13-17.