Antibiotic Resistance - Experience in a Tertiary Care Hospital in South India

MVS Subbalaxmi¹, V Lakshmi², V Lavanya³

Introduction

Ever since the advent of antibiotics, the phenomenon of increasing resistance to antibiotics has been well-recognized. The rapid development of resistance to antibiotics in our country is because of the high prevalence rates of infectious diseases, uncontrolled access to high-end antibiotics combined with unreliable laboratory facilities and weakness in the health care system due to lack of appropriate guidelines for therapy of infections and facilities for infection control. The problem is further compounded by truncated therapy for reasons of cost as the sick-poor do not have insurance and cannot afford to complete course of treatment. In this article we discuss Multidrug resistant organisms (MDROs), the factors responsible for antibiotic resistance, role of clinicians, need for laboratory quality assurance, prevailing pathogens at a south Indian tertiary care hospital and methods to prevent of MDRO.

Major Factors Responsible for Increasing Antibiotic Resistance

1. Irrational and suboptimal usage of Antibiotics:
   Previous exposures to antibiotics favor the emergence of multi drug resistant organisms by two mechanisms.
   a. Antibiotics may modify intestinal flora, leading to colonization with resistant bacteria. For example, third-generation cephalosporins¹, fluoroquinolones and vancomycin² have been found to be risk factors for colonization or infection with vancomycin-resistant enterococci.
   b. Suboptimal doses of antibiotics may favor the selection of MDROs. Inducible beta-lactamase producing Gram-negative bacilli such as Pseudomonas aeruginosa, Enterobacter cloacae, Serratia and Citrobacter freundii.³
   c. Another important issue that contributes to and has to be critically addressed in India is the indiscriminate dispensing of the antibiotics off the pharmacy counters without any licensed prescriptions.

2. Lack of uniform surveillance of antibiotic resistance (within the country & region wise):
   While the extent of resistance and the costs involved in treating infection are well-documented in developed countries, relatively little is known about the burden and consequences of antibiotic resistance in developing countries. Uniform surveillance is needed to monitor the spread of resistance, and thus understand the scale of the problem, in order to provide crucial data for the development of containment strategies. There is an urgent need to develop nation wide policy on dispensing reserve antibiotics. Interventions like discontinuing cephalosporins⁴ in certain settings need to be planned at a large scale. Such measures will help in developing antibiograms across the country and will further help to
   - Categorize the drugs useful for community acquired versus nosocomial pathogens
   - Guide therapy of infections in terms of empiric, broad spectrum & reserve drugs, which will be used only for MDROs.

3. Hospital acquired (nosocomial) infections:
   Nosocomial infections are associated with increased mortality, morbidity, length of hospital stay and cost of treatment. Predisposing factors for increased risk of nosocomial infection are: prolonged hospital stay, antibiotic usage, mechanical ventilation, central venous access, stress ulcer prophylaxis, urinary catheterization, steroid use and poor nutritional status.

Clinicians Role in Management of Infectious Diseases

A thorough clinical assessment of the patient is imperative to ascertain the underlying disease process and to predict the pathogens associated with infection based on local flora and their resistance patterns and select an antibiotic that will target the likely pathogens. The clinicians should be aware of difference between infections, colonization and carrier state.

Antibiotics are frequently prescribed in a community for indications in which their use is not warranted. It is important that the clinician must ensure appropriate bacterial and fungal cultures before initiation of empiric antibiotic therapy. The final selection of antibiotic therapy should be based on the bacterial cultures and clinical response.

The duration and selection of antibiotic for perioperative prophylaxis should be based on prescribed guidelines and the locally prevailing organisms⁵. Extending routine perioperative antibiotic prophylaxis does not protect against infection postoperatively and on the contrary may lead to emergence of infections with resistant strains⁶.

Knowledge of the pharmacokinetics and pharmacodynamics of antibiotics is helpful to the clinician in treating infections successfully. Concentration-dependent bacterial killing is a feature of antibiotics such as amino glycosides and fluoroquinolones, higher concentrations resulting in more rapid killing.⁷ Time-dependent bacterial killing is associated with beta-lactam antibiotics.⁷

The clinician responsible for infection control along with the hospital management should make measures to check and control the prescriptions of antibiotics that are newly introduced and those that target highly resistant bacteria. Study by Rahal et al showed that restricting cephalosporin use resulted in a 44% decline in 1 year in the frequency of ESBL isolates. However, this restriction led to a 140% increase in imipenem use. They also noted 69% increase in the frequency of imipenem-resistant P.aeruginosa and the emergence of imipenem-resistant

¹Assistant Professor, Department of General Medicine, Nizam’s Institute of Medical Sciences, Hyderabad, Andhra Pradesh. ²Professor and Head, Department of Microbiology, Nizam’s Institute of Medical Sciences. ³ Ph.D Scholar, Department of Microbiology, Nizam’s Institute of Medical Sciences
Acinetobacter. Studies like this should enable us to introspect the idea of appropriateness of recycling the antibiotics.

**Action plan – CDC, USA**

The CDC, in collaboration with an interagency task force, has issued a document entitled “A Public Health Action Plan to Combat Antimicrobial Resistance,” which designates monitoring of trends and variations in rates of antibiotic resistance as a top priority. The campaign centers on four main strategies: prevent infection, diagnose and treat infection, use antimicrobials wisely, and prevent transmission.

**Need for Laboratory Quality Assurances and Guided Treatment**

Unlike mathematics, medicine is not an exact science. The microbiology laboratories may not always give answers to clinicians’ questions in infectious diseases, e.g., in case of community acquired pneumonia only 5-14% of cultures of blood from patients hospitalized are positive and most frequently isolated organism is Streptococcus pneumonia. Even in the best microbiology laboratory the sensitivity and specificity of the sputum gram stain and culture is less than 50%.

The greatest benefit of staining and culturing respiratory secretions is to alert physician of unsuspected and resistant pathogens and to permit modification of therapy. Rare causative agents of pneumonia like Burkholderia pseudomallei needs special attention in diagnosis as the treatment is for a prolonged duration. Unusual infections like Nocardia reported from reliable microbiology laboratories should never be mistaken for contamination and colonization.

A serious issue that has to be addressed and resolved is the differences and shortcomings that exist among microbiology laboratories across the country performing antibiotic susceptibility tests without any strict adherence to the standard or recommended procedures. With the type of resistance patterns prevailing, there is an absolute and urgent need for nationwide-specific and standard-operating guidelines for the performance of antibiotic susceptibility tests that should be strictly implemented in all laboratories across the country.

Establishing and maintaining a proper microbiology laboratory is technically demanding and costly. For this reason, many of the times both the patient and clinicians have a tendency to avoid microbiological investigations and rely on empiric antibiotic therapy. Hence, there is a need for reliable and quality assured microbiology laboratories, as per CLSI guidelines, at an affordable cost across the country.

**Multidrug Resistant Organisms (MDROs)**

Microbial resistance is most evident in organisms causing common diseases like diarrhoeal diseases, respiratory tract infections, meningitis, sexually transmitted infections, and hospital-acquired infections. Methicillin Resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), Extended Spectrum Beta-lactamase (ESBL) producing organisms like Escherichia coli and Klebsiella pneumoniae, highly resistant pathogens like Acinetobacter species & Pseudomonas aeruginosa, are now major adversaries in our critical care settings. Broad spectrum antibiotics like the carbapenems, which a couple of years ago were very effective for most gram negative organisms are now experiencing resistance.

Gram positive infections particularly MRSA and VRE are on the rise in critical care units of the hospitals. Recently, MRSA infections have been described in patients without established risk factors who are living in the community. It is important to avoid indiscriminate use of higher antibiotics in the management of methicillin sensitive staphylococcal infections where cloxacillin is the drug of choice. Reserve antibiotics like Linezolid are being misused as they are available in the oral form.

Multi drug resistant gram negative infections account for most of the nosocomial infections. Wide variety of β-Lactams are hydrolyzed by plasmid-mediated ESBL enzymes like TEM1, TEM2, and SHV1 enzymes produced by organisms in the Enterobacteriaceae family. Most of these plasmids also carry genes conferring resistance to several non-β-Lactam antibiotics. The most frequent co-resistances found in ESBL-producing organisms are aminoglycosides, fluoroquinolones, tetracyclines, chloramphenicol, and sulfamethoxazole-trimethoprim. Another variety of ESBL enzymes, AmpC β-Lactamases which are non plasmid mediated are transmitted by chromosomes and are weakly inhibited by β-Lactamase inhibitors and are difficult to treat. Data from the Surveillance and Control of Pathogen of Epidemiologic Importance (SCOPE) program demonstrated that ESBL producing organisms like K. pneumoniae and E. coli were the first and second causes of gram-negative nosocomial bloodstream infections and were associated with a crude mortality of 24% and 27%, respectively.

Multidrug resistant organisms like Pseudomonas and Acinetobacter were cited as 19% and 17% of the isolates in ventilator-associated pneumonias in ICU in other centres in United States.

**Prevailing Pathogens at a Tertiary Care Centre - Data from Nizam’s Institute of Medical Sciences (NIMS)**

The laboratory data from the Department of Microbiology, NIMS, was analysed for the prevailing & common nosocomial pathogens over the past 2 years (2007 & 2008). Only the first isolate from each patient was included in the analysis. Antibiotic sensitivity was performed using the API and the VITEK2, bioMerieux, France.

**Gram positive infections:** Gram positive isolates constitute one third the total number of organisms isolated. Vancomycin is still the most preferred antibiotic both for MRSA and Enterococci at our institute. We do not recommend Linezolid for empiric treatment at our institute.

**Staphylococci:** There is an increasing trend in the prevalence of MRSA over 2 years (Tables 1, 2). No vancomycin resistant isolates were encountered. Vancomycin is the drug choice at our institute. Sensitivity to Teicoplanin and Clindamycin has decreased over the 2 years period studied.

**Enterococci:** These organisms are being increasingly isolated. In 2007, there were < 30 isolates, while in 2008 there were 157 isolates. Majority of the isolates were from urine and blood and caused clinically proven sepsis. The species isolated were mainly *E. faecalis* & a few *E. faecium*. The sensitivity to Vancomycin and Ampicillin were 97% and 55% respectively. This data confirms that Vancomycin is the drug of choice and the requirement for Linezolid is limited and should be used in only highly select cases of VRE.
Gram negative infections: These were the most predominant isolates among the hospitalised patients and often difficult to treat especially in the ICU settings. Extended spectrum betalactamase producing E. coli was the most common organism.

Table 1: Percent of Gram Positive Isolates Susceptible to Specified Antibiotic-2007

| Gram-positive | 2007 Data | No. of Isolates | Ampicillin | Ciprofloxacin | Clindamycin | Erythromycin | Gentamicin | Cefotaxime | Levoflaxacin | Methicillin | Penicillin | Teicoplanin | Teicoplanin | Tetra- cycline | Vancomycin |
|---------------|-----------|-----------------|------------|---------------|-------------|--------------|-------------|------------|--------------|-------------|-------------|-------------|-------------|-------------|---------------|-------------|
| Methicillin Res. Staphylococcus aureus | | 72 | 0 | 15 | 71 | 17 | 3 | 4 | 15 | 0 | 0 | 93 | 28 | 100 |
| Methicillin Sens. Staphylococcus aureus | | 56 | 5 | 43 | 93 | 64 | 45 | 48 | 43 | 100 | 5 | 100 | 5 | 36 | 100 |
| Methicillin Res. Staphylococcus coagulase-neg. | | 64 | 0 | 14 | 88 | 22 | 11 | 28 | 14 | 0 | 0 | 84 | 55 | 100 |
| Methicillin Sens. Staphylococcus coagulase-neg. | | 24 | 13 | 67 | 83 | 54 | 67 | 67 | 100 | 13 | 100 | 63 | 100 |
| Enterococcus spp | | | | | | | | | 100 |

Table 2: Percent of Gram Positive Isolates Susceptible to Specified Antibiotic-2008

| Gram-positive | 2008 Data | No. of Isolates | Ampicillin | Ciprofloxacin | Clindamycin | Erythromycin | Gentamicin | Cefotaxime | Levoflaxacin | Methicillin | Penicillin | Teicoplanin | Teicoplanin | Tetra- cycline | Vancomycin |
|---------------|-----------|-----------------|------------|---------------|-------------|--------------|-------------|------------|--------------|-------------|-------------|-------------|-------------|-------------|---------------|-------------|
| Methicillin Res. Staphylococcus aureus | | 302 | 0 | 39 | 14 | 9 | 0 | 0 | 98 | 39 | 100 |
| Methicillin Sens. Staphylococcus aureus | | 276 | 51 | 66 | 62 | 51 | 55 | 100 | 5 | 100 | 36 | 100 |
| Methicillin Res. Staphylococcus coagulase-neg. | | 257 | 0 | 56 | 78 | 20 | 25 | 0 | 0 | 98 | 100 |
| Methicillin Sens. Staphylococcus coagulase-neg. | | 62 | 7 | 32 | 84 | 35 | 34 | 32 | 100 | 7 | 100 |
| Enterococcus spp | | 157 | 55 | 11 | 15 | 55 | 22 | 22 | 100 |

Fig. 1: Comparison of antibiotic sensitivity for E. coli

The data suggests that only 8% of E. coli were sensitive to third generation cephalosporins like ceftriaxone which is a frequently used empiric antibiotic. Similarly, many clinicians start cefepime as empiric therapy but the sensitivity is as low as 3% for E. coli in the year 2007 at our institute.

1. ESBL producing organisms: The incidence of ESBL producing E.coli & K.pneumoniae has increased during the study period of 2 years. Betalactam & betalactam inhibitor combinations, like the cefaperazone – sulbactam and piperacillin – tazobactam, appear to have better sensitivity rates with 59and61% in years 2007 and 2008 respectively. There is also an increasing cross resistance to other groups of antibiotics such as the Aminoglycosides, Fluoroquinolones and of late the Carbapenems (Fig. 1, 2).

2. Pseudomonas aeruginosa: There is a three fold increase in the number of isolates of P.aeruginosa in our hospital in years 2007 and 2008, (from 154 isolates in 2007 to 475 in year 2008). It is alarming to note that the sensitivity to meropenem decreased from 64% in year 2007 to 35% in 2008.
Enteric fever is one of the frequent and important causes of fever in Indian subcontinent. Other than a positive culture, no specific laboratory test is diagnostic for enteric fever. Hinduja hospital reported the percentage of nalidixic acid–resistant S. Typhi increased from 82% of isolates in 2000 to 88% in 2002. At NIMS there were 57 isolates of Salmonella typhi in 2008. Resistance to nalidixic acid was observed in 27/57 (45%) of isolates. There were 13 isolates from blood culture in year 2007.

**Prevention of MDR**

Cross-infection of patients by health care workers with contaminated hands is a major source of nosocomial infections. If every caregiver would reliably practice simple hand hygiene when leaving the bedside of every patient and before touching the next patient, there would be an immediate and profound reduction in the spread of resistant bacteria. Irrational antibiotic prescribing is documented as one of the main factors that encourage emergence of antibiotic-resistant pathogens e.g. antibiotics for common cold, coughs and bronchitis at the community level. Duration of treatment depends on site of infection and type of organism as complicated urinary tract infection and infective endocarditis needs to be treated for at least 3 weeks. De-escalation of antibiotics should be considered once data on culture reports are available and depending on the patient’s clinical response. Several studies have shown that by limiting the use of Cephalosporins in combination with infection control measures, the frequency of ESBL isolates can be reduced substantially.

**Strategies** such as good infection control practices, establishment of national antimicrobial guideline, surveillance programs, audits, continuous training and education amongst health care personnel are necessary and vital to promote and ensure the quality use of antibiotics.

**References**


