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## ANTIBIOTIC RESISTANCE IN ICU: CLINICAL IMPLICATIONS

### INTRODUCTION

In the past six decades more than 15 classes of systemic antimicrobials have been introduced into clinical practice but antibiotic armamentarium is being lost rapidly due to bacterial resistance. If the medical fraternity does not halt this process, it could lead to disastrous situation, akin to the pre-antibiotic era. We must all make a concerted effort to reverse 50 years of indifference to misuse of antibiotics.

Antibiotic resistance (ABR) is greatest in ICU of large teaching hospitals and medical centers and spreads to general wards and smaller hospitals. ICU are considered the "hotspots" for development of resistance due to various reasons, greater severity of illness of patients being admitted, increased use of invasive therapeutic modalities and devices, colonization or infection by multi drug resistant (MDR) bacteria, widespread use of empirical antibiotics, overcrowding of patients, busy health care staff which promote spread of MDR bacteria within the ICU. These MDR strains are as virulent as their susceptible counterparts and cause higher morbidity and mortality.

As is evident from the history of antibiotics (AB), for every new drug introduced there are resistance mechanisms in the bacteria, which emerge as evolutionary process. Therefore the judicious use of AB is the most important strategy to control this menace in addition to standard infection control policies.

### ANTIBIOTIC RESISTANCE

The risk of emergence antibiotic resistance depends on three factors genetic selection, antibiotic pressure, and risk of cross infection. Genetic mechanisms responsible for AB resistance include mutations; plasmids, transposons and integrons mediated resistance. Transposons are mobile unit of DNA that can jump from from plasmid or chromosome of a bacterium to another without site specificity transferring resistance genes. Integrons are mobile genetic elements, which capture and spread genes by site-specific recombination can cause interspecies spread of resistance genes at alarming rates.

### Beta lactamases

They are major defense of gram-negative bacilli (GNB) against B lactam antibiotics and have co-evolved with introduction of newer drugs. They spread from

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Staphylococci initially to H Influenzae and N gonorrhoeae, but with overuse of third generation cephalosporins (3GCS) in last 2 decades have led to emergence of "new" extended spectrum beta lactamases (ESBL), and carbapenemases, which are capable of neutralizing newer AB to produce multidrug resistant bacteria. There are more than 100 different ESBL named variously as TEM, SHV, CTX, and OXA type enzymes.

Diagnosing ESBL production in the microbiology laboratory is difficult as most do not routinely screen for ESBL production and there is no universal marker for ESBL. Some authors have suggested that ceftazidime resistance be used as a "surrogate" marker. Bacteria having ceftazidime MIC > 2 ug /ml are likely ESBL producers and should be tested further by double disk approximation, three dimensional agar test, ESBL card or strip test (last two are investigational). Authors have recommended screening for ESBL K pneumoniae and E coli with reduced susceptibility to 3GCS. In addition due to "inoculum effect" , a drug sensitive in vitro may fail in vivo due to increase in MIC with increased bacterial load of the ESBL producing organism in vivo.

To give an example of the alarming situation we are faced with, Linezolid, a glycopeptide antibiotic was approved for use in Vancomycin resistant enterococci (VRE) and Methicillin resistant staphylococcus aureus (MRSA) in 2001. Emergence of linezolid resistant VRE and MRSA were documented within a year of its use. It is imperative that the drug must be used with caution in poor penetration sites (infected foreign body) and must not be used in lengthy or repeated courses (cystic fibrosis and CRF on hemodialysis), if further resistance is to be curbed.

## **COMBATING ANTIBIOTIC RESISTANCE**

Combating antibiotic resistance involves two strategies applied concurrently throughout the hospital and in the surrounding medical facilities,

- i) Improve infection control practices
- ii) Reduce selective antibiotic pressure

## **INFECTION CONTROL PRACTICES**

### **Hand hygiene**

Enterococci contaminate hands of caregivers and are carried on uniforms and stethoscopes .The single most

important measure to reduce nosocomial transmission of infection is regular hand washing in between patients. However, compliance rates are low in best of centers (30-60%). Alcohol based hand rubs are useful alternative as they are bactericidal and reduce time spent on hand hygiene. When colonization pressure is high (>50%) these measures cannot prevent transmission and universal use of gowns and gloves for contact with infected patients followed by disinfection with alcohol rubs are recommended.

### **Active surveillance (AS)**

This provides data on local bacterial flora and resistance patterns in the ICU. Routine cultures must be obtained from suspected sites before empirical antibiotics are started. Routine surveillance cultures from respiratory and perianal region help in detection of colonized patients and institution of cohort nursing. Molecular epidemiology methods help in deciding the mechanism of resistance development due to lax hygiene policy or to antibiotic pressure or exogenous introduction of bacteria or both and appropriate corrective measures can be instituted.

## **REDUCING ANTIBIOTIC PRESSURE**

These strategies can be readily be incorporated into day to day practice and can be implemented by the following principles

### **1) Restricting the use of antibiotics**

To minimize the unnecessary AB exposure, AB should be used in proper dosage, intervals and for optimal duration, using AB based on local guidelines drawn by hospital infection control committee consisting clinicians and microbiologists, which are audited regularly. Colonization with nosocomial pathogens is very common in critically ill patients and should never be treated as it promotes drug resistance.

### **2) Using narrow spectrum AB**

For non-life threatening infections such as community-acquired pneumonias, urinary tract infections narrow spectrum older drugs (penicillin, gentamicin, trimethoprim) should be used instead of broad spectrum agents. This reduced incidence of Clostridium difficile infections and minimized resistance of bacteria to cephalosporins, quinolones, and aminoglycosides in some studies.

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### 3) Rationalize AB Prescription practices

Restriction of use of antibiotic by using order forms or concurrent feedback to senior physicians prior to initiating AB. Hospital formulary based restriction of drugs in situations such as emergence of ESBL producers(3GCS) and VRE (Vancomycin) to control their further propagation. Computer based antibiotic prescription have reduced hospital expenditure, and resistance rates without adverse effects on clinical outcomes.

### 4) AB rotation or cycling policy

Cycling or rotation means AB class are withdrawn for a defined period and reintroduced later, has potential for reducing resistance as bacterial isolates regain sensitivity to those classes of AB. The optimal duration of cycles not yet established. Authors have rotated class of drugs (3GCS, Fluoroquinolone, carbapenems, Piperacillin - tazobactam) for empiric therapy for periods of 3-4 months and found reduction in prevalence of resistant organisms (MRSA, VRE and ESBL producing bacteria)

### 5) Selective decontamination of digestive tract (SDD)

SDD aims to selectively eliminate aerobic GNB and yeast from the oral cavity and GIT in order to reduce the occurrence of nosocomial infections. It employs four components, topical antibiotics and antifungals (aminoglycoside, Amphotericin B), systemic antibiotics (3GCS), infection control policies and surveillance cultures. Two meta-analysis involving 8500 patients have shown SDD to be effective in reducing lower airway infection OR 0.35(0.29-0.41) and mortality OR 0.80(0.69-0.93) and 6% overall mortality reduction from 30 to 24% without any increase in infection due to resistant bacteria. However, controversial issues are whether benefits of SDD are due to enteral or parenteral drugs and are medical patients likely to benefit as most series with surgical and trauma patients and some studies have shown emergence of resistant strains of MRSA, VRE. Due to fear of antibiotic resistant strains, SDD has not gained popularity in most centers.

Based on the available evidence and experience with SDD and the likelihood of emergence of resistant bacteria, the routine clinical use of SDD cannot be recommended at the present time.

## HOSPITAL ACQUIRED PNEUMONIA (HAP)

**Early onset HAP** Pneumonia occurring within 4 days after hospitalization is usually caused by sensitive community acquired pathogens.

**Late onset HAP** After 5 days of hospitalization caused by MDR pathogens, and carries high morbidity and mortality

Early onset HAP associated with following risk factors is likely to be due to MDR pathogens and needs to be treated aggressively.

### Risk factors for HAP

- Antimicrobial therapy in preceding 90 days
- Current hospitalization of 5 days or more
- High frequency of antibiotic resistance in the community /hospital
- Immunosuppressive disease and/or therapy

### Risk factors for Health care associated pneumonia (HCAP)

- Hospitalization for 2 days or more in the preceding 90 days
- Residence in a nursing home or extended care facility
- Home infusion therapy (including antibiotics)
- Chronic dialysis within 30 days

Diagnosis of VAP is difficult in critically ill patients and mimicks include atelectasis, pulmonary hemorrhage, drug reaction, pulmonary edema, ARDS and pulmonary embolism. Nosocomial tracheo-bronchitis (NTB) is associated with purulent tracheal secretions with normal radiograph and is not associated with increased mortality. A new biomarker, soluble triggering receptors expressed on myeloid cells (sTREM-1) in BAL (rapid immuno-blot) may make the bedside diagnosis easy in future and facilitate early initiation of AB therapy.

VAP is associated with attributable mortality of 33-50%, which increases further in infections due to Acinetobacter, Pseudomonas sp, presence of bacteremia, inappropriate empirical antibiotics, and delayed antibiotic therapy

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## Empiric AB therapy

Prompt appropriate AB therapy is associated with greatest mortality benefit therefore empiric AB have to be chosen and started early. Most accurate criteria for starting Empiric AB are new or progressive radiological infiltrates, with 2 of 3 clinical features, fever >38 C, leucocytosis or leucopenia, purulent tracheal secretions. Microbiological cultures of lower respiratory tract secretions should be used to confirm the diagnosis and guide further therapy after 48-72hours.

Empiric AB therapy should take into consideration the time of onset of HAP, presence of risk factors for drug resistant pathogens, local microbiological flora and resistance patterns. Tracheal aspirate gram stain have been used to guide initial therapy and use of broad spectrum AB combination reduce chances of inappropriate AB therapy to < 10%.

Avoid changing AB before 48-72 hours, which is the time, required for clinical response unless rapid deterioration occurs. Prompt de-escalation of AB therapy once results of microbiological cultures are available should be attempted. This strategy, reduces unnecessary expenditure, side effects and development of resistance

### Antibiotic therapy recommended for HAP

Early onset HAP-

ceftriaxone/cefotaxime or levofloxacin/moxifloxacin or Amoxicillin - clavulanic acid

Late onset HAP or with risk factors for HCAP-

Cefepime, ceftazidime or

Imipenem or Meropenem or

Piperacillin-tazobactam ( for antipseudomonal cover)

plus

Ciprofloxacin or levofloxacin or Amikacin, gentamicin, or tobramycin

plus

Linezolid or vancomycin(if MRSA is suspected)

Duration of AB therapy of 7-8 days is recommended for uncomplicated HAP with good clinical response to treatment except for non-lactose fermenting GNB (Pseudomonas and Acinetobacter) where longer duration

(10-14 days) is advised to prevent relapses and complications.

Combination therapy is recommended as initial empiric therapy for late onset HAP/ with risk factors for MDR pathogens as inadequate therapy associated with mortality. Pseudomonas HAP in neutropenic host, combination therapy has synergistic effect and prevents emergence of antibiotic resistance. Monotherapy with Quinolones/ carbapenems/ piperacillin- tazobactam is recommended for cases of early HAP with no risk factors for MDR pathogens, documented gram positive HAP (MRSA),mild HAP(clinical pulmonary infection score CPIS <6).

## Conclusions

Combating antibiotic resistance involves simultaneous application of infection control practices and reduction of selective antibiotic pressure. Hand hygiene is the simplest most cost effective measure to reduce nosocomial infections. Avoiding antibiotics unless strong clinical or microbiological evidence of infection exists is possibly the best method of reducing antibiotic pressure.

Early and appropriate therapy based on local data of bacterial infections & resistance patterns is associated with reduced mortality from nosocomial pneumonias. Prompt de-escalation of therapy once results of microbiological cultures are available should be done in all cases.

## Suggested reading

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2. Weinstein R A. Antibiotic resistances in hospitals and intensive care units: the problem and potential solutions. Seminars in Respiratory and Critical Care Medicine 2003; 24 (1): 113,120.
3. Kollef M H , Fraser J A. Antibiotic resistance in the intensive care unit Ann Intern Med. 2001;134:298-314.

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## **EDITORIAL COMMENT**

*Antibiotic resistance is a serious problem in medical practice, particularly in the ICUs, which are considered as the hotspots for such developments. Over the years a number of antibiotics have been discovered and used, but the bugs have their own ways of defying their efficiency. Three important factors, namely, genetic mechanisms, antibiotic pressure, and cross infection, decide about the development of antibiotic resistance. Such resistance is a real tough challenge for the clinician facing the problem. Judicious use of antibiotics is the most important and foremost strategy to control this menace in addition to standard infection control practices.*

## **INVESTIGATIONS AND PROCEDURES IN PULMONOLOGY: BRONCHOSCOPY, BAL & TBLB**

### **HISTORY**

Bronchoscopy originated in 1897 when Gustav Kilian of Germany used rigid bronchoscope. Chevalier Jackson refined rigid bronchoscope and in 1970 Shigeta Ikeda used flexible bronchoscope

### **INDICATIONS of BRONCHOSCOPY**

Bronchoscopy is one of the most common invasive diagnostic & therapeutic procedure in pulmonology. Common indications are:

1. Diagnosis of lung cancer
2. Vocal cord paralysis
3. Occult CA (Positive sputum cytology)
4. Diagnosis of diffuse lung disease: TBLB
5. Diagnosis of pulmonary infections
6. Surveillance bronchoscopy & TBLB: obliterative bronchiolitis in lung transplant patients

### **PRE-PROCEDURE WORKUP**

Spirometry should be done in patients with suspected COPD. Arterial blood gas analysis is required in severe COPD (FEV1 < 40%). Prophylactic antibiotics are not indicated except in patients who are asplenic, with heart valve prosthesis, or a previous H/O endocarditis. Bronchoscopy should be avoided within 6 wks of MI. Asthmatic patients should be given bronchodilator prior to

the procedure. Clear fluids may be allowed 2 hrs prior to the procedure. Patient should be kept nil per-oral for 4 hrs after bronchoscopy.

### **COMPLICATIONS**

In a recent retrospective study 4000 procedures no death were reported. Major complication occurred in 0.5% and minor complication in 0.8%. Major complications included respiratory depression, pneumonia, pneumothorax, cardiorespiratory arrest, arrhythmias, and pulmonary edema. Minor complications encountered were vasovagal attack, fever, haemorrhage, airway obstruction

Complication following transbronchial biopsy:

pneumothorax 1-5%, haemorrhage 9% (uremic and immunosuppressed patients). In view of low complication rate hospitalization is not required for TBLB.

Complications of lidocaine: seizures & cardiac depression caution in patients with malignancies involving liver (recommended maximum dose 8.2 mg/kg). Hypoxemia: especially if BAL done. If sedation is given or in patients with impaired lung function, monitoring by oximetry should be done.

### **Arrhythmia**

Arrhythmia occur commonly in patients who develop hypoxia (40% in pts with hypoxia). ECG monitoring is recommended in patients who have

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abnormal preoperative ECG (in patients with severe cardiac disease) and if hypoxia is refractory to O<sub>2</sub>. Risk of arrhythmia is particularly high during the passage of bronchoscope through the vocal cords. Hypoxia is more common if BAL is done.

O<sub>2</sub> supplementation is beneficial in patients with impaired lung function. Oxygen should be given through nasal cannulae at the rate of at least 2 lpm. In high risk hypoxemic patients requiring bronchoscopy & lavage noninvasive ventilation via face mask can be used. Fever may occur in bronchoscopy without lavage in 1.2%; with lavage in (10-30%) and after TBLB in 15%

### **Ischemia**

Ischemia is more common in patients over 60 yrs of age. Continuous ECG monitoring, O<sub>2</sub> supplementation to prevent hypoxia and adequate sedation should be used if ongoing ischemia is present. Sedation should be used with caution in patients with ischemia

### **Asthma**

In a study of 216 patient asthmatic undergoing bronchoscopy 8% of patients developed bronchospasm. Lignocaine exacerbates bronchospasm. Preoperative bronchodilator beneficial and should be used routinely

### **Bronchoalveolar Lavage**

The earliest indication of BAL was therapeutic in the form of removing inspissated secretions in severe asthma. Later this technique was modified and smaller volumes were used. For obtaining BAL the tip of bronchoscope is wedged in a peripheral small bronchus; either middle lobe/lingula or lower lobe bronchus. Segment is usually selected on the basis of CXR. 20-60 ml of warm buffered saline is injected and gently aspirated. A return of 50-60% is expected in normal persons and lesser in diseased lung

### **STANDARDIZATION OF BAL**

To reduce the problem of variability a standard procedure for BAL is recommended. Standard introduction volume is about 100 ml. Standard no. of input aliquots are four. Standard site of lavage is middle lobe of right lung. If the numbers of ciliated bronchial epithelial cells and squamous epithelial cells present in the BAL samples; exceed 5% of the total BAL cells, the lavage sample may be unsatisfactory for alveolar composition.

### **Precautions**

Coughing & trauma are kept to minimum to avoid contamination with blood & mucus. Pre-warmed saline helps in decreasing cough. Lowering aspiration pressure minimizes chances of trauma. Large introduction volume >300 ml increases risk of post lavage pyrexia

### **Differential diagnosis from BAL**

Lymphocytic BAL is seen in granulomatous diseases, Hypersensitivity pneumonitis (very high counts, ? mast cells, atypical lymphocytes) drug induced ILDs. Neutrophils and Eosinophils are seen in IPF, CT-ILD, asbestosis, ARDS, smokers, contamination. Haemorrhagic BAL is characteristic of cytotoxic medication like Bleomycin. BAL CD4/CD8 ratio can help in differentiating sarcoidosis from lymphoma. This ratio is lowest in lymphomas

### **Atypical BAL counts**

**In chronic sarcoidosis:** BAL lymphocytes may be normal & neutrophils may be increased (usually without Eosinophils). Some cases of IPF and ILD associated with S. Sc may have increased lymphocytes

### **BAL as prognostic indicator**

IPF with increased numbers of lymphocytes in the BAL fluid, with or without granulocytes, are more likely to respond to steroids. Increased granulocytes without lymphocytes suggested a better responsiveness to cyclophosphamide than to prednisolone. BAL neutrophilia and/or eosinophilia is associated with more extensive disease and a poor prognosis. IPF with increased numbers of lymphocytes in the BAL fluid, with or without granulocytes, are more likely to respond to steroids. In a study by Haslam et al increased granulocytes without lymphocytes suggested a better responsiveness to cyclophosphamide than to prednisolone. BAL neutrophilia and/or eosinophilia is associated with more extensive disease and a poor prognosis

### **BAL in pneumonia**

40-60% of CAP, HAP & VAP are without etiologic diagnosis. BAL is used in VAP, pneumonia in immunocompromised, & severe CAP.

Sensitivity and specificity of BAL in pneumonia are 72-93% and 65-100% respectively. Results of BAL can help in guiding change of therapy. A lower mortality was

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seen for patients with VAP who underwent bronchoscopy for BAL. Both groups were similar in duration of ICU stay and mechanical ventilation.

Study by Taylor et al (1956 newly diagnosed HIV patients) 30% underwent bronchoscopy. Pneumocystis carinii was the most commonly detected organism. Commonly isolated bacteria were *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Pseudomonas spp* & *Haemophilus influenzae*. *Mycobacteria* was isolated in 8% and most commonly *M. tuberculosis*. Viral isolates (mainly CMV) were 31%. Endobronchial Kaposi's sarcoma was seen in 15% Detection of HHV8 DNA in BAL is sensitive and specific for pulmonary involvement of Kaposi's sarcoma).

In a recent study bronhoscopies in HIV are decreasing. This decrease correlates with the start of HAART

## **TBLB**

TBLB is carried out for bilateral disease. Tip of bronchoscope is wedged into laterally placed peripheral segmental bronchus of lower lobe. Largest possible toothed biopsy forceps are passed. When forceps are seen out, they are opened and advanced till resistance is felt. Forceps are closed and withdrawn. An elastic tug followed by a feeling of give is an indication of satisfactory biopsy. Additionally the lung tissue may be seen to coil backwards. Good piece is a pale fluffy specimen that floats. Transbronchial lung biopsy in diffuse or peripherally located lung disease without endobronchial lesions is diagnostic in 72%. In the same study 3% of samples were inadequate for daignosis. UIP, DIP, BOOP, pulmonary angiitis and granulomatosis may not be diagnosed by TBLB

In a visible tumor in order to achieve a probability >90% of obtaining a positive malignant biopsy at least 5 samples should be obtained

If bronchial biopsy is combined with bronchial washing & brushing: yield is increased to 87%

TBNA is more sensitive if submucosal infiltration is present. Otherwise yield is similar to forceps biopsy. It is helpful in friable masses which tend to bleed. TBNA can be used to sample hilar glands if they are adjacent to airways (yield: 38% if radiological e/o gland enlargement) improved sensitivity if 22 gauge needle is used.

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## **EDITORIAL COMMENT**

*Fiberoptics bronchoscopy is one of the important diagnostic armamentaria available to the pulmonary physician today. After its discovery by Ikeda, the instrument has been used extensively world over practically by all pulmonologists and has virtually replaced the rigid bronchoscopes. The later has only very few specific uses. Flexible fiber optic bronchoscopes are used for both diagnostic and therapeutic purposes in a wide variety of pulmonary conditions, both malignant and nonmalignant. Recent discovery of ultra thin bronchoscopes have further enhanced the accessibility to the bronchial tree and sampling at the subsegmental and more peripheral areas is possible. The procedure of fiber optic bronchoscopy is practically without any significant morbidity or mortality in carefully chosen patients. In fact, in the absence of this "toy" the present day pulmonary physician feels handicapped!*

## **Announcement**

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For details, please contact:

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