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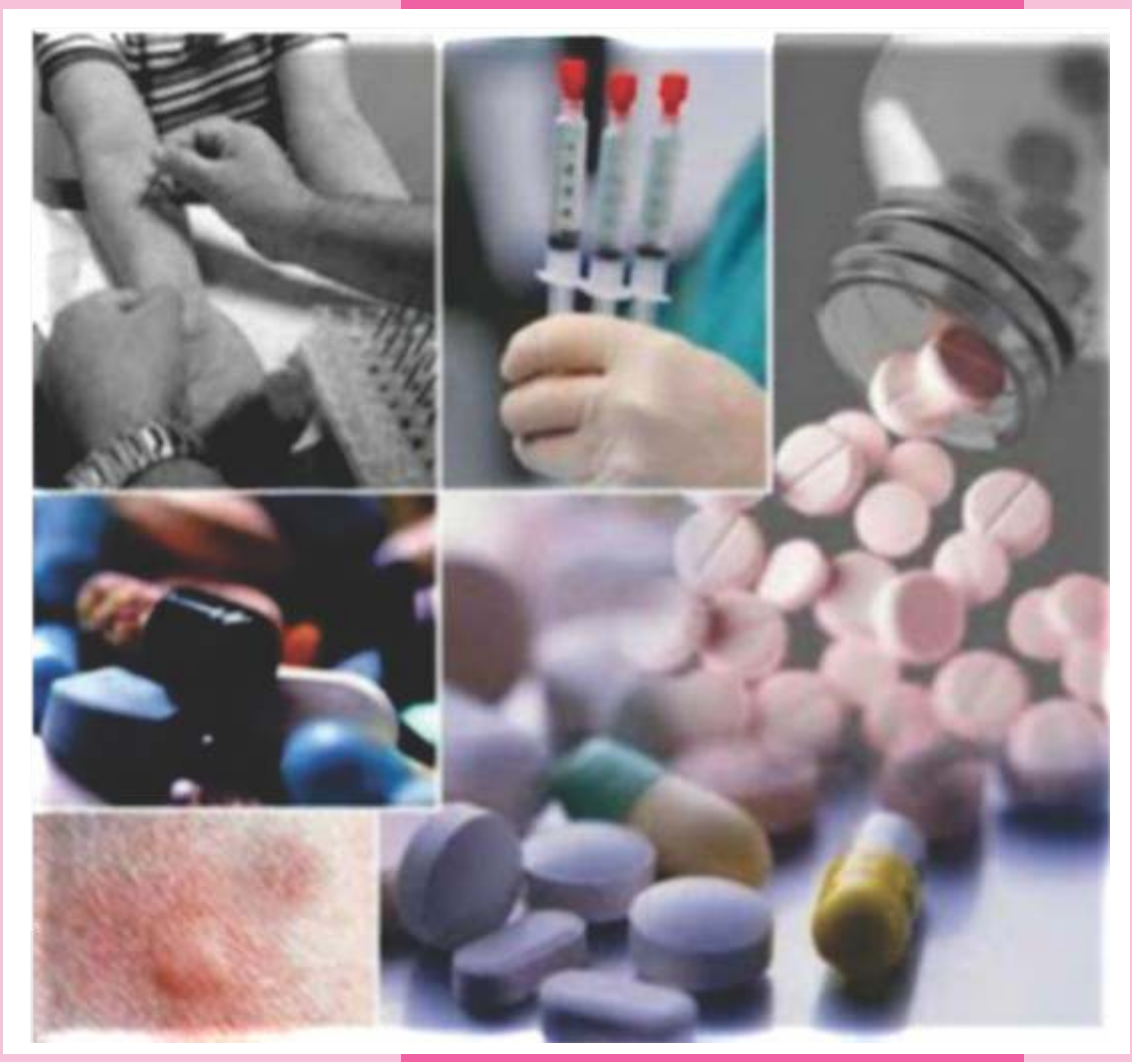
# BULLETIN ON ADVERSE DRUG REACTIONS

## LOKMANYA TILAK MUNICIPAL COLLEGE & GENERAL HOSPITAL



DEPARTMENT OF PHARMACOLOGY,

LTMMC & LTMGH, Sion, Mumbai – 22.

## Committee Members for Bulletin on Adverse Drug Reactions

# INDEX

## *From the Editor's Desk . . . .* ✍

*Dear friends and colleagues,*

*Dear friends and colleagues,*

*With extreme pleasure and pride, I would like to share with you that we are entering into the 10th year for the publication of the "Bulletin on Adverse drug reaction", since its establishment in the year 2011.*

*We have received a lot of suggestions and support from clinicians, colleagues and friends for the improvement of this activity which basically had always aimed towards spreading the awareness of Pharmacovigilance.*

*From this year we are changing the format of the content of the bulletin with the inclusion of the articles on Pharmacotherapy also, without with continued focus on adverse reactions related information.*

*The first article deals with the important dreaded concept of Antimicrobial resistance which is continuously haunting the clinician in patient care. The same article is supported with the succeeding article to address the problem status, effects and remedies which can be undertaken for the prevention and management of Antimicrobial resistance.*

*Apart from this, an interesting case report, mind boggling puzzle and tedious exercise of match the column are the other highlights of this issue.*

*I sincerely hope that this issue enlightens the readers regarding adverse drug reactions.*

*Finally I would like to thank all the clinical departments of our institute for their valued contribution to pharmacovigilance and to the authors for contributing in the bulletin. I would also like to thank all the members of department of pharmacology for their hard work in unfolding our current issue of this bulletin.*

*Thank you,*

*Dr. Sudhir Pawar*

# TREATMENT OF NOSOCOMIAL INFECTIONS AND HEALTHCARE ASSOCIATED INFECTIONS

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## Abstract

*The rate of Nosocomial Infections (NIs) is rising every day in various developed and developing countries. This increasing trend of infection leads to prolonged hospital stay, long term disability, increased antimicrobial resistance flaring up the socio-economic disturbance, which ultimately advances the mortality rate. The most common infection types are ventilator-associated pneumonia (VAP), central line-associated blood stream infection (CLABSI), urinary catheter-related infection and surgical site infection (SSI). Some important risk factors predisposing the NIs are advanced age (>70), malnutrition, alcoholism and healthcare associated risk factors such as invasive procedures like endotracheal or nasal intubation, central venous catheter insertion, urinary catheter. NI can be empirically treated with combination therapy with an anti-pseudomonal penicillin (Piperacillin) plus an aminoglycoside or an antipseudomonal cephalosporin (Ceftazidime) plus an aminoglycoside. The specific therapy relies on identification of the etiological agents with help of efficient clinical microbiology laboratory and good epidemiology practices within the hospital wards. The choice of single or combination antimicrobial therapy depends primarily on the clinical scenario. Appropriate training of hospital staff for biosafety, proper waste management and novel approaches such as implementation of care bundles and spreading awareness among healthcare professionals and patients regarding these endemic infections can also help in reduction of nosocomial infections.*

## Keywords:

*Nosocomial Infections, Antimicrobial agents, Preventive strategies, Antimicrobial stewardship program*

## Introduction

According to the Centers for Disease Control and Prevention (CDC) guidelines, Hospital-acquired infections (HAI) also known as healthcare-associated infections are nosocomially acquired infections that are typically not present or incubating at the time of admission.[1] Occupational-related infection and iatrogenic infections are also classified as HAI.[2] Nosocomial Infections(NIs) are defined as infections acquired between 48 hours after hospital admission and 3 days of hospital discharge.[3] Of every hundred hospitalized patients, seven in developed and ten in developing countries are acquiring one of the healthcare associated infections[4]. Populations at stake are patients in Intensive Care Units (ICUs), burn units, undergoing organ transplant and neonates. According to Extended Prevalence of Infection in Intensive Care (EPIC II) study, the proportion of infected patients within the ICU are often as high as 51% [5]. Based on point prevalence survey of Hospital Acquired Infections (HAIs) and use of indwelling devices and antimicrobials in a large tertiary care hospital in India, noted a total prevalence of HAIs as 7%.[6] In a study conducted in Pune in tertiary care center reported the infection density being 1.75 HAI cases per 1000 patient-days.[7]

The risk to acquire HAI is universal and pervades every healthcare facility in developed as well as developing countries. Nowadays, an increase in the use of antimicrobials and advancements in the medical practices have resulted into frequent use of invasive procedures, which further increases the hazard of new NIs.[8] These infections are considered a threat in this day and modern age of antimicrobials.[9,10,11] Continual mindfulness and timely diagnosis of these conditions with appropriate management improves patient outcomes. Hence, prevention of infection transmission is the key to control NIs. Some of these measures are general practices such as fastidious hand washing, antimicrobial stewardship and the use of best practice 'care bundles'.[3]

**Pathogens involved in NIs**

Pathogens responsible for nosocomial infections are bacteria, viruses and fungal parasites. These microorganisms vary depending upon different patient populations, medical facilities and even difference in the environment in which the care is given.

**Bacteria**[12] - Bacteria are the most common pathogens responsible for NIs. Acinetobacter is embedded in soil and water and accounts for 80% of reported infections in ICUs. C.difficile is transmitted from an infected patient to others through healthcare staff via improper cleansed hands. Enterobacteriaceae high resistance towards carbapenem causes the defence against them more difficult. Methicillin-resistant S.aureus (MRSA) transmit through direct contact, open wounds and contaminated hands. It causes sepsis, pneumonia and SSI by travelling from organs or bloodstream. It is highly resistant towards antimicrobials called beta-lactams.

**Viruses**[12] - Usual monitoring revealed that 5% of all the NIs are because of viruses. They can be transmitted through hand-mouth, respiratory route and feco-oral route. Hepatitis B and C are commonly transmitted through unsafe injection practices to patients as well as healthcare professionals. Other viruses include influenza, HIV, rotavirus, and herpes-simplex virus.

**Fungal parasites**[13] - Fungal parasites act as opportunistic pathogens causing nosocomial infections in immune-compromised individuals. Aspergillus spp. can cause infections through environmental contamination. Candida albicans, Cryptococcus neoformans are also responsible for infection during hospital stay. Candida infections arise from patient's endogenous microflora while Aspergillus infections are caused by inhalation of fungal spores from contaminated air during construction or renovation of health care facility.

**Risk Factors**[14]

Risk factors predisposing to NIs depends upon the environment in which care is delivered, the susceptibility and condition of the patient, and the lack of awareness of such prevailing infections among staff and health care providers. In low income countries, these risk factors are associated with poverty, lack of financial support, understaffed health care settings and inadequate supply of equipment. Other risk factors are enumerated in table 1.

**Table 1- Risk Factors predisposing to NIs[3]**

| Category | Risk factors | |
|---|---|---|
| **Patient-oriented risk factors** | **Acute** | **Chronic** |
| | Surgery | Age > 70years |
| | Trauma | Malnutrition |
| | Burns | Alcoholism |
| | | Chronic smoking |
| | | Chronic lung disease |
| | | Diabetes |
| **Healthcare associated risk factors** | **Invasive procedures** | **Treatment linked risk factors** |
| | Endotracheal or nasal intubation | Blood transfusion |
| | Central venous catheter insertion | Recent antimicrobial therapy |
| | Extracorporeal renal support | Stress-ulcer prophylaxis |
| | Surgical drains | Immunosuppressive treatments |
| | Nasogastric tube | Recumbent position |
| | Tracheostomy | Parenteral nutrition |
| | Urinary catheter | Length of ICU stay |

**Types of Nosocomial Infections[15]**

The most frequent types of infections include central line associated bloodstream infections, catheter-associated urinary tract infections, surgical site infections and ventilator-associated pneumonia. However different studies have mentioned incidences of NI. In a study by Nair V et al (n=1886), Surgical-site infections (SSIs) were identified to be the most common HAI (23.94%), followed by hospital-acquired pneumonia (HAP) (18.31%), urinary tract infection (UTI) (16.9%), catheter-related bloodstream infection (BSI) (16.9%), ventilator-associated pneumonia (VAP) (9.85%), septicaemia (8.45%) and others (5.65%).[6]

1. **Surgical site infections (SSI)[15]** - SSIs are mainly caused by Staphylococcus aureus resulting in prolonged hospitalization and risk of death. The pathogens causing SSI arise from endogenous microflora of the patient. The incidence may be as high as 20% depending upon procedure and surveillance criteria used.

2. **Pneumonia[14]** - The 2016 Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines explain the following types of health care associated pneumonias (HCAP) -

**A. Hospital-acquired (or nosocomial) pneumonia (HAP)** is pneumonia that occurs 48 hours or more after admission and did not appear to be incubating at the time of admission.

**B. Ventilator-associated pneumonia (VAP)** is a type of HAP that develops more than 48 hours after endotracheal intubation. VAP is found in 9-27% of patients on mechanically assisted ventilator. It usually occurs within 48 h after tracheal incubation. 86% of nosocomial pneumonia is associated with ventilation.[14] Fever, leucopenia and bronchial sounds are common symptoms of VAP.

**C. Community acquired pneumonia (CAP)** refers to an acute infection of the pulmonary parenchyma acquired outside of the hospital.[16] It is not a type of HCAP.

3. **Catheter associated urinary tract infections (CAUTI)[15]** - CAUTI is the most usual type of nosocomial infection globally. According to acute care hospital statistics (n=1874) in Lucknow in 2017, the prevalence of CAUTI was 6.93% of reported infections.[17] CAUTIs are caused by endogenous native microflora of the patients. Catheters placed inside serves as a conduit for entry of bacteria whereas the imperfect drainage from catheter retains some volume of urine in the bladder providing stability to bacterial residence. CAUTI can develop to complications such as, orchitis, epididymitis and prostatitis in males, and pyelonephritis, cystitis and meningitis in all patients.

4. **Central line-associated bloodstream infections (CLABSI)**[14] - Catheters are placed in central line to provide fluid and medicines but prolonged use can cause serious bloodstream infections resulting in compromised health and increase in care cost. CLABSI are defined as a laboratory confirmed blood stream infection (BSI) where an eligible BSI organism is identified and an eligible central line is present before the event. They are deadly nosocomial infections with the death incidence rate of 12%-25%. Although there is a decrease of 46% in CLABSI from 2008 to 2013 in US hospitals yet an estimated 30,100 CLABSI still occur in ICU and acute facilities wards in US each year. In 2015, the overall rate of CLABSI in Northern India was 17.04 per 1000 catheter-days and 14.21 per 1000 inpatient-days[11].

5. **Skin and soft-tissue infections (SSTIs)**[14] - Skin and soft tissue infections (SSTIs) result from invasion of the skin, and mostly occur due to trauma or surgery. SSTIs can be classified as simple, necrotizing or suppurative. The frequent pathogens involved in skin and soft-tissue infections are Streptococcus pyogenes, Streptococcus algalactiae, Klebsiella pneumoniae, E. coli, and S. aureus.

6. **Clostridium difficile infection (CDI)** - Clostridium difficile cause inflammation of colon leading to antimicrobial-associated diarrhoea and colitis, mainly due to elimination of beneficial bacteria. Clostridium difficle infection (CDI) in adults is associated with increased morbidity, additional length of hospital stay and an increase in healthcare costs. The prevalence of CDI is ranging between 4%-34% across India.[14] In a recent study from a tertiary care centre in Mumbai, the mean incidence of CDI was estimated to be 0.2/1000 patient days.[18]

**Strategies for management of NIs**[19] - The choice of empiric antimicrobial therapy for the treatment of any NIs before microbiology is available requires –

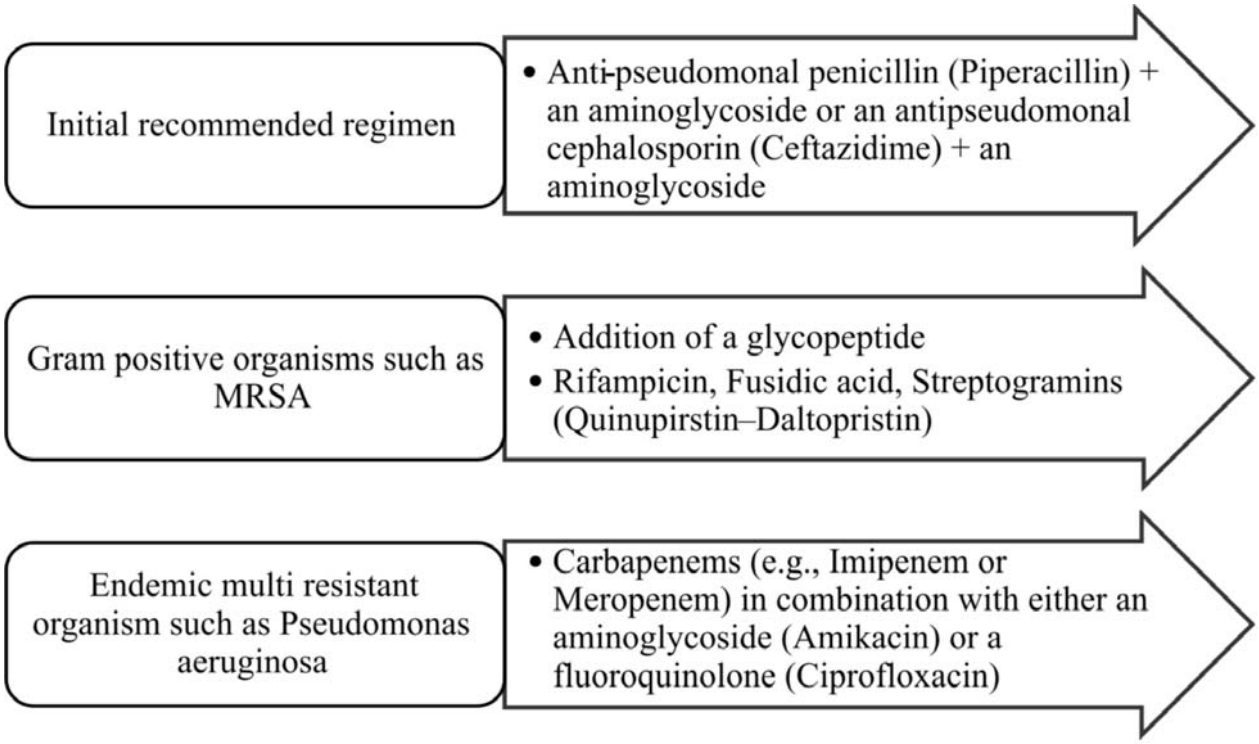
i) Surveillance data on a regular basis of predominant organisms in the hospital/ICU.

ii) Surveillance of the current resistance patterns of these organisms

iii) Identification of outbreaks of NI involving one or more prevalent organisms.

**Principles of Empiric Therapy**[19] : The conventional empiric therapy has to be broad enough to ensure coverage of most of the suspected pathogens. Combination therapy is enlisted in **figure 1**.

**Figure 1- Strategies for Empiric Therapy in NIs**[19]




Any empirical therapy should be reassessed 2 or 3 days after its initiation. Treatment should be readjusted on the basis of report of antimicrobial sensitivity tests available on day 2 or 3, and clinical response of the patient. Potential choice of more suitable combination therapy or switch to less expensive/toxic antimicrobials when the clinical status of patient suggests to do so is recommended.

**Treatment strategies for specific NIs**[19] - The identification of the etiological agents involved in a given outbreak of NIs should rely on an efficient clinical microbiology laboratory and good epidemiology practices within the hospital wards. Moreover the choice of single agent or a combination based on clinical consideration should also refer to the known patterns of susceptibility/resistance as well as patient's condition, severity of underlying disease, the presence of various devices such as catheters, ventilatory equipment, prosthesis etc. Treatment Guidelines for Antimicrobial Use in Common Syndromes were formulated in 2019 by Indian

Council of Medical Research.[21] This guideline highlights the rational use of antimicrobial according to the clinical condition. (Table 2)

**Table 2 : Choice of antimicrobials according to condition**[20]

| **Nosocomial Infection** | **First choice of antimicrobials** | **Alternative** |
|---|---|---|
| **Central Line associated bloodstream infections (CLABSI)** | | |
| Methicillin-resistant S. aureus/ Methicillin resistant Coagulase negative Staphylococcus (CONS) | Vancomycin/ Teicoplanin | Daptomycin |
| Methicillin Sensitive S. aureus/ Methicillin sensitive Coagulase negative Staphylococcus (CONS) | Cefazolin/ Cloxacillin | Vancomycin |
| Ampicillin Susceptible Enterococcus | Ampicillin +/- gentamicin | Vancomycin +/- gentamicin |
| Ampicillin resistant Vancomycin Susceptible Enterococcus | Vancomycin +/-gentamicin | Linezolid/ Daptomycin |
| Ampicillin resistantVancomycin | Resistant Enterococcus | Linezolid/Daptomycin |
| E. coli Carbapenem sensitive | Imipenem/ Cilastatin + Meropenem | Cefoperazone+Sulbactam(2:l) / Piperacillin-tazobactam |
| E. coli Carbapenem resistant | Colistin | Fosfomycin |
| Klebsiella spp Carbapenem resistant | Colistin+ Imipenem / Cilastatin | |
| Klebsiella spp Carbapenem sensitive<br><br>Klebsiella spp Colistin resistant | Imipenem/Cilastatin OR Meropenem<br><br>Fosfomycin OR Imipenem / Cilastatin | Cefoperazone Sulbactam(2:l) OR Piperacillin-tazobactam<br>Chloramphenicol/ Doxycycline |
| Acinetobacter spp Carbapenem resistant | Colistin | Cefoperazone Sulbactam(2:l)/ Ampicillin -sulbactam |
| Acinetobacter spp Carbapenem sensitive | Meropenem | Piperacillin-tazobactam |
| Pseudomonas spp Carbapenem resistant | Colistin | Piperacillin-tazobactam |

| | | |
|---|---|---|
| Pseudomonas spp Carbapenem sensitive | Meropenem / Piperacillin-tazobactam | Ceftazidime / Cefepime |
| Enterobacter / Citrobacter / Proteus / Serratia | Imipenem / Cilastatin, Meropenem | |
| Burkholderiacepacia complex | Meropenem | Ceftazidime / Minocycline |
| Stenotrophomona s maltophilia | Minocycline | Trimethoprim / sulfamethoxazole |
| Candida species (unspeciated)/ C. albicans,C. tropicalis/ C. parapsilosis | Micafungin / Anidulafungin / Caspofungin / Fluconazole | Amphotericin B (lipid)/ Amphotericin B Deoxycholate / Voriconazole |
| C. auris/C. haemulonii/C. krusei | Micafungin / Anidulafungin | Voriconazole |
| C. glabrata | Voriconazole/ Micafungin / Anidulafungin | Fluconazole/ Amphotericin B (lipid) |
| **Catheter associated urinary tract infections (CAUTI)[21]** | | |
| Uncomplicated CAUTI | Trimethoprim-Sulfamethoxazole OR Ciprofloxacin / Nitrofurantoin | Amoxicillin (with or without clavulanate) cephalosporins, doxycycline |
| Complicated CAUTI | TMP-SMX / nitrofurantoin / cephalexin / fluoroquinolones | |
| Pyelonephritis | Ciprofloxacin / Levofloxacin | |
| Complicated Pylonephritis | Trimethoprim - Sulfamethoxazole | Aminoglycoside ± ampicillin or an extended spectrum cephalosporin ± aminoglycoside |
| **VAP/HAP** | | |
| **Culture proved VAP/HAP Most commonly(Acinetobacter baumannii, Klebsiella pneumoniae, Pseudomonas aeruginosa)** | Choose any one according to culture sensitivity from: Piperacillin-Tazobactam, Cefoperazone -Sulbactam, Imipenem-Cilastatin, Meropenem,Colistin, Polymyxin B | |
| **MRSA VAP/HAP** | Linezolid | Vancomycin/Teicoplanin |
| **Skin and soft-tissue infections (SSTIs)** | | |
| Cellulitis (S.pyogenes, S.aureus) | Cefazolin or cephalexin or Amoxicillin-clavulanate +/- Clindamycin | |

| | | |
|---|---|---|
| Necrotizing fasciitis(S. pyogenes S.aureus, anaerobes, Gram negative organisms) (polymicrobial) | Piperacillin-tazobactam + Clindamycin | |
| Necrotizing fasciitis Aeromonas / V.vulnificus | Ciprofoxacin +Doxycycline | |
| Erysipelas Propionibacterium acnes/MSSA | Amoxicillin-clavulanate | |
| Abscess S. pyogenes, Oral anaerobes | Clindamycin OR Ampicillin-sulbactum OR Amoxicillin-clavulanate | |
| Abscess S.aureus, facultative gram negative anaerobes | Linezolid OR Vancomycin + Ciprofloxacin | |
| **Clostridium difficile infection (CDI)** | | |
| Mild to moderate CDI | Vancomycin | |
| Severe CDI with ileus | Vancomycin + Metronidazole | |
| **Healthcare associated intra-abdominal infections** | | |
| **Healthcare associated intra-abdominal infections** | Imipenem/ Meropenem + Vancomycin | Colistin,Tigecyline |
| **Healthcare associated ventriculitis / meningitis** | | |
| Methicillin sensitive Staphylococcus | Cloxacillin | Ceftriaxone |
| Methicillin resistant Staphylococcus | Vancomycin | Linezolid/ Cotrimoxazole if susceptible |
| Non ESBL gram negative | Ceftriaxone | Cefotaxime/ Ceftazidime |
| ESBL gram negative | Meropenem | Cotrimoxazole/ Moxifloxacin |
| Carbapenem resistant gram negative | Systemic Colistin/ Polymyxin B with (depending upon susceptibility) high dose tigecycline / minocycline fosfomycin / cotrimoxazole / quinolones / chloramphenicol with intraventricular / intrathecal colistin / polymyxin aminoglycosides | |

**Table 3 : Antimicrobial prophylaxis for surgical site infections (SSI)[20]**

| Surgical Wound Classification | Common Organisms | Antimicrobial prophylaxis |
|---|---|---|
| Class I / Clean | Gram Positive cocci *(S. aureus*, CoNS) | None or single perioperative dose of cefuroxime / cephalexin (Ideally 2 grams) |
| Class II / Clean - Contaminated | Gram Negative Bacilli<br>Anaerobes<br>*S. aureus* | **1st Line:** Cefazolin or Ampicillin-sulbactam or Ceftriaxone (in patients of acute cholecystitis or acute biliary tract infections)<br>**Alternative: In case of allergies;** if mixture of GP and GN is suspected: Ceftriaxone only if not ESBL, clindamycin or vancomycin with cefazolin, aztreonam, gentamicin, or single-dose fluoroquinolone in b-lactam allergic |
| Class III / Contaminated<br><br>Class IV / Dirty-Infected | Gram Negative Bacilli<br>Anaerobes<br>Gram Negative Bacilli<br>Anaerobes<br>May be mixed with Gram positive bacteria | **1st Line:** Cefazolin + Metronidazole<br>**2nd Line:** Metronidazole+ Aminoglycoside/ Fluoroquinolone<br>**1st Line:** Cefazolin + metronidazole,<br>**Treatment for infected surgical wounds**<br>Ertapenem + Clindamycin + aminoglycoside / aztreonam **Or** fluoroquinolone + metronidazole + aminoglycoside / fluoroquinolone |

**Table 4 : Preferred surgical prophylaxis medication before and during various surgeries[20]**

| SURGERY | MEDICATION |
|---|---|
| Breast | Inj. Cefazolin 2gm or Inj. Cefuroxime 1.5gm IV stat |
| Gastroduodenal & biliary | Inj. Cefaperazone - Sulbactam 2gm IV stat & BD for 24hrs (maximum) |
| ERCP | Inj. Piperacillin -Tazobactum 4.5gm or Inj. Cefaperazone - Sulbactam 2gm IV stat |
| Cardiothoracic | Inj. Cefuroxime 1.5gm IV stat & BD for 48hrs |
| Colonic surgery | Inj. Cefaperazone - Sulbactam 2gm IV stat & BD for 24hrs (maximum) |
| Abdominal surgery (hernia) | Inj. Cefazolin 2gm or Inj. Cefuroxime 1.5gm IV stat |
| Head & Neck/ ENT | Inj. Cefazolin 2gm IV stat |
| Neurosurgery | Inj. Cefazolin 2gm or Inj. Cefuroxime 1.5gm IV stat |

| | |
|---|---|
| Obstetrics & Gynecology | Inj. Cefuroxime 1.5gm IV stat |
| Orthopaedic | Inj. Cefuroxime 1.5gm IV stat & BD for 24 hrs(maximum)<br>**OR** Inj. Cefazolin 2gm IV stat<br>Open reduction of closed fracture with internal fixation -<br>Inj. Cefuroxime 1.5gm IV stat and q 12h or<br>Inj.Cefazolin 2gm IV stat and q 12h for 24 hrs |
| Trauma | Inj. Cefuroxime 1.5gm IV stat and q 12h (for 24 hrs)<br>or Inj. Ceftriaxone 2gm IV OD |
| Urologic procedures | Antimicrobials only to patients with documented bacteriuria |
| Trans- rectal prostatic surgery | Inj. Cefaperazone - Sulbactam 2gm IV stat |

**Preventive strategies for NIs**[21] - Prevention plays a major role in the control of NI. Numerous guidelines have been established in US and European Union. Hospital infection control committees are increasingly organized in modern hospitals to advice regarding the control and prevention of NI. According to National Infection Prevention and Control Strategic Framework March 2020 guidelines, the preventive strategies mainly focusses on isolation policies, administrative measures and hospital epidemiology surveillance.[2] Among the published guidelines, general approaches are as follows[2,21]:

1. Educational programmes, checking catheters, recruiting aseptic team for checking surgical gloves, gowns, etc. and infections at risk for suctioning devices, immunisation.
2. Patient isolation : single room for high risk patients, topical treatments for colonised sites
3. Optimal use of antimicrobial, control of antimicrobial use, performing regular audits
4. Hospital nosocomial infection surveillance such as close cooperation with microbiology, computerised systems in surveillance and fast transmission of data, proper elimination of medical waste.
5. Application of Infection Control committee restriction policies, updating hospital formulary, applying appropriate use of guidelines.
6. Healthcare waste management such as source segregation, safe transport, appropriate end point disposal
7. Recruiting hospital design engineers for suitable structure of wards, rooms, specific isolation units and health care facilities. Close co-operation between authorities, microbiologist, infectious diseases consultants.

**1. Nosocomial pneumonia infection prevention**[21] - Maintenance, disinfection of respiratory equipment

control of (endotracheal tubes, technique for insertion; careful use of invasive) exploratory endoscopies, Oro-pharyngeal decontamination by treating nosocomial sinusitis by local antimicrobials (aerosols), gastric alkalinisation by semi-recumbent position and care of enteral nutrition. Environmental measures such as Surveillance of air conditioning humidities, hot water nebulisers to eliminate legionella, isolation precautions by following isolation guidelines.

**2. Bloodstream infection prevention**[21] - Careful manipulation of search for source of healthcare workers: ventilators, etc): bacteraemia (infection foci). The duration of catheterisation should be changed at regular intervals. Adjusting for severity of underlying disease, blood cultures with automated techniques for rapid identification of pathogens. Environmental infection control by Hospital and Intensive Care Unit surveillance, disposable catheters, close cooperation with microbiology. The novel concept of 'care bundles' grouping best practices for care of invasive devices have proven highly effective for reducing the rates of HAIs in the ICU. A 'care bundle' is a group of three to five evidence-based interventions which, when performed together, have a better outcome than if performed individually.[3] The *PROHIBIT trial* (n=3500) analysed the rate of catheter related blood stream infection (CRBSI) after Central Venous Catheter (CVC) insertion in ICU when both a hand hygiene and best practice care bundle were used and demonstrated a decreased rate of CRBSI from 2.4/1000 CVC days to 0.9/1000.[22]

**3. Surgical Site infection prevention**[21]- Preparation of operative hand-washing, gloves, gowns, masks, etc. Minimise pre-operation stay : suitable skin preparation, hair removal : antimicrobial prophylaxis. Limiting source of exogeneous contamination by using appropriate surgical technique, limiting "dead space" exposing wound, proper wound dressing.

## Antimicrobial stewardship program (ASP)

Antimicrobial stewardship refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial regimen, dose, duration of therapy and route of administration.[23] The antimicrobial stewardship criterion requires that all healthcare services have an antimicrobial stewardship program (ASP) in practice. The first global survey by Howard P et al on implementation of antimicrobial stewardship activities worldwide reports 53% coverage in Asia.[23] The ultimate aim is to achieve optimal clinical outcomes related to antimicrobial use with minimal toxicity and other adverse events; reduce health care costs for infections and limit the selection for antimicrobial strains. ASP have shown 22-36% reduction in antimicrobial use. Also, one of the key strategies of ASP is to prevent the emergence of antimicrobial resistance and decrease preventable healthcare-associated infections.[24]

## Conclusion

With increased burden of nosocomial infections and antimicrobial resistance, it has become difficult for healthcare administrations and infection control committees to reach the goal for elimination of intervals. However, by practicing sound and healthy ways for care delivery designed by infection control committees,

controlling transmission of these infections using appropriate methods for antimicrobial use, the resistance in emerging pathogens against antimicrobials can be reduced easily. An efficient surveillance method guided by WHO can help healthcare institutes to devise infection control programs. Proper training of hospital staff for biosafety, proper waste management and healthcare reforms and making general public aware of these endemic infections can also help in reduction of nosocomial infections.

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# ANTIMICROBIAL RESISTANCE AND STEWARDSHIP

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## Abstract

*Antimicrobial resistance (AMR) has emerged as a major threat to public health. India carries one of the largest burdens of drug-resistant pathogens worldwide. One of the key contributing factors is high antibiotic use due to poor prescription practices, self-medication, over-the-counter sale of drugs and lack of awareness. AMR occurs when a drug loses its ability to inhibit bacterial growth effectively and is reported to have emerged among both Gram-positive and Gram-negative species. Comprehensive efforts are needed to minimize the pace of resistance by studying emergent microorganisms, resistance mechanisms and antimicrobial agents. Antimicrobial stewardship programme (AMSP) has been proved to be successful in restraining sale and use of antibiotics to a large extent in many countries. An AMSP programme for a hospital is imperative for rational and evidence-based antimicrobial therapy. The ultimate aim is to improve patient outcomes, reduce emergence of bacterial resistance and ensure longevity of the existing antimicrobials. The primary goal of AMSP is to encourage cautious use of available antibiotics by training the healthcare workers and creating awareness.*

## Keynotes:

*Antimicrobial resistance, Antimicrobial Stewardship Program, infection prevention and control*

## Introduction

Antibiotics are the 'wonder drugs' extensively used to combat pathogenic microbes. For decades, multiple varieties of antibiotics have been used for therapeutic and prophylactic purposes not only for humans but across other industries such as agriculture and animal husbandry.[1] In 1928, the discovery of penicillin opened the door to the modern era of antimicrobial medicines. Ever since then, these "magic bullets" have transformed medicine and saved countless lives.[2] The period from the 1950s to 1970s was considered as the golden era for the discovery of novel antibiotics classes.[3] The beginning of modern "antibiotic era" was synonymously associated with two names Alexander Fleming and Paul Ehrlich. Antibiotics were considered a magic bullets that selectively targeted microbes that were responsible for disease causation, but at the same time would not affect the host.[4] The discovery, commercialization and routine administration of antimicrobial compounds to treat infections revolutionized modern medicine and changed the therapeutic paradigm.[5] Unfortunately, this era ended because researchers were unable to maintain the pace of antibiotic discovery in the face of emerging resistant pathogens. Persistent failure to develop or discover new antibiotics and non- judicious use of antibiotics are the predisposing factors associated with the emergence of antibiotic resistance.[6]

Antimicrobial resistance (AMR) occurs when microbes (i.e., bacteria, viruses, fungi, and parasites) develop mechanisms to evade antimicrobials (i.e., antibiotics, antivirals, antifungals and antiparasitic) rendering them ineffective.[7] It is reported to occur when a drug loses its ability to inhibit bacterial growth effectively.

Bacteria become 'resistant' and continue to multiply in the presence of therapeutic levels of antibiotics.[1] Antibiotic resistant strains have emerged among both Gram positive and Gram negative species. Examples include *Staphylococcus aureus, Enterococcus species, Pseudomonas aeruginosa, Acinetobacter species, Escherichia coli, Klebsiella pneumoniae, and Neisseria gonorrhoeae*. Antibiotic resistance in *Mycobacterium tuberculosis* has led to the emergence of multi drug resistant tuberculosis and extensively drug resistant (XDR) strains causing tuberculosis (XDR-TB).[8]

**The Global Problem**

AMR has been identified as a global health threat with serious health, political and economic implications.[3] The progress made in modern medicine is under serious threat because of the emergence of AMR. Annual deaths due to AMR are anticipated to rise to 10 million worldwide by 2050.[9] This public health problem is receiving growing attention globally. Several countries are facing the emergence of bacteria that are completely resistant to available antibiotics and countries are preparing country-specific action plans for AMR based on the global action plan of the WHO.[7]

**Challenges of Antimicrobial resistance in India**

As antibiotic consumption is the most important factor for making bacteria resistant against the most powerful class of antibiotics. India is at a severely high risk of becoming the 'AMR capital of the world. In addition to the rampant use of powerful antibiotics, India is faced with perennial public health concerns like inadequate access to toilets and poorly implemented infection-control measures in hospitals.[10] Not only misuse and overuse but underuse due to lack of access is common in India. Lack of access to good quality, affordable antibiotics leads to significant mortality (especially in children), and hence, there is an urgent need to maximize access and limit excess antibiotic use.[11]

Besides the health sector another crucial factor that is contributing to the rising AMR incidence is the injudicious use of antibiotics in agriculture and livestock for increasing productivity of agricultural/livestock output. India, like many developing countries, lacks regulatory mechanisms for antibiotic use in livestock and agriculture, as a result of which antimicrobial residues have often been found in agricultural produce, chicken, meat and milk in several parts of the country.[12] AMR is also exacerbated by a wide range of fixed-dose combinations in the market, often without scientific or medical merit or evaluation. A recent study reported 48 fixed dose combinations and 22 loose antimicrobials for tuberculosis. Loose antimicrobials come without packaging and do not mention the name of the drug, its manufacturer, the date of manufacture, or the date of expiry. There is poor clinician awareness of the rationality and dosing of fixed-dose combinations.[13]

India spends only 4.7% of its total Gross Domestic Product on health, with government share only one-fourth (1.15%) of it, makes the task massive. One study found the median cost of treatment of a resistant bacterial infection to be more than a year wages of a rural worker.

Poor public health infrastructure, a high burden of disease, and unregulated sales of antibiotics have contributed

to a rapid rise in resistant infections in India. This has a huge socioeconomic impact due to deaths and increased costs due to prolonged stay in hospital, additional and repeated laboratory investigations, and loss of work for treating resistant bacterial infections. There are no proper documented estimates on the economic impacts of AMR in India. It can be assumed that due to the high incidence of malaria, tuberculosis, and HIV in India and lack of regulations on the use of antibiotics in humans and the production of food-producing animals, the impacts of AMR on the Indian economy could be huge.[7]

**Origin of Antimicrobial resistance** [10]

❖ **Natural resistance**

Natural resistance may be intrinsic or induced. Intrinsic resistance may be defined as a trait that is shared universally within a bacterial species, is independent of previous antibiotic exposure, and not related to horizontal gene transfer. The most common mechanisms involved in intrinsic resistance are reduced permeability of the outer membrane & activity of efflux pumps. Multidrug-efflux pumps are also a common mechanism of induced resistance.

❖ **Acquired resistance**

Acquisition of genetic material that confers resistance is possible through all of the main routes by which bacteria acquire any genetic material: transformation, transposition, and conjugation (all termed horizontal gene transfer-HGT); plus, the bacteria may experience mutations to its own chromosomal DNA. Plasmid-mediated transmission of resistance genes is the most common route for acquisition of outside genetic material.

**Mechanisms of Antimicrobial Resistance[14]**

Antimicrobial resistance mechanisms fall into four main categories:

(1) **Limiting uptake of a drug** - Gram positive bacteria do not possess an outer membrane, and restricting drug access is not as prevalent. The structure and functions of the Lipopolysaccharide layer in gram negative bacteria provide a barrier to certain types of molecules. The porin channels in gram negative bacteria generally allow access to hydrophilic molecules and a decrease in the number of porins present and mutations that change the selectivity of the porin channels affect its drug uptake.

(2) **Modifying a drug target** - Resistance to beta-lactam drugs occurs via alterations in the structure and/or number of PBPs (penicillin-binding proteins). For drugs that target nucleic acid synthesis (fluoroquinolones), resistance is via modifications in DNA gyrase. Vancomycin resistance is mediated through acquisition of van genes which results in changes in the structure of peptidoglycan precursors that cause a decrease in the binding ability of vancomycin.

(3) **Inactivating a drug** - By actual degradation of the drug, or by transfer of a chemical group to the drug. Drug inactivation by transfer of a chemical group to the drug most commonly uses transfer of acetyl, phosphoryl, and adenyl groups.

(4) **Active drug efflux** - Bacteria possess chromosomally encoded genes for efflux pumps. The efflux pumps function primarily to rid the bacterial cell of toxic substances, and many of these pumps will transport a large variety of compounds (multi-drug [MDR] efflux pumps).

| Drug | Limiting drug uptake | Drug target modification | Drug inactivation | Efflux pumps |
|---|---|---|---|---|
| Beta-Lactams | Decreased numbers of porins, no outer cell wall | Gram +ve: alterations in PBPs | Gram +ve & gram -ve: Beta-lactamases | Resistance-nodulation-cell division family (RND) |
| Aminoglycosides | Cell wall polarity | Ribosomal mutation methylation | Modifying enzymes, acetylation, phosphorylation, adenylation | RND |
| Tetracyclines | Decreased numbers of porins | Ribosomal protection | Antibiotic modification, oxidation | Major Facilitator Superfamily (MFS), RND |
| Fluoroquinolones | | Gram neg-DNA gyrase modification | Acetylation of drug | Multidrug & Toxic compound extrusion family (MATE), MFS RND |
| Streptogramins | | | | Adenosine triphosphate-binding cassette (ABC) |
| Sulfonamides | | Dihydropteroate synthase reduced binding, overproduction of resistant DHPS | | |
| Glycopeptides | Thickened cell wall, no outer cell wall | Modified peptidoglycan | | |

## Actions taken so far and possible strategies for control of AMR

### Global Action Plan (GAP) for anti-microbial resistance [15]

To overcome these critical challenges to development, the global community has now joined hands. GAP is the framework to guide countries in developing respective national action plans (NAP) and implementing the following broad objectives of GAP:

- Improve awareness and understanding of AMR.
- Strengthen the knowledge and evidence base through research and surveillance, thus enhancing awareness.
- Reduce the incidence of infectious diseases and cross-colonization of multidrug-resistant organisms in healthcare settings and in the community.
- Optimize the use of antimicrobials in human and animal health.
- Ensure sustainable funding for programme implementation and development of new medicines, diagnostic tools, vaccines and other interventions.

### India's National Action Plan (NAP)

The first major step towards tackling this problem of AMR was taken in the form of a National Task Force on AMR Containment in 2010 followed by the adoption of National Policy for Containment of AMR, the Jaipur Declaration and the inclusion of antimicrobial containment in the 12th 5-year plan in 2011. However, this policy made little progress due to difficulties in implementation. Further progress was made with the active involvement of the Indian Council of Medical Research (ICMR), and the adoption of the "Chennai Declaration" at the second annual conference of the Clinical Infectious Disease Society at Chennai on August 24, 2012. This was the first-ever meeting of medical societies in India on this issue. The declaration provided a roadmap to tackle the challenges of AMR from an Indian perspective. The declaration has had an unprecedented impact at national and international arena.[7]

The Government adopted a National Action Plan (NAP) on AMR in 2017. The strategic objectives of NAP-AMR are aligned with the global action plan based on national needs and priorities.

Six strategic priorities have been identified under the NAP-AMR[16]

(i) Improving awareness and understanding of AMR through effective communication, education and training;

(ii) Strengthening knowledge and evidence through surveillance;

(iii) Reducing the incidence of infection through effective infection prevention and control;

(iv) Optimizing the use of antimicrobial agents in health, animals and food;

(v) Promoting investments for AMR activities, research and innovations

(vi) Strengthening India's leadership on AMR.

The World Health Organization (WHO) developed a global action plan (GAP) in 2015, which mandates Member States to produce national strategic plans for AMR through surveillance and reporting, antibiotic stewardship and preventing infection. The WHO has identified antimicrobial stewardship programme (AMSP) as one of the interventions in GAP. Implementation of AMSP has been found to reduce excessive antibiotic usage and has resulted in reduced resistance rates in many countries like Australia, USA, France, etc.[17]

**Antimicrobial Stewardship Program (AMSP)**

AMSP refers to comprehensive strategies designed for rational use of antimicrobial agents (AMAs) by optimal antimicrobial drug, dosing, duration of therapy and route of administration with minimal toxicity. The various AMSP strategies include building capacity for stewardship activities, developing policies and guidelines, establishing systems, educating healthcare workers and introducing useful interventions, specifically customized for the national setting.[17]

**Purpose of Antimicrobial Stewardship Program**[18]

1) Primary goal

- To optimize safe and appropriate use of antibiotics to improve clinical outcomes and minimize adverse effects of antibiotics.

2) Secondary goals

- To reduce health care costs without adversely impacting quality of patient care
- To reduce the incidence of antibiotic induced collateral damage

**Strategic approaches to antimicrobial stewardship**[18]

- Appropriate antimicrobial therapy
- Optimizing antimicrobial prophylaxis for operative procedures
- Developing and implementing an antibiotic policies and standard treatment guidelines (STG)
- Prospective auditing and providing feedback and timely intervention in streamlining the antibiotic prescriptions
- Formulary restriction/ pre-authorisation
- Improving antimicrobial prescribing by educational and administrative means

To achieve these, a comprehensive approach through a hospital policy on the rational use of antibiotics is essential. The core strategies can be in the form of two major approaches, with the most successful programmes generally implementing a combination of both. The front-end or pre-prescription approach to stewardship uses restrictive prescriptive authority which requires approval to use certain restricted antibiotics, except trained clinicians. The back-end or post-prescription approach to stewardship uses prospective review and feedback. Based on the review and feedback, the clinicians are recommended by

the AMSP team to modify or discontinue specific antibiotic use.[17] In addition to using one or both of these common approaches, comprehensive antimicrobial stewardship programs (ASPs) use the following strategies and techniques to optimize antimicrobial use in the hospital.

## Active strategies

### Prospective audit with feedback intervention:[19]

In programs that utilize prospective audit and feedback (PAF), trained staff (typically stewardship pharmacists or infectious disease physicians) review antimicrobial orders and provide verbal or written recommendations to prescribers regarding optimization of antimicrobial use. The intervention does not delay the first dose of antimicrobial therapy, and acceptance of recommendations is voluntary. With this approach, prescriber autonomy in clinical decision-making is preserved. PAF has been shown to reduce inappropriate antimicrobial use in multiple settings, including intensive care units, long-term care facilities, and pediatric and community hospitals as well as in outpatient clinics. It has been associated with cost savings and, in some cases, reduction in hospital-acquired infections. A disadvantage of audit and feedback is increased time and clinical expertise compared to other interventions.

### Formulary restriction/Pre-authorization [20]

A simple method for carrying out formulary restrictions is to establish a defined institutional formulary. This approach enforces formulary restriction by strictly limiting which antimicrobials are available to prescribers at a given institution. Implementation of an institutional formulary may be the least controversial approach in that it poses minimal threat to the authority of the prescriber. It can also result in substantial cost savings. Another formulary restriction method is setting institutional utilization criteria. This requires the prescriber to indicate appropriate rationale for the selection of a particular agent. This can be accomplished electronically in institutions with computer physician order entry (CPOE) by requiring the prescriber to select the criteria for use from a pre-populated menu on the order entry screen. Lastly, antimicrobial restriction can be accomplished by requiring prior approval for use by an infectious diseases (ID) physician or pharmacist (i.e., preauthorization-based restriction). This approach is typically instituted in the setting of a pre-existing restricted formulary. This method is perhaps the most effective but requires trained personnel to be available for approvals.

## Supplemental strategies

### Didactic education [18]

Education is the most frequently employed intervention and is considered to be an essential element of any program designed to influence prescribing behavior. Education effects include conference presentations, student and house staff teaching sessions, provision of written guidelines or e-mail alert. Academic medical centers and teaching hospitals should integrate education on fundamental antibiotic stewardship principles into their pre-clinical and clinical curricula. Sharing facility specific information on antibiotic use is a tool to motivate improved antibiotic prescribing practices. There are many options for providing education on

antibiotic use including presentations, posters and flyers, newsletters or electronic communication to staff.

**Facility specific clinical practice guidelines for common infectious diseases syndrome** [21]

Antimicrobial stewardship programs should develop facility-specific clinical practice guidelines and pathways for common infections based on local epidemiology, susceptibility patterns, and drug availability or preference. Infectious disease syndromes include community-acquired pneumonia, urinary tract infections, skin and soft tissue infections, fever, and neutropenia.

Clinical pathways for surgical prophylaxis should include the choice of antimicrobials (narrowest spectrum to cover the most likely pathogens based upon surgical site), optimize dosing to allow for appropriate drug concentrations at the incision site (including weight-based dosing), and limit the duration of antibiotic exposure. Implementation of inpatient pathways has been associated with more appropriate antimicrobial use and reduced length of hospital stay, readmission, and cost.

**Guidelines and clinical pathways** [22]

The development of standard treatment guidelines (STG) should be based on cumulative antibiogram of organisms, antimicrobial policy, surveillance on antimicrobial resistance, antibiotic consumption data and hospital acquired infection (HAI). One of the advantages of guideline development is that it provides the opportunity to incorporate many thought leaders within a hospital to develop hospital- or network-specific algorithms. Guidelines can use national recommendations but should incorporate local trends in antimicrobial resistance and hospital-specific targets for decreased use.

**Antibiotic cycling** [22]

Antibiotic cycling is the scheduled removal and substitution of specific antimicrobials or antimicrobial classes in a given patient care unit. The hypothesis is that by removing specific classes of antimicrobials on a regular basis, the development of resistance can be avoided. For example, all patients with suspected ventilator-associated pneumonia in a certain ICU might be treated with a fourth-generation cephalosporin in January, an anti-pseudomonal beta-lactam/beta-lactamase inhibitor in February, and an antipseudomonal carbapenem in March; then the cycle is repeated.

**Antimicrobial order forms** [18][22]

Order sets, whether on paper or as part of a computerized physician order entry system, can be an important tool in the stewardship team's efforts to ensure guideline-based appropriate empiric antibiotic ordering. Depending on the level of sophistication of the paper or electronic order set, the system can prompt the prescriber to make guideline-based antibiotic choices based on relevant clinical factors, to think about allergies, to remember to adjust for renal function, to consider the cost of therapy, and to order the appropriate tests, monitoring, and consultations. Antimicrobial order forms decrease antimicrobial consumption through the use of automatic stop orders and the requirement of physician justification. Automatic stop orders should not replace clinical judgment, and renewal requirements must be clearly communicated to providers to avoid inappropriate treatment interruptions.

**Antibiotic use measures** [18]

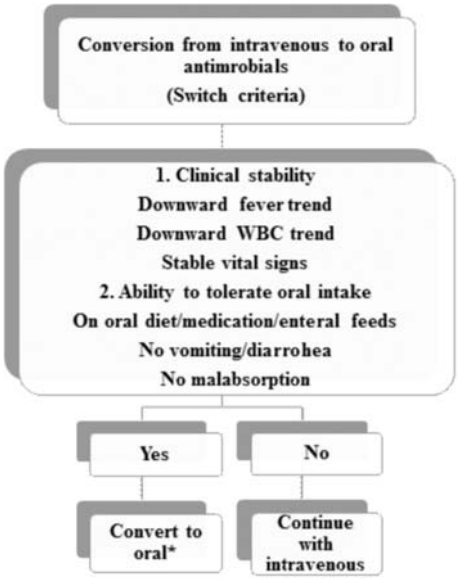
Periodic assessment of antibiotic use for treatment of infection should be performed to determine the quality of antibiotics use. Antibiotic use can be optimized by using accurate diagnostic criteria for infection, prescribing recommended agents for a particular indication, planned duration of antibiotic therapy, obtained blood culture prior to antibiotic therapy. Antibiotic use can be measured by two strategies, days of therapy or defined daily dose (DDD). Days of therapy is an aggregate sum of days for which any amount of an specific antimicrobial agent is administered or dispensed to a particular patient divided by a standardized denominator (patient days). DDD metric estimates antibiotic use in hospitals by aggregating the total number of grams of each antibiotic purchased, dispensed or administered during a period of interest divided by WHO assigned DDD.

**Streamlining/de-escalation** [18]

Excessively broad spectrum therapy contributes to the selection of antimicrobial resistant pathogens. This conflict can be resolved when culture results become available which in turn promote judicious use of antibiotics by streamlining or de-escalating empiric therapy to more targeted therapy that decreases antimicrobial exposure and contains cost. An antibiotic timeout promotes the reassessment of continuation, choice of antibiotic or change to targeted therapy. All clinicians should perform a review of antibiotics 48 hours after prescription.

**Switch from parenteral to oral therapy** [18]

Antimicrobial therapy for patients with serious infections requiring hospitalization is generally initiated with parenteral therapy. Enhanced oral bioavailability among certain antimicrobials-such as fluoroquinolones, oxazolidinones, metronidazole, clindamycin, trimethoprim-sulfamethoxazole -allows conversion to oral therapy once a patient meets defined clinical criteria. This can decrease the length of hospital stay and health care costs.




** unless Severe sepsis, febrile neutropenia, deep seated abscess*

**Figure 1: A systemic plan for parenteral to oral conversion of antimicrobials**

## Other strategies [18]

### ❖ Information technology - Computer surveillance and decision support

With the advent of improved modern health care information technology has offered the opportunity to expand the breadth, depth, and efficiency of AMS programs. Point-of-care access to current medical information is easily available to the practitioner through the use of smart phones, iPads, and other personal digital assistants. In addition, mobile health has enormous scope within AMS to both assist patients with antibiotic reminders, and to assist busy clinicians with antimicrobial information, clinical prescribing support and efficient collection of antimicrobial data. Computer physician order entry (CPOE) and electronic medical records is considered as one of the most important "leaps" that organizations can take to substantially improve patient safety. Computer surveillance program presents epidemiological information with detailed recommendations and warnings regarding antimicrobial regimens and courses of therapy.

### ❖ Role of microbiology laboratory

The clinical microbiology laboratory plays a critical role in the timely identification of microbial pathogens and the performance of susceptibility testing. Susceptibility testing can aid in the prudent use of antimicrobials and direct appropriate therapy based on local guidelines. Molecular diagnostics allows the identification of difficult-to-culture pathogens, potentially avoiding the need for extended courses of broad-spectrum empirical therapy. Local antibiogram with pathogen-specific susceptibility data should be updated at least annually, to optimize expert-based recommendations for empirical therapy.

## Antimicrobial stewardship Team [13]

- Medical directors-They should provide supportive efforts to improve antibiotic use in hospitals through assessing, monitoring and communicating the changes by setting standard antibiotic prescribing practices.
- Pharmacists- Responsibilities of pharmacist include: avoiding the dispensing of drugs over the counter without prescription, emphasizing the correct drug, dose, duration and educating the patient on antimicrobial use and quality assurance activities.
- Microbiologist - can guide accurate and reliable diagnostic test for infectious disease. They can suggest empirical therapy derived from cumulative antibiotic resistance reports available in hospitals. Clinical Microbiologist plays a crucial role in sending alerts of multidrug resistant pathogens and educating about the rapid diagnostic tests available in healthcare settings.
- Infection prevention control committee-They should monitor and prevent the spread of health care associated infections through auditing, analyzing and reporting data. They track antibiotic use in hospitals, adherence to evidence-based published criteria and review antibiotic resistance patterns in the healthcare facility. They educate staff on the importance of appropriate antibiotic use and implement antibiotic stewardship strategies to optimize antibiotic use.

## Goal and Targets of the AMSP and the future vision [13]

AMSP is a coordinated, quality improvement strategy designed to encourage the appropriate use of antimicrobial agents to optimize clinical outcomes while minimizing collateral antimicrobial effects. Collateral effects are primarily AMR but also include any other adverse antimicrobial event. AMS promotes prudent, effective prescribing through optimization of antimicrobial selection, dosage, duration of treatment, and route of administration. An AMS programme comprises both clinical leadership in prescribing and corporate responsibility for prescribing practice, including strategy, surveillance of antimicrobial use, and education relating to antimicrobial therapy.

## Conclusion

There has been an alarming increase in AMR in India due to unwarranted use of antibiotics. Implementation of AMSP on priority will help rationalize antimicrobial usage in our country. The ultimate goal of antimicrobial stewardship is to reduce the adverse consequences of antibiotics and the emergence of resistant organisms. Availability of physicians, pharmacists trained in IDs and documentation such as antibiograms and treatment guidelines is crucial for implementation of an AMSP. AMSP efforts would also need to be supported with improved diagnostic facilities and infection prevention control programmes. There is a need to customize solutions for AMSP relevant to our needs based on healthcare system in the country. This would require funding research to devise and implement ideal AMSP practices addressing the local needs. It is the need of the hour that all hospitals in India initiate AMS strategies and start implementing to benefit patients and also for spill over benefits to community by reducing AMR.

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# LEVOFLOXACIN INDUCED SEIZURES

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## Abstract

*Seizures, encephalopathy, optic neuropathy, peripheral neuropathy, and exacerbation of myasthenia gravis) are important examples of neurotoxic adverse events due to antimicrobials. They are more common in the elderly patients with renal insufficiency, and in patients with pre-existing problems in the central nervous system (CNS). Beta-lactams and quinolones are the antibiotics most commonly associated with neurotoxic side effects. Neurotoxicity like seizures is an effect of decrease GABA inhibition and/or increase glutamate mediated excitation which is a direct effect of the culprit drug or effect of a drug interaction. Here we present an adverse event report of a young female patient with no predisposing factors who experienced seizures after administration of levofloxacin for pneumonia.*

## Introduction

Levofloxacin, which is the active isomer of ofloxacin, is a broad spectrum third-generation fluoroquinolone. Levofloxacin is a safe and effective medicine on the World Health Organization's essential medicines list. It was patented in 1987 and subsequently received FDA-approval in 1996 for medical use in the United States. [1] Levofloxacin's therapeutic use ranges from the common respiratory, urinary tract and gastrointestinal infections to management of drug resistant tuberculosis and febrile neutropenia in immunocompromised patients.[2] Pooled safety data for levofloxacin (n=7,537) suggest that the most common adverse drug reactions leading to discontinuation of the medication are gastrointestinal adverse reactions (1.4%), nausea (0.6%), vomiting (0.4%), dizziness (0.3%), and headache (0.2%).[3] Central nervous (CNS) toxicity caused by levofloxacin is a known but rare adverse effect, with symptoms including headache, dizziness, sleep disturbance, psychosis, delirium, seizures, myoclonus, and others.[4]

Here we present a rare case of Levofloxacin induced generalised tonic clonic seizure in an adult woman with no prior history of seizures.

## Case

A 47-year old woman who is a known case of type 2 diabetes mellitus, hypertension, and rheumatic heart disease was brought to the emergency room with dyspnoea grade III-IV. She complained of chest pain, breathlessness and dry cough since the past two days. On examination her vitals were BP - 140/90, Pulse - 110 beats/minute, SpO2 - 80%, Respiratory rate - 40/min and she presented with generalised pallor and limb oedema. On respiratory examination bilateral crepitations were heard. In view of respiratory distress she was intubated and admitted to the intensive care unit. Laboratory findings showed a white blood cell count - 15600/microL, haemoglobin - 10.10gm%, and normal liver function tests, serum creatinine and serum electrolytes. Chest X-ray was suggestive of pulmonary oedema and bilateral fluffy shadows. She had no prior history of drug allergy, psychiatric disorders, seizure disorder or any other neurologic problems.

She was diagnosed as a case of septicaemia with pneumonia and was started on injection Meropenem 1gm three times a day and injection Amikacin 500mg once a day. The next day injection Levofloxacin 750mg once a day was added to the antibiotic therapy. All three antibiotic drugs were given intravenously in 100cc normal saline over two hours. She has also been taking Gliclazide 80mg for type 2diabetes mellitus, aspirin 75mg for rheumatic heart disease and telmisartan 40mg for hypertension.

On the fourth day after starting intravenous levofloxacin, while the drug was being administered the patient suddenly developed generalised tonic clonic seizure (GTCS) with uprolling of eyes which lasted for two minutes and post ictal drowsiness for a duration of ten minutes. Immediately after this the patient was given injection levetiracetam 1gm intravenously in 100cc normal saline over 30 minutes and she was also put on VAC (ventilation assist control) mode with 100% O2. Levofloxacin was discontinued after this event and was not started again. The patient recovered from the event without any permanent damage and had no episodes of GTCS after levofloxacin was discontinued. Meropenem and amikacin were continued in the above mentioned doses.

As per the ICH E2 seriousness criteria, the reaction is serious as it is life threatening. The causality of this reaction as per the WHO UMC causality assessment scale is "Probable" as dechallenge was positive, the patient did not have any episodes of GTCS after discontinuation of levofloxacin and rechallenge with levofloxacin was not done. According to the Modified Schumock & Thornton Preventability Scale, the occurrence of this reaction in case of our patient was preventable in view of the possible drug-drug interaction between levofloxacin and NSAIDs.

**Discussion**

Levofloxacin is a bactericidal antibiotic of the fluoroquinolone drug class that directly inhibits bacterial DNA synthesis by inhibiting the bacterial enzyme DNA gyrase thereby interfering with replication, transcription and repair of bacterial DNA.[5] Levofloxacin (molecular weight of 361 daltons) is 24%-38% protein-bound, has a mean volume of distribution of 1.1 L/kg and is 80% cleared by the kidneys.[6] It is FDA-approved for the treatment of nosocomial pneumonia, community-acquired pneumonia, acute bacterial rhinosinusitis, acute bacterial exacerbation of chronic bronchitis, prostatitis, acute pyelonephritis, urinary tract infection (uncomplicated or complicated) and skin or skin structure infections.[7]

The primary adverse effects of levofloxacin include photosensitivity, nausea, diarrhea, headache, tendinitis, tendon rupture, hyper-hypoglycemia, seizures, prolonged QT interval, and peripheral neuropathy.[8] The safety and efficacy of levofloxacin have been well documented, and CNS toxicity is low, occurring in just 1 out of every 6 million prescriptions.[9,10]

The neurotoxic potential of levofloxacin is closely related to its antagonistic activity on gamma-aminobutyric acid (GABA) receptors. Proposed mechanisms include inhibition of GABA-A receptors and activation of excitatory N-methyl-D-aspartate (NMDA) receptors.[11] As GABA is an inhibitory

neurotransmitter, blocking its action favours excitatory neurotransmission, which can lead to adverse effects such as seizures.[12] It has been claimed that binding to the GABA-A receptor, and consequently seizure risk, would be enhanced by certain substitutions at the 7-position of the quinolone ring system, notably piperazine groups as in ciprofloxacin.[13,14] Levofloxacin also has a similar substitution.

Electrolyte abnormalities are well recognized causes of seizures. In our case, however, it is unlikely as the serum electrolytes of the patient were normal. The epileptogenic nature of fever is also a well recognized cause of seizures. Nevertheless, in our case, it does not appear to be a determinant factor considering the patient did not have fever at the time or before the episode of GTCS. A report by Kushner et al suggested that the elderly and patients with decreased renal function are at a higher risk of fluoroquinolone-induced seizure.[15] In his case, however, these factors do not apply as our patient is only 47 years old and has a normal creatinine level of 0.6 mg/dl.

There is a clear temporal relationship between the initiation of levofloxacin and the appearance of seizures. As evident in previous literature seizures can occur in days or even hours of initiating levofloxacin as it readily crosses the blood brain barrier and enters CNS.[16] In current case they occurred on the fourth day of therapy and there was no recurrence on withdrawal of the drug. This confirms the WHO UMC causal association to be probable in our case. Possibility of drug interaction between levofloxacin and aspirin causing predisposition to seizures cannot be negated in our case as literature suggest that this interaction is possible due to GABA-B receptor antagonism.[16,17]

Other than this levofloxacin can increase epileptogenic potential of CYP1A2 substrates, such as mirtazapine, metoclopramide, and theophylline by decreasing their metabolism.[16] A case report by Gervasoni C et al mentions that ATP-binding-cassette (ABC)-transporters are known to play a major role in limiting the passage of drugs like levofloxacin into the brain, and genetic polymorphisms in namely ABC-B1 and ABC-G2 increases concentration of levofloxacin in the central nervous system.[18] The implications of these pharmacogenetic aspects in our patient are not confirmed.

Majority of drug induced seizures are self-limited. However, prolongation of the convulsive muscle activity can lead to hypoxia, hypercarbia, pulmonary aspiration of gastric contents, lactic acidosis, hyperthermia and rhabdomyolysis. Initial treatment consists of airway management with adequate oxygenation and ventilation, stabilization of the blood pressure and heart rate and rapid testing of serum glucose concentration and core body temperature. Intravenous lorazepam is preferred initial benzodiazepine, although intravenous midazolam is also widely used. If not effective a barbiturate, phenytoin, ketamine and levetiracetam can be used.[19]

**Conclusion**

Levofloxacin is a commonly used antimicrobial agent. Clinicians are advised to be cautious regarding the use of levofloxacin in patients who have a prior history or predisposing risk factor for seizures and also using it in combination with drugs which have a proconvulsant action namely the CYP1A2 substrates and

NSAIDs. Last but not the least a robust pharmacovigilance mechanism is essential for determining and monitoring the CNS adverse effects of levofloxacin and other fluoroquinolones.

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# SHORT REVIEW OF BETA LACTAMASE INHIBITORS

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Beta-lactam antibiotics constitute 60% of antibiotic consumption all over the world and the highest level of concern and threat to global health is the evolution of antimicrobial resistance.[1][2] Beta lactamase inhibitors (BLI) extend the spectrum of its companion beta lactam (BL) antibiotic by destructing the beta lactamase produced by the particular organism providing the inhibitor is active against the beta lactamase that is produced. It restores the effectiveness of the β-lactam antibiotics.[3] This article focuses on the recent studies illustrating the newer agents in past 3 years that are on the threshold of clinical application.

## 1) VABORBACTUM

It is the first boronic acid β lactamase inhibitor found to exhibit its action against Escherichia coli, Klebsiella pneumoniae, and Enterobacter cloacae species complex in patients ≥18 years of age. Vaborbactam is administered in combination with meropenem.[2]

Approved by U.S FDA in August 2017

Approved by European Medical Agency in November 2018

CDSCO: Not Available

Uses [4]

1) Treatment of Urinary Tract Infections including pyelonephritis.

2) Complicated Intra-abdominal infections.

3) Hospital-acquired pneumonia, including ventilator-associated pneumonia.

| Dose | Frequency | Infusion time | Forms |
|---|---|---|---|
| meropenem 2 grams and vaborbactam 2 gram | every 8 hours | 3 hours | Injection is supplied as a sterile powder for constitution in single-dose vials |

Adverse drug reactions- Headache, diarrhea, inflammation of the vein around the infusion site and nausea.[5]

## 2) RELEBACTUM

Relebactam is a small serine-based molecule with a diazabicyclooctane core and in contrast, also possesses a piperidine ring. Addition of relebactam to imipenem broadens the spectrum and act against imipenem-resistant Enterobacteriaceae and P. aeruginosa strains. [2]

Approved by U.S FDA in July 2019

Approved by European Medical Agency in February 2020

CDSCO: Not Available

Uses [6]

1) Complicated urinary tract infections, including pyelonephritis

2) Complicated intra-abdominal infections.

| Dose | Frequency | Infusion time | Forms |
|---|---|---|---|
| Imipenem 500 mg, Cilastatin 500 mg, Relebactam 250 mg | every 6 hours | 30 minutes | An injection is supplied as a sterile powder for constitution in single-dose vials |

**Adverse drug reactions** - Most common side effect with (which may affect up to 1 in 10 people) is diarrhea and hypersensitivity reactions – anaphylaxis and skin reactions. [7]

**3) CEFIDEROCOL**

It is a novel antibiotic hybrid having a siderophore-containing cephalosporin agent act against A. baumannii, P. aeruginosa, Burkholderia cepacia and S.maltophilia species. [8]

Approved by U.S FDA in December 2019

Approved by European Medical Agency in April 2020

CDSCO: Not Available

Uses [9] - Patients with complicated UTI without pyelonephritis, with uncomplicated pyelonephritis, and with complicated pyelonephritis.

| Dose | Frequency | Infusion time | Forms |
|---|---|---|---|
| Cefiderocol 2 grams | every 8 hours | 3 hours | Lyophilized powder for reconstitution in single-dose vials |

Adverse drug reactions-Diarrhea, infusion site reactions, constipation, rash, candidiasis, cough, elevations in liver tests, headache, hypokalemia, nausea, and vomiting.[9] [10]

**Newer drugs**[11]

| DRUGS | USE | CLINICAL TRAIL |
|---|---|---|
| Sulopenem, iv/oral | Uncomplicated and complicated UTI | Phase 3 |
| Durlobactam + sulbactam, iv | A, baumannii infections | Phase 3 |
| Cefepime-taniborbactam | UTI and acute pyelonephritis | Phase 3 |
| Meropenem-nacubactam | Enterobacteriaceae infections | Phase 1 |
| Cefepime-zidebactam | Enterobacteriaceae infections | Phase 1 |

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# TRENDS IN SAFETY ALERTS OF FLUOROQUINOLONES

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## Background

Fluoroquinolones (fluorinated-4-quinolones), are synthetic fluorinated analogues of nalidixic acid. Quinolones act by blocking bacterial DNA synthesis, their target being bacterial DNA gyrase (topoisomerase II) for many gram-negative microbes and topoisomerase IV for many gram-positive bacteria[1, 2]

Fluoroquinolones are potent bactericidal agents having a broad anti-microbial activity(3). However, due to potentially fatal side effects, many quinolones had to be withdrawn. Many of these side effects were discovered during the post marketing surveillance(4). It is important that both health care providers and patients are aware of both the risks and benefits of fluoroquinolones and make an informed decision about their use. FDA-approved fluoroquinolones include levofloxacin, ciprofloxacin, ciprofloxacin extended-release tablets, moxifloxacin, ofloxacin and Gemifloxacin.

This focuses on the important safety alerts trend of fluoroquinolones that have been added over the course of the years.

## SAFETY ALERTS:

### 1. TENDINITIS AND TENDON RUPTURE:

FDA first added a BOXED WARNING, in the year **2008 (8th July)**, to systemic use of fluoroquinolones for the increased risk of developing **tendinitis and tendon rupture** [5]. This risk increases in those over age 60; in kidney, heart, and lung transplant recipients and with use of concomitant steroid therapy. The mechanism for fluoroquinolone-induced tendon rupture remains uncertain, but has been linked to changes in collagen fibrils following alterations in the regulation of matric metalloproteinases associated with non-traumatic rupture [11]. Fluoroquinolone exposure caused an estimated 2.9 tendon ruptures and 2.1 Achilles tendon ruptures per 10,000 patients per year and was greatest in patients aged 60 years and over. Concomitant oral corticosteroid exposure had a large impact on absolute risk, with the highest rates of tendon rupture associated with concomitant fluoroquinolone and corticosteroid exposure in males and in patients aged 60 years and over [12]. A recent database study of 6.4 million patients found that use of fluoroquinolones was associated with a 4-fold increased risk of Achilles tendinopathy, and a 2-fold increased risk of tendon rupture [26].

The information regarding warnings for fluoroquinolones and adverse effects on tendons applies to fluoroquinolones for systemic use (e.g., tablets, capsules and injectable formulations); it does not apply to fluoroquinolones for ophthalmic or otic use (e.g., eye drops and ear drops) [5]. Patients should be advised to stop taking the fluoroquinolone at the first sign of tendon pain, swelling, or inflammation, to avoid exercise and use of the affected area.

## 2. MYASTHENIA GRAVIS:

Fluoroquinolone exposure may result in potentially life-threatening **myasthenia gravis** exacerbations in patients with underlying disease [6]. There are reports of the exacerbation of myasthenia gravis by ciprofloxacin, levofloxacin, norfloxacin, ofloxacin, trovafloxacin, moxifloxacin, gatifloxacin, pefloxacin and prulifloxacin [7,8,9]. The occurrence of increased myasthenic weakness shortly after the start of fluoroquinolone treatment and the rapid improvement after withdrawal of the antibiotic in each reported case are consistent with a fluoroquinolone block of neuromuscular transmission. Mechanism by which fluoroquinolone cause myasthenia gravis is by reducing the amplitude of the miniature endplate potentials [8].

The risk of worsening symptoms for those with myasthenia gravis was added to the **boxed Warning** [10] in the month of **February 2011** by FDA. The risk is increased in patients taking corticosteroid drugs, patients with kidney, heart or lung transplants; and was greatest among men and older patients >60 years.

Myasthenia gravis exacerbation can be life-threatening and require ventilatory support. Healthcare professionals should be aware of this serious drug-disease association and carefully weigh the benefit-risks of fluoroquinolones when treating infections in non-ventilated myasthenic patients.

## 3. PERIPHERAL NEUROPATHY:

**In August 15th, 2013,** The U.S. Food and Drug Administration (FDA) strengthened its drug labels and medication Guides for all fluoroquinolone antibacterial drugs be updated to better describe the serious side effect of **peripheral neuropathy** [13].

Peripheral neuropathy encompasses single and multiple mononeuropathies as well as polyneuropathy [14]. It has a diverse manifestation, usually involving sensory disturbances affecting the nerves leading to hypoesthesia or hyperesthesia, affecting functional ability and quality of life.

The exact mechanism of peripheral sensory disturbances due to fluoroquinolones is unknown. The diversity of symptoms and difference in onset and recovery times suggest that more than one mechanism is likely. The pathological changes in drug-induced peripheral neuropathy consist of axonal degeneration with secondary breakdown of the myelin sheath, or more rarely primary segmental demyelination [15].

Fluoroquinolone exposure was associated with an increased relative incidence of peripheral neuropathy, incident rate ratio by 1.47. Risk increased was approximately by 3% for each additional day of current fluoroquinolone exposure and persisted for up to 180 days following exposure. The absolute risk with fluoroquinolone exposure was 2.4 per 10000 patients per year[16]. The risk of peripheral neuropathy occurs only with fluoroquinolones that are taken orally or by injection [13]. The topical formulations of fluoroquinolones, applied to the ears or eyes, are not known to be associated with this risk. The risk was greater in men and in those older than 60 years of age.

## 4. NEW LABEL CHANGES-HYPOGLYCAEMIA & MENTAL HEALTH:

In the year 2018, July 10, the FDA strengthened the existing warnings in the prescribing information that fluoroquinolone antibiotics may cause significant decreases in blood sugar and certain mental health side effects[17]. Most fluoroquinolone antibiotic drug labels include a warning that blood sugar disturbances, including high blood sugar and low blood sugar. A range of mental health side effects are also described under central nervous system effects in the warnings and precautions section of the drug label. The label changes added that low blood sugar levels, can lead to coma and also make the mental health side effects more prominent and more consistent across the systemic fluoroquinolone drug class. The mental health side effects to be added to or updated across all the fluoroquinolones are: disturbances in attention, disorientation, agitation, nervousness, memory impairment, serious disturbances in mental abilities called delirium.

Animal studies suggest that the mechanism of action by which fluoroquinolones cause hypoglycaemia is by blocking ATP-sensitive potassium channels in pancreatic beta cells leading to calcium influx through voltage-gated calcium channels causing insulin secretion and subsequent hypoglycaemia [18,19]. Fluoroquinolones have caused at least 67 cases of life-threatening hypoglycaemic coma, including 13 deaths and 9 permanent and disabling injuries, according to an internal safety review by the Food and Drug Administration. Most cases were associated with levofloxacin. The agency reviewed cases in the FDA Adverse Event Reporting System, and in published medical literature, during 1987-2017. Most of the incidents were in the system; 11 additional cases were published. Levofloxacin caused most of the incidents, followed by ciprofloxacin, moxifloxacin, and ofloxacin. Four of the fluoroquinolones have a labelled drug interaction with sulfonylurea agents, which can cause hypoglycaemia[20].

The newest fluoroquinolone, delafloxacin, was not included in the class review. However, FDA expects that similar adverse events will be associated with delafloxacin and labelling on that drug will include the new warnings[20].

The low blood sugar levels can result in serious problems, including coma, particularly in older people and patients with diabetes who are taking medicines to reduce blood sugar. It has been illustrated that that even patients without a history of diabetes, or hypoglycaemic agent use can manifest profound hypoglycaemia secondary to fluoroquinolone use [21].

The proposed mechanism involved in the development of mental health side effects seems to be related to the quinolones' ability to inhibit the binding of  -aminobutyric acid (GABA) to the GABA receptors, leading to CNS excitation[22]. The mechanism(s) by which quinolones affect the CNS are not convincingly elucidated. However, there are studies indicating that GABA receptor interaction cannot be the only mechanism of quinolone neurotoxicity[21]. Another possibility which should be investigated is that quinolones stimulate production of interleukin-2. In animals, interleukin-2

produces side effects similar to those seen when high doses of fluoroquinolones are administered [23]. Many of the more severe CNS reactions seem to be due to metabolic interaction with theophylline (23).

A number of studies demonstrated that serum concentrations of norfloxacin and ofloxacin were significantly elevated by coadministration with fenbufen. It has also demonstrated that fenbufen facilitated the entry of ciprofloxacin, norfloxacin and ofloxacin into the CNS, thus elevating the concentrations of these quinolones in the brain and CSF[24].

CNS effects associated with quinolones range from the trivial to severe (dizziness to convulsions) and vary among class members. Ofloxacin and its L-isomer, levofloxacin, have been observed to induce a range of CNS-related adverse reactions, including headaches (9% ofloxacin, 6% levofloxacin), dizziness (5% ofloxacin, 3% levofloxacin), and less common events include confusion, impaired thinking, insomnia and rarely psychosis[24]. With trovafloxacin, dizziness is the most frequently reported adverse event at 19%; however, with other new agents, dizziness is less common (moxifloxacin 2.9%, gatifloxacin 3%, gemifloxacin 2.8% [25]. The new label changes will make the mental health side effects more prominent and more consistent across the systemic fluoroquinolone drug class.

## 5. AORTIC ANEURYSM/DISSECTION

In 20th December 2018, a U.S. Food and Drug Administration (FDA) review found that fluoroquinolone antibiotics can increase the occurrence of rare but serious events of ruptures or tears in the aorta [27]. Current use of fluoroquinolone was associated with more than a 2-fold increased risk of aortic aneurysm or dissection[26]. It was associated with a statistically significantly increased risk of aortic dissection and aortic aneurysm in a fixed effects metanalysis[28]. Past use and any prior-year use were similarly associated with an increased, although attenuated, risk for these severe adverse events. Longer duration of fluoroquinolone therapy was also associated with higher incidence of aortic aneurysm or dissection. The risk increase of aortic aneurysm or dissection was more substantial in patients older than 70 years and in female patients[26].

While the exact mechanism of how use of fluoroquinolone can cause aortic aneurysm and dissection is unknown, there are several possibilities. The strength of the aortic wall relies on the structural integrity of the extracellular matrix proteins, which are regulated by proteolytic enzymes such as matrix metalloproteinases (MMPs). It has been demonstrated that MMPs play an important role in the pathogenesis of aortic aneurysm and dissection. Dysregulation of MMP production and activity leads to extracellular matrix degradation and medial layer degeneration. Examination of smooth muscle cells from abdominal aortic aneurysm shows an upregulated expression of MMP-9 and MMP-2[26]. Animal studies have shown that fluoroquinolones may induce the expression of MMP-9 and MMP-2. Both MMP-2 and MMP-9 are gelatinases that have collagenolytic activity. Therefore,

it is possible that fluoroquinolones destroy the collagen and connective tissue along the aortic wall causing aortic aneurysm and dissection.

Fluoroquinolones should not be used in patients at increased risk (those with a history of blockages or aneurysms of the aorta or other blood vessels, high blood pressure, certain genetic disorders that involve blood vessel changes, and the elderly) unless there are no other treatment options available. Clinicians should continue to be vigilant for the appearance of aortic aneurysm and dissection in high-risk patients treated with fluoroquinolones

## CONCLUSION:

Fluoroquinolones are widely used in the treatment of various infections. Because the risk of these serious side effects generally outweighs the benefits for patients with acute bacterial sinusitis, acute exacerbation of chronic bronchitis and uncomplicated urinary tract infections, fluoroquinolones should be reserved for use in patients with these conditions who have no alternative treatment options. For some serious bacterial infections, including anthrax, plague and bacterial pneumonia among others, the benefits of fluoroquinolones outweigh the risks and it is appropriate for them to remain available as a therapeutic option. Hence it is important to be aware of adverse effects of these drugs, which should be used for treatment only under close supervision.

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## MATCH THE ADVERSE EFFECT WITH THE DRUG

**Dr. Sharmada Nerlekar & Dr. Abhilasha Rashmi**
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| | | | |
|---|---|---|---|
| 1 | Sulfonamides | A | Myopathy |
| 2 | Fluroguinolones | B | Serotonin Syndrome |
| 3 | Penicillin | C | CCF |
| 4 | Demeclocycline | D | Seizures, Psychosis |
| 5 | Clindamycin | E | Histamine release on rapid infusion |
| 6 | Linezolid | F | Requires vit K prophylayis |
| 7 | Methyl triotetrazole group | G | Dose Dependant Pancreatitis |
| 8 | Daptomycin | H | Nephrolithiasis |
| 9 | Isoniazid | I | Pseudomembranous colitis |
| 10 | Cefoperazone | J | Retinopathy |
| 11 | Eehinocandins | K | Kernicterus |
| 12 | Didanosine | L | Disulfiram-like reaction |
| 13 | Chloroquine | M | Jarisch-Herxheimer reaction |
| 14 | Carbenicillin | N | Nephrogenic diabetes insipidus |
| 15 | Indinavir | O | Can precipitate seizures with NSAIDs |

**Answers :** 1-K; 2-O; 3-M; 4-N; 5-I; 6-B; 7-L; 8-A; 9-D; 10-F; 11-E; 12-G; 13-J; 14-C; 15-H

# ALPHABET 'Y' and 'Z' PUZZLE

**Dr. Abhilasha Rashmi & Dr. Sharmada Nerlekar**

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| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 1 Z | | | | | | | | | |
| 2 | Z | | | | | | | | |
| 3 | | Z | | | | | | | |
| 4 | | | Z | | | | | | |
| 5 | | | | Y | | | | | |
| 6 | | | | | Y | | | | |
| 7 | | | | | | Y | | | |
| 8 | | | | | | | Z | | |
| 9 | | | | | | | | Y | |
| 10 | | | | | | | | | Y |

1. Erythrocytic macrocytosis is seen in about 90% of patients who are on this antiretroviral drug, but is usually not associated with anemia.
2. _____, FDA approved in December 2017, is a novel non-fluorinated topical quinolone indicated for the treatment of impetigo.
3. Drowsiness, asthenia and dizziness may limit the use of this ?2 antiadrenergic drug which is used as an antispastic agent.
4. _____, a derivative of Sisomicin, is FDA approved in 2018 for treatment complicated cases of UTI including pyelonephritis.
5. This aminoglycoside should not be used parenterally as there is a danger of toxic action on the eighth cranial nerve and kidney.
6. Dose related nephrotoxicity & neurotoxicity are the major adverse reactions seen with Colistin which is also known as_____.
7. This aminoglycoside is used for the treatment of acute acquired toxoplasmosis in early pregnancy to prevent transmission to the fetus.
8. This antitubercular irreversible MAO inhibitor drug is of very limited use because of its hepatotoxicity.
9. Acute encephalopathy and fatty degeneration of liver following an acute viral illness in children having a history of aspirin is named after Dr _____.
10. The CNS stimulants Modafinil and Armodafinil are the first line agents for the treatment of this condition of hypersomnia, including day time sleepiness.

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**ALPHABET 'Y' PUZZLE: ANSWERS :**

1. Zidovudine
2. Ozenoxacin
3. Tizanidine
4. Plazomicin
5. Framycetin
6. Polymyxin B
7. Spiramycin
8. Ipronizaid
9. Ralph D Reye
10. Narcolepsy

We would like to request all the departments to contribute in ADR reporting.

Please feel free to contact us for the same.

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