‘Bugs and drugs’ in the Intensive Care Unit

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INTRODUCTION
Infection remains one of the most important threats for patients admitted to an Intensive Care Unit (ICU). A global point-prevalence study conducted in ICU in 2007 revealed that 51% of adult ICU patients were infected and 71% were receiving antibiotics. In this cohort of 13796 patients, infection was independently associated with an increased risk of hospital mortality. Bacteria most commonly cause infections in ICU patients, but fungal and viral pathogens are also important considerations in this group. There are many factors that leave ICU patients at risk of infections. In this article, we provide a basic introduction to the common organisms encountered in an ICU setting, diagnosis of infections caused by them and an overview of the antimicrobials used to treat them.

RISK FACTORS FOR ACQUIRING INFECTION IN ICU

Nutritional status
Poor nutrition suppresses host defences. In addition, procedures to correct nutritional status, such as parenteral nutrition or nasogastric tubes in turn increase the risk of infections, due to damaged integrity of the normal barriers and aspiration.

Glucocorticosteroids
Steroids hamper neutrophil responses and their ability to arrive at inflammatory sites. They decrease their adherence and chemotactic activity. Steroids also reduce phagocytosis and intracellular killing of microorganisms. The lack of functioning neutrophils leaves the host susceptible to serious infections.

Physical barriers (Figure 1)
Micro-organisms normally present on the skin can get easy access to the bloodstream due to insertion of vascular access devices. Broad-spectrum antibiotics can disrupt the ecology of the gastro-intestinal tract, predisposing to colonisation by hospital acquired pathogens and fungi.

Underlying medical conditions
Clearance of respiratory secretions is impaired in smokers and the airways of smokers are prone to colonisation with virulent encapsulated microorganisms. The increased risk of infections in diabetic patients is well recognised.

GRAM POSITIVE BACTERIA
Gram staining divides bacteria into Gram positive and Gram negative, based on the structure of their cell walls, staining properties and the antibiotics they are susceptible to. Some common bacterial pathogens encountered in ICU are:

Staphylococcus aureus
• Gram positive coccus, occurring in clusters.
• Possesses the enzyme coagulase, which causes plasma to clot and distinguishes it from the coagulase negative Staphylococci.
• Part of the normal flora in the nose, throat, perineum, axillae, groin, hairline, etc in almost one third of the population. A ‘screen’ is usually requested from these sites.
• Responsible for skin and soft tissue infections like boils, abscesses, impetigo, furuncles, carbuncles, etc.

<table>
<thead>
<tr>
<th>Defect / condition</th>
<th>Pathogen</th>
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<td>Damaged skin / vascular access devices</td>
<td>Coagulase negative Staphylococci, Staphylococcus aureus, Enteric Gram negative bacilli, Pseudomonas</td>
</tr>
<tr>
<td>Total parenteral nutrition</td>
<td>Blood stream infections due to Candida species</td>
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<tr>
<td>Gastrointestinal tract mucosal barrier injury</td>
<td>Translocation of gut organisms (Gram negative bacilli, Enterococci, Candida, anaerobes) into the blood stream, colonisation and toxin production by Clostridium difficile</td>
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</table>
• Can cause deep-seated infections such as those involving bone and joints, infective endocarditis (especially in intravenous drug users), pyomyositis, prosthetic device related infections.

• Capable of producing several exotoxins, some of which can cause food poisoning. Toxic shock syndrome or Staphylococcal scalded skin syndrome.

• Over 90% are resistant to penicillin, however fluocxacillin covers meticillin sensitive strains (MSSA).

• Cefoxitin or oxacillin is used in the lab for screening for meticillin resistance as these antibiotics are more stable than meticillin.

**MRSA – Meticillin resistant Staphylococcus aureus**

• Meticillin resistance is due to the mecA gene which encodes for an altered penicillin binding protein, PBP2*, consequently altering the structure of the cell wall.

• Classically used to be hospital acquired, but community acquired strains are increasingly common, known as CA-MRSA.

• Disease spectrum is similar to MSSA.

• Risk factors for acquiring MRSA include – old age, residence in nursing homes, previous hospital admission, prior use of antibiotics.

• Meticillin resistance renders the strain resistant to all beta lactam antibiotics.

• Glycopeptides such as vancomycin or teicoplanin are the treatment of choice for MRSA and should be included in the empirical treatment for all patients with known risk factors for acquiring MRSA, until such an infection can be ruled out.

• In the UK, it is mandatory for the laboratory to report MRSA bacteraemia to the Department of Health.

**Glycopeptide resistant Staphylococcus aureus**

• First case in USA in 2002, possibly due to the transfer of vanA gene from *Enterococcus faecalis*, conferring resistance to vancomycin.

• *Staphylococcal* strains with minimum inhibitory concentration (MIC) >2mg.L⁻¹ for vancomycin are considered resistant, MIC determination being more reliable than disc diffusion.

Minimum Inhibitory Concentration (MIC) = antimicrobial concentration required to kill 90% of bacteria

**Panton-Valentine Leucocidin (PVL) producing Staphylococcus aureus**

• PVL is a toxin produced by <2% strains of *Staphylococcus aureus*.

• This is a pore forming toxin that destroys leucocytes and can be produced by meticillin sensitive or meticillin resistant strains.

• Usually responsible for skin and soft tissue infections like boils and abscesses in healthy young adults.

• Clinical spectrum extends to severe life threatening infections such as necrotising pneumonia, necrotising fascitis or purpura fulminans (mimicking meningococcal sepsis).

• PVL staphylococcal necrotising pneumonia is associated with high mortality - the typical presentation is in a previously fit young adult with recent flu-like illness with a high temperature (>39°C), tachycardia, hypotension, marked leucopenia (due to the nature of the toxin) and multi-lobular alveolar infiltrates on chest Xray that often cavitate.

**Coagulase negative Staphylococci**

• Includes several species, prominently *Staphylococcus epidermidis* and *Staphylococcus saprophyticus* (a urinary pathogen).

• Part of the normal skin flora.

• Commonly cause infections related to prosthetic devices such as catheters, orthopaedic implants, shunts etc.

• Capable of producing a biofilm which hides the organisms from the host immune system and makes antibiotic penetration difficult.

• Meticillin resistance is common in coagulate negative *Staphylococci*.

• Some organisms in this group, such as *Staphylococcus lugdunensis* and *Staphylococcus intermedius*, can cause severe infections.

**Beta haemolytic Streptococci**

• Gram positive cocci that occur in chains.

• So called because of the beta or complete clearing they produce around their colonies growing on blood agar.

• Classified into groups – A, B, C, D, F, G etc based on cell wall antigens.

**Group A Streptococci**

• Also known as *Streptococcus pyogenes*.

• Common cause of sore throat and skin infections like erysipelas, but can cause severe invasive infections like toxic shock syndrome, necrotising fascitis and purpural sepsis.

• Invasive Group A Streptococcal infections are increasing in incidence and are associated with a mortality of up to 25%.

• Always sensitive to penicillin.

**Group B Streptococci**

• Common cause of neonatal infections and infections in diabetic patients.

**Group C and G Streptococci**

• Responsible for sore throat and skin and soft tissue infections, similar to Group A Streptococci.

• Lymphoedema is a risk factor for recurrent infections with Group G Streptococci.

**Alpha haemolytic Streptococci**

• Produce greenish discoulouration around the growth on blood agar, due to the partial haemolysis of red blood cells in the agar (alpha haemolysis).

• Commonest example is *Streptococcus pneumoniae* (*Pneumococcus*).
**Streptococcus pneumoniae (Pneumococcus)**

- Common cause of community acquired pneumonia and can cause other serious infections like meningitis.
- Part of the normal upper respiratory tract flora.
- Increased risk of empyema following pneumococcal pneumonia.
- Severe pneumococcal pneumonia in an otherwise healthy adult is an AIDS defining illness.
- Penicillin resistance is rising - oxacillin discs are used in the laboratory, along with penicillin E test to determine MIC to penicillin.
- Ceftriaxone or vancomycin is the treatment of choice for serious infections caused by drug resistant *Pneumococci*.

**Viridans (oral) Streptococci**

- Cause dental caries and can cause infective endocarditis and bacteraemia in immunosuppressed patients.

**Enterococci**

- As their name suggests, they are part of the normal bowel flora.
- Cause intra-abdominal and pelvic infections and can cause bacteraemia and infective endocarditis.
- Intrinsically resistant to cephalosporins and ciprofloxacin.
- Common species are *Enterococcus faecalis* and *E. faecium*.
- Some species like *E. gallinarum* and *E. casseliflavus* are intrinsically resistant to glycopeptides, such as vancomycin.

**Glycopeptide Resistant Enterococci (VRE – Vancomycin Resistant Enterococcus)**

- Most commonly *E. faecium*.
- Organisms with intrinsically low virulence.
- Cause opportunistic infections, especially in immunosuppressed patients.
- Risk factors include prior hospitalisation, stay in specialist units—renal / ICU / haematology-oncology, prior use of antibiotics, especially glycopeptides.

**Clostridium difficile**

- Gram positive bacillus.
- Most important cause of hospital acquired diarrhoea – ranging from mild to severe life threatening pseudomembranous colitis.
- Risk factors – elderly population, prior use of antibiotics (sometimes even a single dose of an antibiotic can serve as a trigger), history of hospitalisation in the past.
- Stool frequency is a less reliable indicator of severity, severe infections are characterised by white cell count >15, serum creatinine > 50% increase above baseline, temperature > 38.5°C or evidence of severe colitis on examination or radiologically.
- Mnemonic protocol – SIGHT:
  - Suspect when no clear cause for diarrhoea,
  - Isolate patients with diarrhoea,
  - Gloves and apron to be used in this environment,
  - Hand-washing is crucial as the organism, especially the spore state, is resistant to alcohol based disinfectants,
  - Test the stool for toxin.
- Treatment consists of stopping all unwanted antibiotics and commencing either oral metronidazole or oral vancomycin, depending on the severity of infection. *C. difficile* infection is the only indication oral vancomycin, as it is not absorbed systemically.

**GRAM NEGATIVE BACTERIA**

**Coliforms**

- This is the generalised term for enteric Gram negative bacilli such as *E. coli* and *Klebsiella*.
- They cause intra-abdominal and pelvic infections, urinary tract infections, opportunistic infections, such as catheter related blood stream infections, and ventilator associated pneumonia.

**Extended spectrum beta lactamas (ESBLs)**

- Enzymes produced by coliforms like *E. coli* and *Klebsiella*, that render the organisms resistant to all penicillins and cephalosporins.
- Predisposing factors include old age, prior use of antibiotics and prior hospitalisation.
- Infections range from simple urinary tract infections to bacteraemia and pneumonia.
- Organisms carrying the ESBL are more likely to be resistant to other classes of antibiotics like aminoglycosides, quinolones and trimethoprim, thus limiting treatment options. Treatment of choice is carbapenems.
- Eradication of colonisation is difficult.

**New Delhi metallo-beta lactamas (NDMs)**

- Enzyme rendering resistance to broad spectrum antibiotics like carbapenems, usually produced by *E. coli* and *Klebsiella*.
- First isolated from a patient who had travelled through New Delhi, where he was hospitalised.
- Risk factors are hospital admission / medical tourism in the Indian subcontinent.
- Infections can be mild or life threatening.
- Treatment options are very limited. Colistin and tigecycline may be used in some cases depending on the antimicrobial susceptibility testing results.

**Pseudomonas**

- Gram negative bacillus, ubiquitous in soil, water and moist environments.
• Successful opportunistic pathogen.
• Disease spectrum includes community acquired infections like otitis externa, folliculitis associated with jacuzzis and hospital acquired infections such as blood stream infections, surgical wound infections and pneumonias.
• Important pathogen and coloniser in patients with cystic fibrosis.
• Antimicrobial susceptibility testing of isolates in the laboratory is crucial and susceptibility to anti-pseudomonal agents cannot be assumed, as it can acquire resistance to antibiotics rapidly on treatment.

Acinetobacter
• Gram negative short bacillus and nosocomial and opportunistic pathogen.
• Multi-resistant strains such as OXA-23 clone 1 and SE clone are seen in the UK, particularly in London and south-east England.
• Cross infection occurs through equipment or colonised health-care workers and the organism is extremely difficult to eradicate from established environments.

Viruses
These are organisms containing DNA or RNA, but never both. Viruses depend on the host cell machinery for replication. The clinical spectrum varies with the class of virus. In an ICU setting, one needs to be aware that bacterial super-infections of primary viral infections can occur, for example, Staphylococcal or Streptococcal pneumonia after infection with influenza virus.

Fungi
These are eukaryotes with a cell wall containing ergosterol, that is different from that of a bacterial cell. They can be either yeasts (e.g. Candida) or moulds (e.g. Aspergillus, Zygomycetes). Fungal spores are ubiquitous in the environment. Fungi are opportunistic pathogens capable of causing life threatening systemic infections in immunosuppressed patients. Fungal infection should be suspected in patients who fail to improve on anti-bacterial agents, particularly where no bacterial organism has been isolated.

Diagnosis of Infection
The type of sample submitted to the microbiology laboratory for the diagnosis of infection depends on the site of infection. The significance of mentioning all relevant information on the laboratory request forms cannot be over-emphasised. The information provided acts as a trigger for the laboratory staff to carry out any additional tests on the sample as required.

Gram stain
This is a quick and useful method of screening the sample for bacterial pathogens. A high number of organisms (almost up to 105 per ml of the sample) is required for a Gram stain to be positive.

Culture
This is a ‘gold standard’ test that involves growing organisms on appropriate culture media. Once the organism grows, an antimicrobial susceptibility test can be performed. Bacteria usually take 24 to 48 hours to grow in cultures.

Blood culture
The sensitivity of this investigation depends on the volume of blood cultured - 20ml blood collected in two bottles (aerobic and anaerobic) is the minimum volume, except in neonates and children, where smaller volumes are collected in paediatric bottles. In septic patients blood should be cultured even in the absence of fever. When line sepsis is suspected, blood cultures should be drawn through the line as well as peripherally and the bottles and request forms should be labelled accordingly. Proper skin antisepsis is crucial to avoid contaminated blood cultures.

Antimicrobial susceptibility testing
This is a key investigation in the management of infections and can be done once an organism grows in culture. It is usually done by the disc diffusion method. The sample is spread uniformly across an agar plate and discs of filter paper containing various antimicrobial agents are placed on the agar. The agent diffuses into the agar, reaching higher concentrations nearest to the disc. The bacteria fail to grow where the level of antimicrobial agent is above the effective concentration. The results reported as susceptible, resistant or intermediate.

Serology
Serological tests usually detect the IgG or IgM antibody response to infections. It is a useful habit to collect a serum sample from an infected patient as a baseline. Serological tests are extremely useful to diagnose infections caused by organisms that cannot be grown in culture, such as viruses, Chlamydia, Mycoplasma, Bartonella and Brucella.

Polymerase chain reaction (PCR)
This is a rapid molecular diagnostic method for pathogens that do not easily grow in culture. It cannot distinguish between live and dead organisms as it detects DNA, and it cannot determine antimicrobial susceptibility. PCR on cerebrospinal fluid for Herpes simplex virus (HSV) is useful in the diagnosis of HSV encephalitis.

Urinary antigen testing
This test may be available for pathogens such as Streptococcus pneumoniae, Legionella and Histoplasma. It is based on the secretion of capsular antigens of organisms in urine.

Other blood tests
White cell count, differential count, liver and renal function tests and C reactive protein are very useful for the day-to-day management of ICU patients. Procalcitonin (PCT) is a new measurable molecule that is induced by severe bacterial or fungal infection and severe sepsis. It can distinguish between bacterial infections from viral infections.
ANTIMICROBIAL DRUGS
The choice of antimicrobial agent should be made after thorough consideration of:

- Therapeutic drug monitoring,
- De-escalation based on microbiology and clinical outcomes.

**Host factors**
- underlying medical conditions
- allergies
- renal function
- liver function
- age
- weight
- interactions with other medications
- risk factors for acquiring resistant organisms (e.g. MRSA)

**Organism factors**
- likely susceptibility
- local resistance patterns for organisms

**Factors related to the antimicrobials themselves**
- appropriate route of administration
- appropriate dose, depending on severity of infection

In critically ill patients, antimicrobial concentrations in plasma may fluctuate, resulting in either over-exposure (for example in renal impairment) or under-exposure (for example oedema, effusions, IV fluid therapy). Therapeutic drug monitoring is an important technique to monitor these effects. Once culture and antimicrobial susceptibility results are available, de-escalation from the empirical antimicrobials should be considered. When in doubt, the advice of clinical microbiology colleagues should be sought. The tables on the following pages attempt to give an overview of the different classes of antibiotics, their mechanism of action and spectrum of activity.

**Practices promoting optimisation of antimicrobial use in ICU setting**

- Adequate empirical treatment of infections based on causative agents,
- Awareness of local pathogens and their antimicrobial susceptibilities,
- Removal of infected foreign bodies,
- Drainage of pus at any site, e.g. empyema, abscess, etc,
- Risk factors for acquiring resistant organisms (e.g. MRSA)

**Conclusion**
Sepsis is both a major cause of admission to ICU and also a frequent complication of the therapies offered there. This article has given an overview of the more common infective agents, and also describes bacteria that are increasingly causing issues with antibiotic resistance. Choice of antibiotic must be guided by local prevalence, but may also be limited by availability in low income settings. It is very useful to establish regular contact with a clinical microbiologist, in order to gain current and appropriate advice.

**REFERENCES**
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<td>Inhibition of cell wall synthesis</td>
<td>MSSA</td>
<td>MRSA</td>
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<tr>
<td>Benzylpenicillin</td>
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<td>✓</td>
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<td>Amoxicillin / Ampicillin</td>
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<td>Flucloxacillin</td>
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<tr>
<td>Coamoxiclavulanate</td>
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<tr>
<td>(Augmentin)</td>
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<td>✓</td>
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<tr>
<td>Piperacillin – tazobactam</td>
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<tr>
<td>(Tazocin)</td>
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<td>✓</td>
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<tr>
<td>Ampicillin-sulbactam</td>
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<td>✓</td>
<td>✗</td>
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</table>

**Key:**
- ✓ sensitive
- ✗ resistant
- * >90% MSSA are resistant to penicillin
- ○ treatment of choice in susceptible strains
- ✓ determined by antimicrobial susceptibility
- ○ covers penicillin sensitive isolates only
- $ E. faecalis is susceptible
- ** flucloxacillin is much more effective than vancomycin or teicoplanin to treat MSSA
- MSSA Meticillin Sensitive *Staphylococcus aureus*
- MRSA Meticillin Resistant *Staphylococcus aureus*
- NDM New Delhi Metallo-beta-lactamase
- ESBL Extended Spectrum Beta-lactamase
- TDK time dependent killing, antibiotic effective due to the extensive amount of time it binds to the organism
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<td><strong>Cephalosporins</strong></td>
<td>Inhibition of cell wall synthesis</td>
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<tr>
<td>1st generation</td>
<td>Cefadine, Cephalexin</td>
<td>MSSa</td>
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<tr>
<td>2nd generation</td>
<td>Cefuroxime</td>
<td>MSSa</td>
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<td>3rd generation</td>
<td>Cefotaxime, Ceftriaxone, Ceftazidime</td>
<td>MSSa</td>
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<tr>
<td><strong>Carbenepenos</strong></td>
<td>Inhibition of cell wall synthesis</td>
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<td>Imipenem</td>
<td>MSSa</td>
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<td>Meropenem</td>
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<td>Ertapenem</td>
<td>MSSa</td>
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</table>

**Key:**
- **GP** Gram positive
- **GN** Gram negative
- **×** sensitive
- **✓** resistant
- **TP** Covers penicillin sensitive isolates only
- **TDK** Time dependent killing, antibiotic effective due to the extensive amount of time it binds to the organism

**Spectrum of activity**
- **MSSa** Methicillin Sensitive Streptococcus aureus
- **MRSa** Methicillin Resistant Streptococcus aureus
- **eSbls** Extended Spectrum Beta-Lactamase
- **ndMs** Non-Drug Methylcephalexinase
- **Anaerobes**
- **Acinetobacter**
- **Pseudomonas**
- **Enterococci**
- **Vibriods**
- **Streptococci**
- **Beta haemolytic**
- **MRSA**
- **MSSa**

**Notes:**
- Penicillin allergy (rash) treatment
- E. faecalis is susceptible
- Meropenem has better activity against Pseudomonas than imipenem.
- Only cefazidime in this group has anti pseudomonal activity.
- TDK = time dependent killing
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<td>Glycopeptides</td>
<td>Inhibition of cell wall synthesis</td>
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<td>MRSA</td>
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<td>e.g. Vancomycin, Teicoplanin</td>
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<td>Amino-glycosides</td>
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<td>e.g. Gentamicin</td>
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<tr>
<td>Macrolides</td>
<td>Inhibit protein synthesis (50S subunit)</td>
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<td>e.g. Erythromycin, Clarithromycin</td>
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<td>Lincosamides</td>
<td>Inhibition of cell wall synthesis</td>
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<td>e.g. Clindamycin</td>
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**Key:**
- ✓ sensitive
- × resistant
- ☑ determined by antimicrobial susceptibility
- ☀ E. faecium is susceptible provided not glycopeptide resistant (VRE)
- ♦ treatment of choice for penicillin resistant strains causing serious infections
- ☑ lab should look for high level gentamicin susceptibility
- **flucloxacillin is much more effective than vancomycin or teicoplanin to treat MSSA**
- CDK concentration dependent killing, high concentration at binding site which kills the organism
- VRE vancomycin resistant *Enterococci*
- MLSB stands for macrolide, lincosamide, streptogramin type B antibiotics. Bacteria with inducible resistance to erythromycin become resistant to other MLSB agents in the presence of erythromycin. Detected in the lab in *Staphylococci* by the 'D' test 11. Avoid using clindamycin for *Staphylococci and Streptococci* that are resistant to erythromycin.
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<td>Tetracyclines</td>
<td>e.g. Doxycycline Inhibit protein synthesis (30S subunit)</td>
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<td>Nitroimidazoles</td>
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<td>Trimethoprim</td>
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<td>Chloramphenicol</td>
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**Comments**
- Cover atypicals such as *Chlamydia*
- Related to tetracyclines
- CDK, Resistance common with ESBLs
- Used to treat *C. difficile* infection
- Used to treat PCP
- Bacteriostatic for gram positive organisms
- Use determined by sensitivity testing. Good CSF penetration - alternative for meningitis in penicillin - allergic patients. May cause dose-dependent bone marrow suppression.

**Key:**
- DHFR  dihydrofolate reductase,
- PCP  *Pneumocystis jirovecii* pneumonia
- *  also covers remcomycin resistant *Enterococcus* (VRE)