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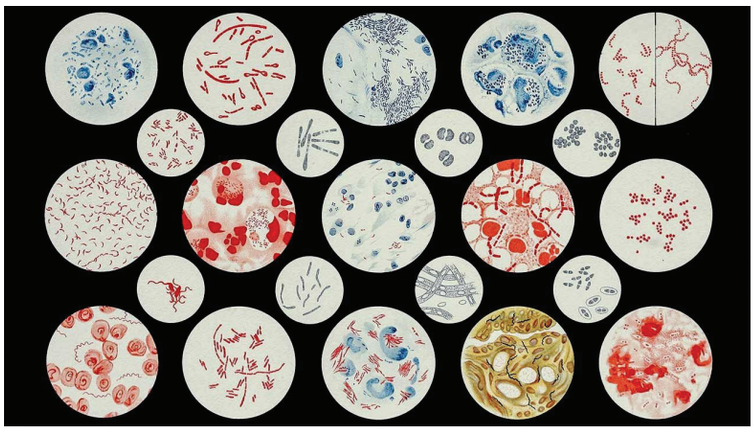
Medical Bulletin

News You Can Use

Triple Drug Combinations Can Fight Bacterial Resistance

Combinations of three different antibiotics can overcome bacterial resistance to antibiotics, even when none of the three drugs on their own or even two of the three together – is effective, scientists have found.

In drug-drug interactions, there are surprising cases in which the growth inhibition of bacteria by a single antibiotic decreases when a second antibiotic is added. These interactions are termed *suppressive* and have the potential to limit the evolution of resistance. Nevertheless, little attention has been given to suppressive interactions because clinical studies typically search for increases in killing efficiency and because suppressive interactions are believed to be rare based on pairwise studies.

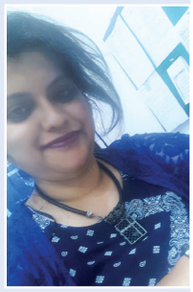


Each year, approximately 700,000 people die from drug-resistant bacterial infections, researchers said. They grew *E.coli* bacteria in a laboratory and treated the samples with combinations of one, two and three antibiotics from a group of 14 drugs. The biologists studied how effectively every single possible combination of drugs worked to kill the bacteria. Some combinations killed 100% of the bacteria, including 94 of the 364 three-drug grouping tested.

According to Pamela Yeh from the University of California, Los Angeles (UCLA), the success rate might have been even greater if the researchers tested higher doses of the drugs. Elif Tekin, UCLA graduate student, helped create a sophisticated framework that enabled the scientists to determine when adding a third antibiotic was producing new effects that combinations of just two drugs could not achieve. ***"Three antibiotics can change the dynamic. Not many scientists realise that three-drug combinations can have really beneficial effects that they would not have predicted even by studying all pairs of the antibiotics together,"*** she said.

Suppressive antibiotic combinations (triple drug combinations) might provide unusual antibiotic effects which simultaneously treat infections while guarding against evolution of resistance.

Greetings from Blue Cross Laboratories!



Dear Colleagues,

Hope all of you are in the best of health and spirit, and I hope you have had a fabulous first quarter for 2018 !

It gives me immense pleasure and satisfaction to present you with the first issue of the Blue Cross Medical Bulletin for this current financial year.

This issue will have you updated on a few recent medical discoveries/developments, and novel clinical insights involving diverse therapeutic facets. We have also included two brief tutorials and a new segment called "Beyond the Pharmacodynamic Frontier", in which we will highlight therapeutic benefits of molecules extending beyond the realm of their current indications and efficacy. We hope all these topics make for interesting reading !

I am sure you would enjoy reading this edition of the Medical Bulletin as you did in the past. Please do remember to send in your feedback, so that we can incorporate the same in future editions.

Happy Reading!

Cheers!

Best wishes & Warm regards,

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Correlation of Compliance to Statin Therapy with Lipid Profile in Dyslipidemic Patients

Indians are more prone to cardiovascular disease due to a higher prevalence of dyslipidemia as compared to the Western world. Statins are the most effective lipid-modifying agents with a 17–26% reduction in risk of coronary events. The benefits of statin therapy on the desired clinical outcomes may be lost when patients are poorly compliant to therapy, as ≥ 40% of patients being treated with statins discontinue medication after one year.

In a prospective, observational study conducted in 200 dyslipidemic patients by *Grover, et al* to correlate the quantitative effect of compliance on lipid profile, **a higher compliance to statin therapy (assessed by pill count) correlated with lower serum levels of total cholesterol, LDL-C, triglycerides (TG), and higher HDL-C** (published in the *Indian Heart Journal*). **The study demonstrated the association and correlation of total cholesterol, TG, HDL-C, LDL-C, ApoA1, ApoB and levels of HMGCoA-reductase (HMGCoA-R) levels with compliance of the patient to statins.** The levels of LDL-C and HMG-CoA-R fell with increase in compliance to statin therapy, and it was suggested that prior to directly switching over to a higher intensity statin, enhancing improvement in compliance (up to 60%) should be considered. Compliance can be improved by patient education, enhancing patient–physician communication, simplification of drug regimens, and increased patient monitoring and follow-up. Monitoring levels of HMG-CoA-R may be explored as a tool to aid physicians in optimizing and individualizing statin therapy.

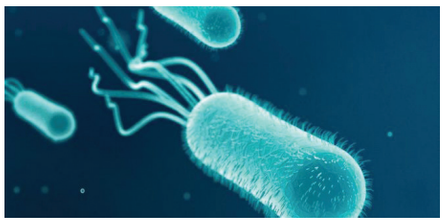
Short Tutorial

Extended-spectrum beta-lactamases (ESBLs): Basic Overview

Extended-spectrum beta-lactamases (ESBLs) are a group of enzymes that break down the beta-lactam ring of antibiotics belonging to the penicillin and cephalosporin groups and render them ineffective. ESBLs have generally been defined as transmissible β-lactamases that can be inhibited by clavulanic acid, tazobactam or sulbactam, and which are encoded by genes that can be exchanged between bacteria. There is no consensus as to the precise definition of ESBLs.

ESBLs confer resistance to most beta-lactam antibiotics, including penicillins, cephalosporins, and the monobactam aztreonam.

Community and hospital-acquired infections with ESBL-producing organisms have been associated with poor outcomes. Reliable identification of ESBL-producing organisms in clinical laboratories can be challenging, so their prevalence is likely underestimated.



There are at least 200 different types of ESBL enzymes. Researchers still have a lot to learn about them, in part because the infections involving ESBLs were only recently discovered. The first plasmid-mediated β-lactamase in gram-negative bacteria was discovered in Greece in the 1960s. It was named TEM after the patient from whom it was isolated (Temoniera). **Subsequently, a closely related enzyme was discovered and named TEM-2.** It was identical in biochemical properties to the more common TEM-1, but differed by a single amino acid with a resulting change in the isoelectric point of the enzyme. The United States reported its first case in 1988.

These two enzymes are the most common plasmid-mediated beta-lactamases in gram-negative bacteria. TEM-1 and TEM-2 hydrolyze penicillins and narrow spectrum cephalosporins, such as cephalothin or cefazolin. However, they are not effective against higher generation cephalosporins with an oxyimino side chain, such as cefotaxime, ceftazidime, ceftriaxone, or cefepime. Consequently, when these antibiotics were first introduced, they were effective against a broad group of otherwise resistant bacteria. A related, but, less common enzyme was termed **SHV** because sulfhydryl reagents had a variable effect on substrate specificity. **So far, ESBLs have only been reported in Gram-negative bacterial infections. Bacterial groups known to produce ESBLs include:**

- *Escherichia coli (E.coli)*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *K. oxytoca*
- *Proteus mirabilis*
- *Salmonella enterica*
- *Neisseria gonorrhoeae*
- *Haemophilus influenzae*
- *Kluyvera species*
- *Enterobacter aerogenes*
- *Enterobacter cloacae*

Anyone who has contact with a surface, object, animal, or another person that is infected with or has been exposed to ESBL-producing bacteria can spread the infection. **Most ESBL infections, however, develop in healthcare settings and involve exposure to infected fecal matter.**

According to a 2015 study, most people infected with ESBL-producing bacteria had been hospitalized for an average of between 11 and 64 days before developing the infection. **While traditionally associated with immune-compromised individuals, hospitals, and nursing homes, the infection is becoming more frequent and widespread.**

Bacterial infections involving ESBLs are known to cause the following conditions:

- Diarrhea
- Skin infections
- Wound infections
- Pneumonia
- Urinary tract infections
- Sepsis and organ failure

Treatment and Outlook

- **The carbapenems (meropenem, ertapenem, doripenem) are still the first choice of treatment for serious infections with ESBL-producing *E. coli* and *K. pneumoniae.*** It has been reported that >98% of the ESBL-producing *E. coli, K. pneumoniae,* and *P. mirabilis* are still susceptible to these drugs.
- With the emergence of the carbapenem-resistant *Enterobacteriaceae,* the *"magic bullet"* is actually difficult to find. There are some older drugs which can be used to treat ESBL-producing *E. coli* or *K. pneumoniae* infections like fosfomycin and colistin.
- Close monitoring for the development of side effects can improve the safety margin when prescribing the drug. In some situations, especially if a person has a weakened immune system, hospitalization and isolation may be necessary. Most infections take several weeks or months to treat.

Prevention

People with chronic illnesses and people who are hospitalized are the most at-risk of developing ESBL-involved infections. **General tips for preventing ESBL-involved bacterial infections include:**

- Avoiding close contact with people or animals with bacterial infections.
- Wearing gloves in healthcare settings or around infected individuals.
- Avoiding touching the face and mouth.
- Wearing long-sleeved clothing when around infected individuals.
- Washing hands before and after exposure to infected individuals.
- Washing all clothing and bedding that may have been exposed to infected individuals in hot water.
- Disinfecting surfaces, especially in bathrooms and kitchens.
- Disinfecting fixtures, such as doorknobs and faucets.
- Taking antibiotics exactly as directed.

Short Tutorial

Urinary Tract Infection (UTI) in Pregnancy: Overview and Management

Pregnant women are at a higher risk for UTI because of physiological adaptations, like increase in plasma volume which could result in decreased urine concentration, facilitating bacterial growth. Additionally, 90% of pregnant women develop anatomical changes such as dilatation of urethra and decreased bladder tone leading to urinary stasis. **Risk of UTI begins in the 6th week and has its peak during the 22-24th weeks.** Incidence of bacteriuria in pregnant women is roughly the same as in non-pregnant women; however, **recurrent bacteriuria is more frequent during pregnancy.**

Asymptomatic bacteriuria means the isolation of a specified semi-quantitative count of bacteria in an adequate sample of urine collected from a person without symptoms related to UTI. However, the optimal method for collecting urine is not yet established. Routinely, recommendation is to clean urethral meatus and collecting urine midstream, intending to minimize contamination of the sample. For women, bacteriuria is defined as two consecutive urine specimens with isolation of the same bacterial strain in quantitative counts ≥ 105 colony forming units (cfu)/mL or a single catheterized urine specimen with one bacterial species isolated in a quantitative count ≥ 100 cfu/mL. Prevalence of bacteriuria during pregnancy varies between 2-10%, remaining constant even in the developing countries.

Factors that have been associated with a higher risk of bacteriuria include history of prior UTI, pre-existing diabetes mellitus, increased parity, and low socioeconomic status. ***Escherichia coli* is the predominant uropathogen in approximately 70 to 90% of cases.** Group B Streptococcus, *Klebsiella* and *Enterobacter* species, and *Proteus* and *Staphylococcus saprophyticus* are also frequently associated. Chlamydial infections are associated with sterile pyuria and account for more than 30% of atypical pathogens. Isolation of more than one species or the presence of *Lactobacillus* or *Propionibacterium* may indicate a specimen contaminated by vaginal or skin flora. However, repeated isolation of *Lactobacillus* with high colony counts (≥105 cfu/mL) can be eligible for treatment. Infections caused by ESBL-producing strains are increasing in number, even in uncomplicated UTI, and becoming a global health problem even in community settings.

Untreated UTI or asymptomatic bacteriuria during pregnancy may lead to serious consequences for maternal life and fetus, like higher risk of pyelonephritis, sepsis and renal failure; and complicated outcomes such as intrauterine growth restriction, preeclampsia and premature delivery.

UTI may manifest clinically as one or more of the following:

- **Cystitis** (Symptomatic infection of the bladder)
  - o Clinical symptoms are the same in pregnant and non-pregnant women: dysuria, hematuria, pyuria, urinary urgency and frequency.
  - o Acute cystitis should be suspected in pregnant women who complain about dysuria, which can result from vaginitis or urethritis and can be distinguished by the presence of bacteriuria.
  - o The diagnosis is confirmed by finding bacterial growth on urine

culture in a symptomatic pregnant woman: quantitative count ≥105 cfu/mL, or ≥103 cfu/mL and pyuria (>7 white blood cells/mL).
  - o Urinalysis and urine culture should be performed in order to guide the best antibiotic treatment.
- **Pyelonephritis** (Infection of the upper urinary tract and kidneys)
  - o Typical symptoms in the pregnant and non-pregnant women are the same: Fever (>38ºC or 100.4ºF), flank pain, nausea, vomiting, pyuria, costovertebral angle tenderness, and is confirmed by coexisting bacteriuria.
    - * Flank pain is a common symptom due to pregnancy-induced hydronephrosis and most commonly unilateral over the involved kidney, although bilateral discomfort may be present.
    - * Calyceal and ureteral dilatation are more common on the right side.
  - o Complications include septic shock syndrome, anemia, bacteremia, respiratory insufficiency, and renal dysfunction.

Pregnant women are at risk of serious complications from symptomatic and asymptomatic urinary tract infections. The table below lists antibiotics which can be used for UTI management in pregnant women. Oral antibiotics are the treatment of choice for asymptomatic bacteriuria and cystitis, while pyelonephritis requires hospital admission and intravenous antibiotics. However, optimal duration of antimicrobial therapy is still controversial.

Since some women fail to clear asymptomatic bacteriuria following a short course of therapy, a follow-up culture should be obtained as a test of cure after completion of the treatment.

Antibiotic prophylaxis is indicated in recurrent infection and daily prophylactic antibiotics should be continued for the duration of the pregnancy. Prevention of UTI recurrence during pregnancy is essential given the severity of possible complications. Amoxicillin (250 mg) or cephalexin (250 to 500 mg) given orally at bedtime are good options for antibiotic prophylaxis.

Antibiotic	Dose	Duration	Indication	Comments
Amoxicillin	500 mg orally every 8 hours	3-7 days	AS, C	Bactericidal against uropathogens.
Amoxicillin-clavulanate	500 mg orally/IV every 8 hours	7-10 days	C, P	Choice for beta-lactam resistant pathogens.
Cefpodoxime	100 mg orally every 12 hours	3-7 days	AS, C	Bactericidal against uropathogens.
Nitrofurantoin monohydrate/ macrocrystals	100 mg orally every 12 hours	5-7 days	AS, C	Avoid during the first trimester.
Piperacillin-tazobactam	3.375 g IV every 6 hours	10-14 days	P	Choice for HAI.
Meropenem	1g IV every 8 hours	10-14 days	P	ESBL treatment.

AS: Asymptomatic Bacteriuria; C: Cystitis; P: Pyelonephritis; IV: Intravenous; IM: Intramuscular; HAI: Healthcare-Associated Infection; ESBL: Extended-Spectrum Beta-Lactamase (ESBL)-Producing Bacteria.

Beyond The Pharmacodynamic Frontier

Amoxicillin-Clavulanic Acid is Equal in Safety and Efficacy to Amoxicillin-Sulbactam for Management of Lower Respiratory Tract Infections (LRTIs).

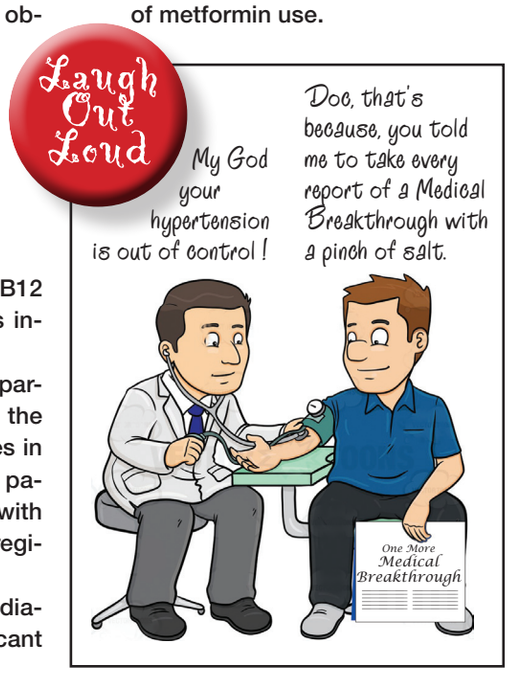
Khanna N, *et al. JIMI.* 2016; Vol. 11.

- Beta-lactam antibiotics play a major role in the treatment of LRTIs, although the β-lactamase enzyme produced by bacteria presents a major problem. To overcome this hurdle, β-lactam antibiotics are administered with β-lactamase inhibitors like sulbactam or clavulanic acid.
- In a comparative, randomized study in 179 adult patients with LRTI, the efficacy, safety and tolerability of a 7-10 day course of amoxicillin-clavulanic acid (625 mg) was similar to amoxicillin-sulbactam (1000 mg).
- Clinical cure rates were ≥86.3%. No serious adverse effects were observed.

No Consistent Link of Metformin Use with Vitamin B12 Deficiency.

Rodríguez-Gutiérrez R, *et al. Am J Med Sci.* 2017; 354(2): 165-171.

- Current evidence linking vitamin B12 deficiency with metformin use is inconsistent.
- A cross-sectional study (150 participants) was conducted with the objective of assessing differences in serum vitamin B12 levels among patients with and without diabetes with different metformin-treatment regimens.
- When patients with or without diabetes were compared, no significant difference was found in relation to their vitamin B12 levels. No difference in vitamin B12 levels was found among the participants, irrespective of metformin use.



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