ALL INDIA INSTITUTE OF MEDICAL SCIENCES, MANGALAGIRI

PHARMACOLOGY BULLETIN

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FROM THE EDITORIAL DESK….

Dear Friends, Greetings from AIIMS Mangalagiri and Welcome to the 20th issue of ESSENCE.

Drug discovery and development is a long and expensive process involving multiple phases. Once a candidate molecule has successfully passed the pre-clinical (Invitro and animal) phase, it is designated as Investigational New Drug (IND) and enters the phases of clinical trial to study its effect on humans. The current issue of ESSENCE summarises the role of Phase I clinical trial in new drug development and its purpose, approach, and process.

Antibiotic abuse/ overuse is a global problem with wide ranging ramifications. It is crucial that all stakeholders understand the importance of judicious use of antibiotics. Defined Daily Dose (DDD) is an important tool to understand the extent of use of antibiotics in each set up so that necessary steps can be taken to rationalise their use. The current issue has a write up on this important tool of antibiotic consumption.

Clinicians have always relied on antimicrobial susceptibility testing [AST] as a means of choosing an optimally effective antibiotic. However, relying purely on MIC for selection of an antibiotic may not be the correct approach. Breakpoint to MIC Quotient (BMQ) is a novel indicator that can help the clinicians to select the most appropriate antibiotic for a particular bacterial isolate. The Guest Column in the current issue has a very relevant and useful article on this aspect.

Further, as always, the current issue has new drug approvals, interesting news from the world of medicines, crossword puzzle on 'Drugs causing Rhabdomyolysis' and the cartoon corner.

We hope you enjoy reading it.

Jai Hind.

Feedback and Suggestions may be sent to Department of Pharmacology, All India Institute of Medical Sciences, Mangalagiri, Andhra Pradesh at email id: pharmacology@aiimsmangalagiri.edu.in

Drug discovery and development is a long and expensive process involving multiple phases including Target selection and lead development, preclinical development, and then clinical trials. Once a candidate molecule has successfully passed the pre-clinical (Invitro and animal) phase, it is designated as Investigational New Drug (IND) and enters the phases of clinical trial to study its effect on humans. Various phases of clinical trials (phase 0- phase 3) need to be conducted extensively to evaluate efficacy and safety. During Phase 1 studies, researchers test a new drug in normal healthy volunteers. In most cases, 20 to 80 healthy volunteers participate in Phase 1. However, if a new drug is intended for use in cancer patients, researchers conduct Phase 1 studies in patients with that type of cancer.

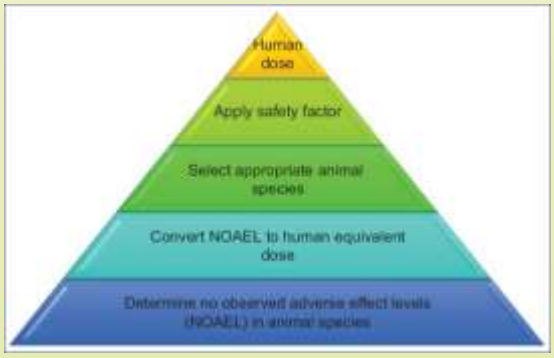
Objectives of Phase 1 trial:

Phase 1 studies are closely monitored with the primary aim to assess the tolerability and safety of 'single dose' of the drug and to determine the 'Maximum Tolerated Dose' of the drug. Phase I studies also gather critical, important information about pharmacokinetics of the drug. However, in phase 1 studies in which patients are enrolled, the volunteers (or the actual physicians who enrol patients) may misinterpret its objective as therapeutic. For example, despite strong evidence that objective response rates in phase I trials of anti-cancer agents is exceedingly low (as low as 2.5%), patients may still have a "therapeutic misconception" of potentially receiving a direct medical benefit from trial participation. It is important to address to address and dispel these misconceptions through robust informed consent process.

Selection of starting dose for Phase 1 clinical trial:

In Phase I trials, the IND will be given to the humans for the first time; hence it is important to select the correct starting dose to be given. Subsequently, depending upon the tolerability, the dose escalation is done in a pre-defined manner. Selection of this First in Human (FIH) dose or the Maximum Recommended Starting Dose (MRSD) is a challenge and is calculated based on the data from preclinical animal studies.

Calculation of FIH/MRSD



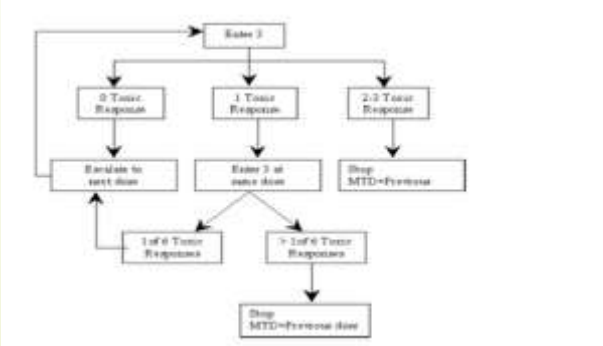
The MRSD for the phase I trial is derived from no-observed-adverse effect-levels (NOAELs). The NOAELs from animal data is taken and converted to human equivalent dose (HED) based on body surface area by the formula.

HED (mg / kg = Animal NOAEL mg/kg) × $(\text{Weight}_{\text{animal}}\ [\text{kg}]/\ \text{Weight}_{\text{human}}\ [\text{kg}])^{(1-0.67)}$

(Weight is in kg and 0.67 is a correction factor to convert mg/kg to mg/m2. Once HED is calculated, the MSRD for the phase 1 trial is determined by dividing the HED by a default safety factor of 10.

Dose escalation in phase 1 trials:

Once the MRSD/FIH dose is calculated as above, dose escalation is done to determine the Maximum Tolerated Dose (MTD). Dose escalation is based on very strict criteria, and subjects are closely followed for evidence of drug toxicity over a sufficient period. The increasing dose levels are selected in order that the percentage increments between successive doses diminish as the dose is increased, Modified Fibonacci sequence is often employed. In this once the MRSD is selected and given to one set of patients, subsequent increases of 100%, 67%, 50%, 40% and then 33% (x, 2x, 3.3x, 5x, 7x, 9.3x) are done if more than 5 doses are planned. This follows a diminishing pattern with modest increases in subsequent doses thus decreasing the possibility of adverse effects.



3 x 3 design in phase 1 clinical trials

The traditional 3+3 design originally introduced in the 1940s is a commonly used design. In a "3+3 design," three patients are initially enrolled into a given dose cohort. If there is no dose-limiting toxicity (DLT) seen in any of these participants, the trial proceeds to enrol additional three participants into the next higher dose cohort. If one patient manifests a DLT at a specific dose, an additional three individuals are accrued into that same dose cohort. Development of DLTs in two or more out of six patients at a specific dose level indicates that the MTD has been exceeded; further dose escalation is not pursued, and the prior dose level is expanded to six patients; if there is no more than one patient who experiences a DLT among those six patients, that dose level is considered the MTD. The MTD is determined in the first cycle of therapy (often about 4 weeks). The MTD is therefore defined as the highest dose level in which six patients were treated and, at most, one patient experienced a DLT during the first cycle of therapy.

Conclusion:

At the end of Phase 1 trial, researchers answer research questions related to how the drug is absorbed, its movement inside the body and any adverse effects associated with increased dosage. This provides to help to determine how best to administer the drug to limit risks and maximize possible benefits. This is important to the design of Phase 2 studies.

Recent new/Update from the world of medicines ….

BCG: how a century-old vaccine is being used against everything from cancer to autoimmune diseases

In March 2020, as the UK was preparing to go into lockdown, two new trials were posted on the clinicaltrials.gov database. The researchers were proposing that BCG, an old vaccine against tuberculosis (TB), should be tested for its protective effect against COVID. In fact, almost since its first use against TB just over 100 years ago, BCG has been known to have "non-specific protective effects". In other words, it can prevent diseases other than TB. The administration of live or dead bacteria as a treatment for cancer was pioneered in the 19th century. The effects against cancer of mycobacteria in particular were noted in the early 20th century, leading to the establishment of BCG delivered directly to the bladder as a treatment against non-muscle invasive bladder cancer. In both multiple sclerosis and type 1 diabetes, BCG's ability to reprogram metabolism in cells as well as its capacity to increase numbers of special immune-dampening T-cells are thought to play key roles.

"Magic" Drug- Roflumilast- Restores Lost Memories and Unleashes Hidden Knowledge

An FDA-approved asthma drug some are calling 'magic' has shown the ability to restore lost memories and reveal previously hidden knowledge. A similar recovery of seemingly inaccessible memories was also demonstrated using optogenetic therapy, but the relatively safe drug is non-invasive and equally successful. If proven effective, this novel approach could offer a new ray of hope for millions suffering from conditions like dementia and Alzheimer's, or simply help everyday people remember critical elements of their lives lost to the passage of time. On a hunch, and hoping to find a less invasive solution, the researchers tried an already FDA-approved asthma drug called roflumilast, which is known to enter the brain and cause neuron activation. And just as they had hoped, the drug's ability to activate key neurons and restore lost memories was just as effective as the genetically engineered, light-activated method.

Be Cautious…. Drug Safety Alerts

S. No.	Drug	Safety Alerts
1.	Denosumab	Atypical fracture in non-femur sites
2.	Cefoperazone and Sulbactam	Acute coronary syndrome accompanying allergic reaction
3.	Fingolimod	Liver injury
4.	Ivermectin	Disturbed consciousness
5.	Hydrocortisone	Hypertrophic cardiomyopathy in neonates and infants
6.	Magnesium Sulfate	Rickets-like bone lesion in neonates at birth

In the 1960s, the area of drug utilisation research (DUR) started to gain popularity. The necessity for an internationally recognised classification system for drug consumption research was noted at the WHO workshop in 1969. The WHO approved the ATC/DDD system as the global benchmark for drug utilisation studies in 1981, and the WHO Collaborating Centre for Drug Statistics Methodology was founded and charged with overseeing the creation and application of the ATC/DDD system in 1982. The purpose of the ATC/DDD system is to serve as a tool for drug utilization monitoring and research to improve the quality of drug use. One component of this is the presentation and comparison of drug consumption statistics at international and other levels. It is critical to have both a classification system and a unit of measurement when attempting to quantify drug use. The Defined Daily Dose (DDD), a technical unit of measurement, was created for use in drug consumption studies to address criticisms of existing units of measurement.

The DDD is the assumed average maintenance dose for an adult patient receiving the drug for its primary indication. For each ATC code and route of administration, only one DDD is assigned (e.g., oral formulation). Because it may be an average of two or more routinely administered doses, the DDD is occasionally a "dose" that is infrequently, if ever, prescribed. Data on drug usage reported in DDDs only provide an approximate picture of actual use, not an accurate picture of actual intake.

General principles of DDD

DDDs are only given to medications with an ATC number, and they are often not given to substances before they have received marketing authorization in at least one nation. The fundamental rule is to only allocate one DDD per administration route under an ATC code. The ATC index does not include DDDs for herbal medicines. To get the most comprehensive picture of the actual or anticipated use of a substance, several sources are used when a new DDD is assigned. Specific assignment guidelines for various categories of pharmaceuticals are defined (e.g., the DDDs for the selective serotonin agonists in the treatment of migraine are based on the approved initial dose). Usually, the therapeutic dose is applied. A DDD is typically established based on the product's declared content (strength). In most cases, distinct DDDs are not assigned to different salts of a drug. Typically, different stereoisomeric forms are given unique DDDs and ATC codes. Prodrugs that do not have a unique ATC code typically do not have a unique DDD. Various DDDs can be established when the bioavailability is substantially varied for distinct routes of administration (e.g., oral, and parenteral administration of morphine) or if the dose forms are utilized for different purposes. The same DDD applies to parenteral drugs administered via various routes (e.g., intravenously, and intramuscularly).

Combination Products

The DDDs assigned for combination products are based on the fundamental tenet that, regardless of the number of active ingredients present in the combination, the combination is counted as a single daily dose.

- For combination products where the ATC code identifies the main ingredient, the DDD for the combination product should be equal to the DDD for the main active ingredient.
- For combination products used for the treatment of hypertension, DDDs are based on the average number of dosing intervals per day. This means that: 1 tablet is the DDD for combinations given once daily, whereas 2 tablets are the DDD for combinations given twice daily and 3 tablets is the

DDD for combinations given three times daily etc.

Advantages of DDD

- Published by WHO and well known internationally.
- Updated annually.
- Does not require patient-level data.
- Ease of having antibiotic use information for ward/unit/hospital.

Disadvantages of DDD

- DDD might change.
- Based on a standardized dose, not prescribed dose
- Loading doses
- Need to consider changes in dosing recommendations.
- Inappropriate for children
- Underestimation of use in renally impaired patients
- PO vs IV (amoxicillin: 3g for IV and 1.5g for PO)
- Piperacillin and enzyme inhibitor (WHO DDD refers to piperacillin)
- Combination therapy of narrow spectrum agents contributes more to DDD than monotherapy of broad-spectrum agents.

Calculation

DDDs = Number of boxes x number of tablets in the box or number of vials x tablets in grams or the weight of the vial / the DDD value of the antibiotic in grams.

Antimicrobial consumption index (ACI) is used for in-bed patients as the ratio of the total DDD per 100-bed-days. ACI = DDD/bed−days X 100

Also, the antibiotic consumption index of a country or geographical area at a certain period is calculated by DDD per 1000 people. The number obtained is the antibiotic consumption index of that hospital/clinic or population. The denominators can be number of patient days = number of admissions during a designated time X average LOS, occupied bed days, admissions, and days present. These can be access from hospital data.

Drug Utilization figures should ideally be presented using a relevant denominator for the health context such as *DDD per 1000 inhabitants per day, DDD per 100 bed days, DDD/patient, and DDDs per inhabitant per year*. Drug utilization data presented in DDDs give a rough estimate of consumption and not an exact picture of the actual drug use, and the estimates described above are only true if there is good agreement between the prescribed dose and the DDD.

Reference:

1. Guidelines for ATC classification and DDD assignment [Internet]. Oslo: WHO Collaborating Centre for Drug Statistics Methodology; 2023 [cited 2023 24 March]. Available from: https://www.whocc.no/atc_ddd_index_and_guidelines/guidelines/

New Drug Approvals…

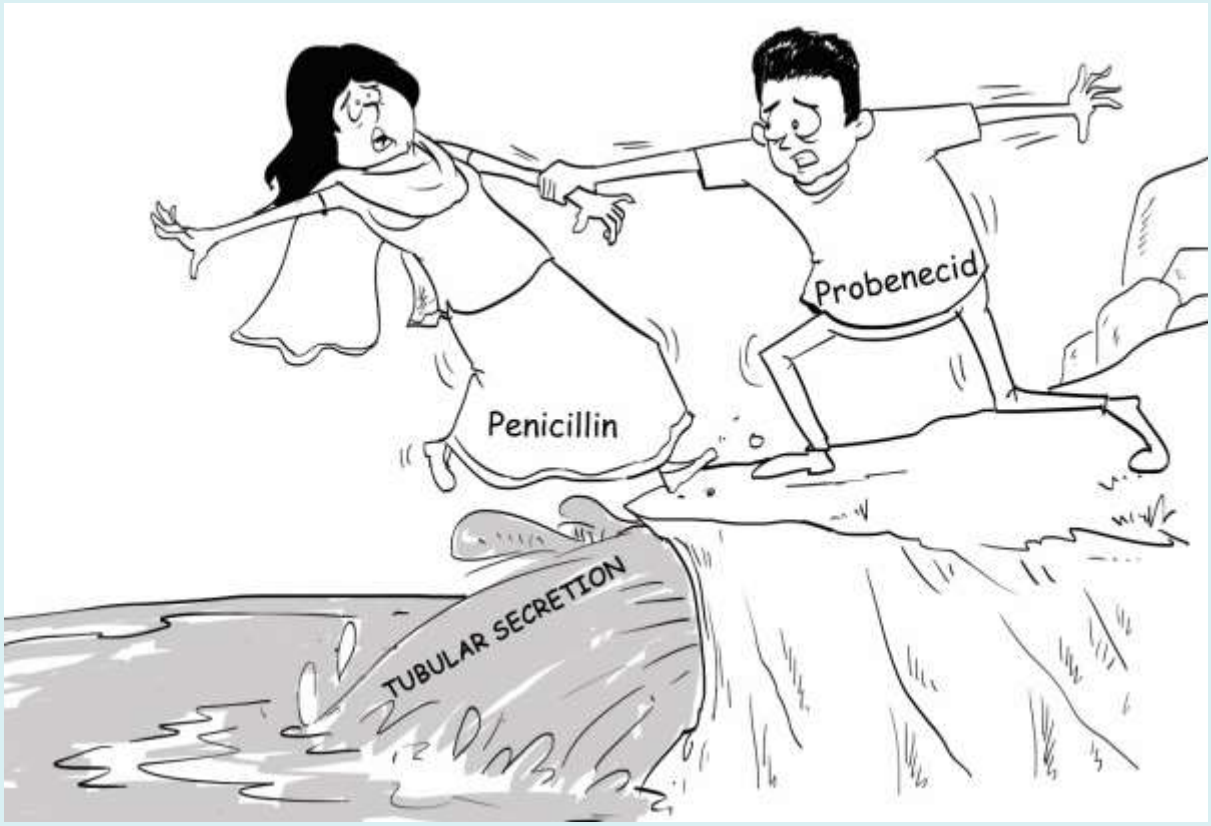
Lecanemab is an amyloid beta-directed antibody approved for the treatment of Alzheimer's disease. The recommended dose is 10 mg/kg IV biweekly.

Elacestrant is an estrogen receptor antagonist approved for the treatment of postmenopausal women or adult men, with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy. The recommended dose is 345 mg orally once daily with food.

Daprodustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) approved for the treatment of patients with anemia of chronic kidney disease. The recommended dose is 4 mg orally once daily.

Bexagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor approved for the treatment of type 2 diabetes mellitus to improve glycemic control in adults. The recommended dose is 20 mg orally once daily in the morning.

Cartoon Corner…



Excerpt from "Drug Autobiographies in Pharmacology" by Dr. Sushil Sharma

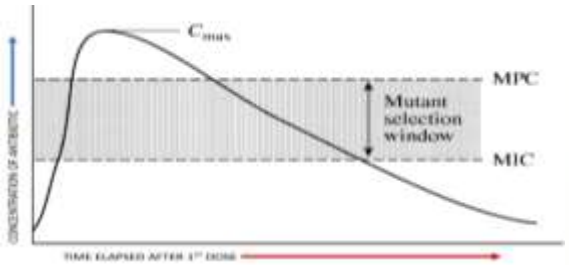
Guest Corner: Breakpoint to MIC Quotient: An Emerging Parameter for Antimicrobial Efficacy

The treatment of severe invasive and systemic bacterial infections requires the most effective antibiotics in vivo to optimise efficacy and decrease the risk of antibiotic resistance selection. Typically, this choice is based on in vitro antimicrobial susceptibility testing [AST], which identifies the minimum inhibitory concentration [MIC] for specific antibiotics for which ideally the broth microdilution is the gold standard method. The European Committee on Antimicrobial Susceptibility Testing [EUCAST] as well as Clinical Laboratory Standards Institute [CLSI] provide a list of clinical MIC breakpoints, which categorise microorganisms as susceptible or resistant to specific antimicrobial agents and guide their clinical use. The clinical breakpoint of an antibiotic is established according to defined rules, including microbiological considerations through the epidemiological cut-off [ECOFF] value, pharmacokinetic / pharmacodynamics [PK/PD] considerations through the PK/PD breakpoint, and clinical considerations through association with clinical cure. Antibiotic choice also can be based on the minimum bactericidal concentration [MBC], although this extremely tedious and time-consuming method may not provide results in time to assist in choosing the optimal antibiotic.

Patients infected with Gram-negative Enterobacterales or Pseudomonas aeruginosa isolates showing borderline MICs [near the susceptible breakpoint] may be at higher risk of clinical failure, even mortality, than those with infections having lower MICs. Similarly, Falagas et al. found that more treatment failures occurred in patients infected with Salmonella enterica strains with high fluoroquinolone MICs [near the susceptible breakpoint] than those with Salmonella strains with low MICs, and mortality rate for patients infected by Gram-negative non-fermentative bacilli with high MICs was also higher than for those with low MICs. Classically speaking, the closer the MBC is to the MIC, the most likely are the chances for a better kill and such antibiotics are bactericidal in nature and farther away the MBC is to the MIC, the more chances are, that the drug is bacteriostatic. Traditionally speaking the ideal ratio between the maximum concentration reached in the blood [Cmax] should be four times the susceptibility breakpoint MIC.

In terms of PK / PD, antibiotics are primarily of two types. Concentration dependent antibiotics have a good post antibiotic effect as they affect the genetic machinery of the bacteria thus causing long term to kill. Besides this, their ability to bind to proteins, causes them to elute slowly, even once the antibiotic is stopped. Such antibiotics do not require multiple dosing's. Once daily dose not only raises the Cmax at one shot but also reduces incidences of renal toxicity and these antibiotics are defined by the PK / PD index, Cmax/MIC. Aminoglycosides [act on 30s ribosome] and Fluoroquinolones [act on DNA Gyrase] are classical examples of concentration dependant antibiotics. At the same time, there are Time Dependant antibiotics, which primarily act on the actively dividing bacteria and time of exposure of the antibiotic to the bacteria is more important than the concentration reached. No matter how high one may raise the dose, the efficacy is determined by the duration of exposure of the antibiotic. Therefore, such antibiotics are given with increased frequency and mandatorily, as extended infusions of not less than 3 hours duration per dose and they are defined by the PK / PD index %T>MIC.

However, in both cases, whether time dependant or concentration dependant, maximal drug efficacy is achieved when Cmax/MIC ratio is ≥4 after one single dose or percentage of time of dosing interval i.e., %T is maximally above, four times the MIC values i.e., %T>4MIC. This is done to cover the region in the antibiotic time concentration curve [Figure] where mutant strains emerge, which happens just above the MIC and below the hypothetical concentration of the highest MIC of the mutant strains present at the site of infection, called the Mutation Prevention Concentration [MPC]. This distance between the MIC and the MPC is known as the Mutant Selection Window [MSW].



Therefore, greater the gap between the susceptible breakpoint MIC or the Clinical breakpoint MIC [as per CLSI or EUCAST] and the MIC of the isolate that is tested, greater are the chances of achieving a better kill, with the usual doses against which the Clinical Breakpoint MIC was calculated. The greater the gap, the better are the chances that the emerging resistant strains in the MSW will get easily killed at the usual doses. This ratio of the Clinical breakpoint MIC to the MIC of achieved for the isolate for that antibiotic is called the "Breakpoint to MIC Quotient" or BMQ. Therefore, greater the BMQ, lesser is the Minimum Bactericidal Concentration [MBC] and therefore better is the kill. This concept may be easily understood using the Table below. The first column shows the antibiotic. Second shows the MIC of the antibiotic achieved for that strain for different antibiotics [A]. Third column shows the clinical breakpoint MIC which decides the basis of an antibiotic being resistant or susceptible [B]. The last column shows the Breakpoint to MIC Quotient [BMQ], which indicates the therapeutic efficacy of the antibiotic and gives the Clinical Microbiologist the right judgment to pinpoint the most efficacious antibiotic. Based on the data in the table, this E. coli isolate is an ESBL phenotype and based on the BMQ's, the best carbapenem sparing options would include either Cefepime with Aminoglycoside or piperacillin / tazobactam with Aminoglycoside, depending upon the severity of the infection.

Organism: Escherichia coli, isolated from a Patient with Community Acquired Sepsis

ANTIBIOTIC	*MIC of the Isolate [A] µg/ml*	*Susceptibility Breakpoint MIC for Enterobacterales [B]*	*BMQ=B / A >4 = Best Option ≥1: S, <1-0.5: I, <.5: R*
Amikacin	*1*	*≤4*	*4*
Amoxi – Clav	*8*	*≤8*	*1*
Cefepime	*0.25*	*≤2*	*8*
Cefoperazone-Sulbactam (FDA)	*8*	*≤8*	*1*
Ceftriaxone	*>32*	*≤1*	*0.031 Resistant*
Cefuroxime	*>32*	*4*	*0.031 Resistant*
Ciprofloxacin	*1*	*≤0.25*	*0.25 Resistant*
Ertapenem	*0.25*	*≤0.5*	*2*
Fosfomycin (E. coli, UTI)	*N/A*	*≤64*	*N/A*
Fosfomycin (E. coli from Non-UTI Site)	*8*	*≤8*	*1*
Gentamicin	*0.5*	*≤2*	*4*
Imipenem	*0.25*	*≤1*	*4*
Meropenem	*0.5*	*≤1*	*2*
Piperacillin-Tazobactam	*1*	*≤8*	*8*
Tigecycline (FDA) Not for Blood & Urine	*N/A*	*≤2*	*N/A*
Cotrimoxazole	*20*	*≤40*	*2*

BMQ also removes the confusion when the MIC values appear higher, like Piperacillin / Tazobactam [1µg/ml] and Meropenem [0.5 µg/ml] in this case, but the BMQ of Piperacillin / Tazobactam is higher than Meropenem. and therefore, the BMQ is an easy-to-calculate parameter for most routinely detected bacteria with known MIC values. It may predict the bactericidal activity. This indicator may represent an easy-to-use method for clinicians to use MIC values. Of particular interest would be to extend the concept to other antibiotic families and sites other than blood and serum.

Contributed by:
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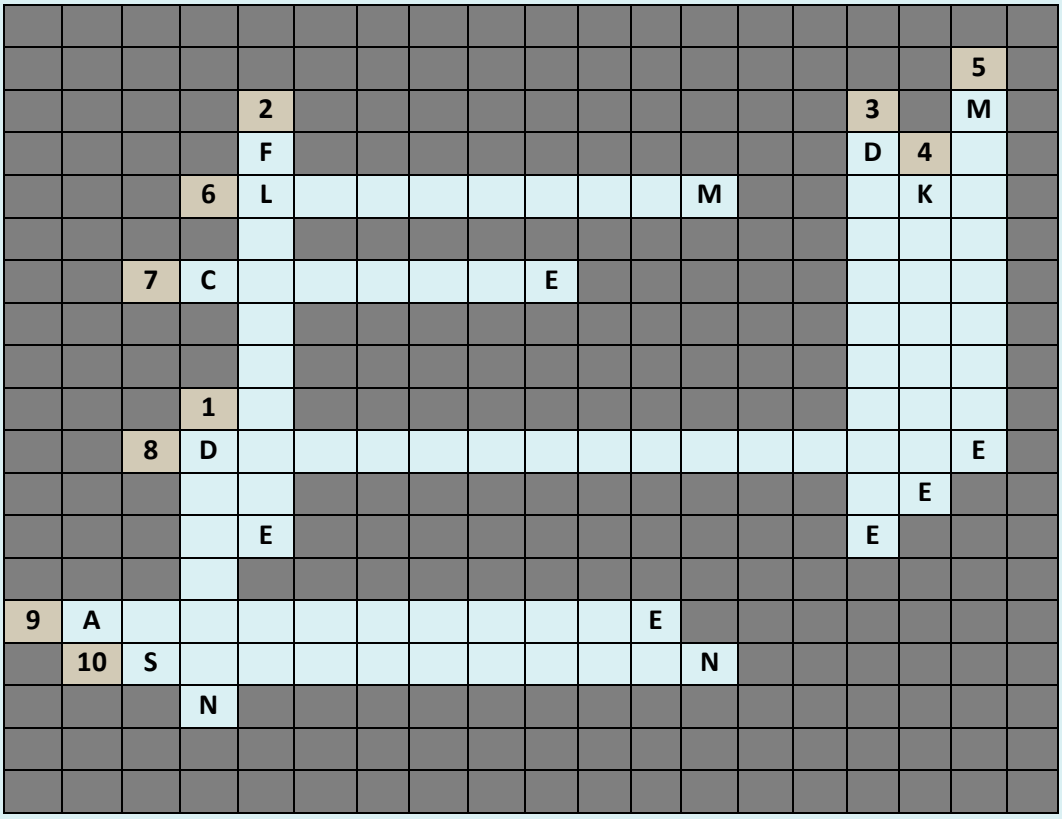

Downward	Across
1. Tricyclic antidepressant (7) 2. Selective Serotonin Reuptake Inhibitor (10) 3. Broad spectrum antimicrobial agent (10) 4. Intravenous anesthetic agent associated with dissociative anesthesia (8) 5. Used to treat opiate addiction (9)	6. Benzodiazepine preferred in treatment of status epilepticus (9) 7. Local anesthetic obtained from the plant (7) 8. Highly sedative H_1 antihistaminic (15) 9. CNS stimulant can be used in ADHD and narcolepsy (11) 10. HMG-CoA reductase inhibitor (11)

Answer to the Crossword Puzzle (20th Issue) is given below:

Downward
1. Doxepin 3. Doxylamine 4. Ketamine 5. Methadone
2. Fluoxetine

Across
6. Lorazepam 7. Cocaine 8. Diphenhydramine 9. Amphetamine
10. Simvastatin