FROM THE EDITORIAL DESK….

Dear Friends, Greetings from AIIMS Mangalagiri and Welcome to another issue of ESSENCE.

With Anti-Microbial Resistance increasing worldwide at a rapid pace and very few new antibiotics being developed, existing antibiotics are becoming a limited resource. World Antimicrobial Awareness Week (WAAW) is celebrated from 18-24 November every year to ensure. Celebrated annually, it aims to increase awareness of global antimicrobial resistance and to encourage best practices to avoid the further emergence and spread of drug-resistant infections. The 2021 theme, **Spread Awareness, Stop Resistance,** called on all Health stakeholders, policymakers, health care providers, and the general public to be Antimicrobial Resistance (AMR) Awareness champions. Anti-Microbial Stewardship (AMS) is one of the most important pillars in this regard and can help to preserve antibiotics for our future generations. The current issue of ESSENCE tackles this burning issue with two articles devoted to Anti-Microbial Stewardship.

Interesting news in terms of the first FDA approved eye drop that could replace reading glasses for millions and the potentially beneficial effect of Metformin in Pulmonary Tuberculosis are also part of this issue.

Further, as always, the current issue of ESSENCE also covers the new drug approvals and drug safety alerts. Finally, the readers can test their knowledge with the cross-word puzzle on 'Drugs causing Thrombocytopenia'.

Happy Reading and Stay Safe.

Jai Hind.

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Antimicrobial resistance (AMR) has emerged as a major public health problem all over the world. Infections caused by resistant microbes fail to respond to treatment because of limited therapeutic options resulting in prolonged illness and greater risk of death. The WHO in its statement stated that "AMR is a slow tsunami that threatens to undo a century of medical progress with the potential to push the humankind into the post-antibiotic era". AMR is already responsible for up to 7 lakh deaths a year. Unless urgent measures are taken to address this threat, the world could soon face an unprecedented health crisis of 10 million annual deaths by 2050.

Inappropriate, over use and misuse of antimicrobial agents is the single most important reason that contributes to the growing problem of antimicrobial resistance and is considered as a most serious threat to public health. Antibiotic use has been seen to be high in India with one recent surveillance study indicating 40 per cent of patients in the community on antibiotics, and around half of these are taking them in an inappropriate manner.

One of the crucial strategies to counter this the initiation of antibiotic stewardship programmes. Antimicrobial Stewardship (AMS) programme involves a coherent set of actions which promote using antimicrobials responsibly.

- Restrict inappropriate use of antibiotics

- Optimize selection, dose, route and duration for best patient outcomes

- Reduce anti-microbial resistance and

- Decrease the spread of infections by MDR organisms

The team involved in Antibiotic Stewardship is multidisciplinary and consists of Clinicians, Pharmacologist, Microbiologist, Infection control team and Hospital administrator.

Important aspects of Anti-Microbial Stewardship include:

1. Creating an Antibiotic Policy: This is based on the cumulative Antibiogram of one year which shows that most common microbial flora and resistance pattern & is coupled with Standard treatment guidelines so as to create institution specific guidelines for management of infections. The antibiotic policy helps in more appropriate selection of antibiotics; thus, reducing the empiric use of broad-spectrum antibiotics.

2. Continuing Medical Education (CME): Regular educational programmes for the health care professionals are important to create an awareness of the appropriate ways of using antibiotics and the dangers of irrational and overuse of antibiotics.

A Balancing ACT
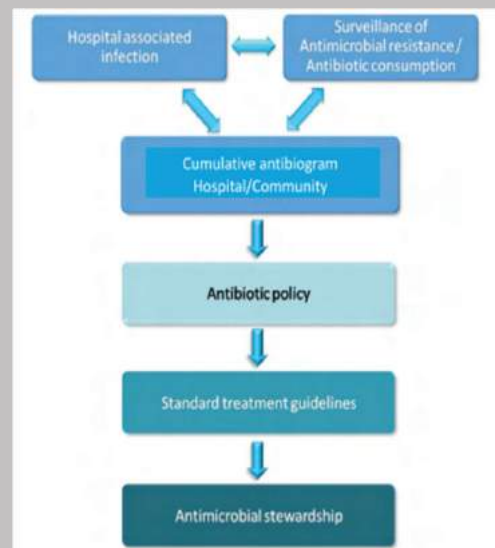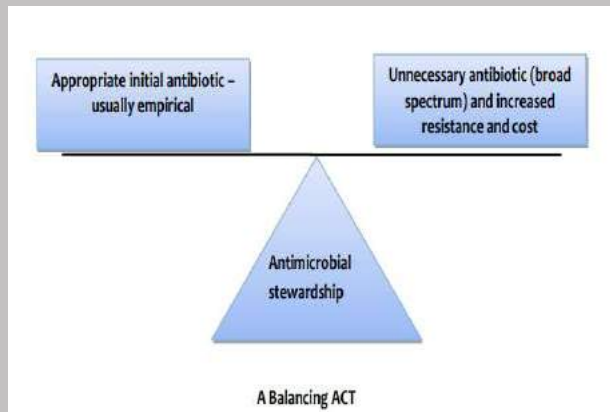
3. <u>Patient Education</u>: Community awareness and educational interventions to educate the public regarding self-medication of antibiotics, un-necessary and improper use of antibiotics.

4. <u>Formulary Restriction & Prior authorization of restricted antimicrobials</u>: This puts in a system of checks and balances to ensure that the reserve antibiotics are not used without adequate justification. The AwaRe antibiotic classification given by WHO is an important step in this regard.

5. <u>Audit and feedback</u>: The prescriptions with antibiotics are monitored/scrutinized on a regular basis to check the appropriateness of the antibiotics prescribed. Feedback is then given to all concerned with a view to ensure that mistakes are corrected and rational use of antibiotics is followed.

6. <u>Strict Implementation of regulations</u>: The regulatory agencies must be prevailed upon to ensure that public access to restricted antibiotics is controlled so that these crucial antibiotics are not freely available without prescriptions. This will help in preventing the overuse and misuse of these antibiotics.

7. <u>Use of antibiotics in animals and crops</u>: use of anti-microbial agents in food producing animals and crops leads to the development of drug resistant bacteria which can then enter the humans through food, water, soil. This leads to spread of drug resistant bacteria in the community. Hence, use of antibiotics in animals and crops must be regulated to prevent the spread of antibiotic resistance.

References:

1. Antimicrobial stewardship interventions: a practical guide (WHO) https://apps.who.int/iris/handle/10665/340709

2. Antimicrobial Stewardship Program Guideline (ICMR). https://main.icmr.nic.in/sites/ default/files/guidelines/AMSP_0.pdf

New FDA-approved eye drops could replace reading glasses for millions

Pilocarpine hydrochloride (1.25%) ophthalmic solution has been approved by USFDA for the treatment of Presbyopia (age related blurring of near vision). It is marketed by Allergan as VYITY eye drops and is a first of its kind treatment that could replace reading glasses. The drops act within 15 mins and the effect can last for 8-10 hrs, improving near and intermediate vision, at the same time distance vision is well maintained. The regulatory approval by US-FDA was mainly based on two pivotal randomized placebo-controlled trials GEMINI-1 & 2 conducted among patients with presbyopia (n=750). In comparison to placebo, the 1.25% pilocarpine hydrochloride ophthalmic solution treated patients showed significant improvement in terms of "gaining vision by three lines or more". Interestingly no serious adverse events were observed and the commonest adverse

Metformin may have Protective effect against Pulmonary Tuberculosis

Inhibition of intracellular growth of mycobacterium tuberculosis is reported among patients who are concurrently on Metformin. The intracellular growth inhibitory action of metformin is mediated through adenosine monophosphate activated protein kinase (AMPK) dependent pathway. In observational studies, reduced "risk of TB" was observed among diabetic patients who were on metformin compared to who were not. However, metformin failed to show benefit in terms of sputum conversion in randomized controlled trials. On the other hand, an anti-inflammatory action of metformin was evident with faster radiological clearance (in X-ray) indicating reduction of damage of lung tissue (as indicated by reduced cavitary lesions) and also reduced level of inflammatory markers.

Be Cautious…. Drug Safety Alerts

S. No.	Drug	Safety Alerts
1.	Bupropion	Serotonin syndrome
2.	COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19)	Capillary leak syndrome (CLS)
3.	Olanzapine	Olanzapine
4.	Sertraline	Microscopic colitis
5.	Tamoxifen	Contraception duration extended
6.	Oseltamivir	Haemorrhages

Antimicrobial resistance (AMR) is no longer a looming threat; it has evolved into a serious public health issue that defies all available control measures and necessitates multidisciplinary, creative solutions. Antimicrobial stewardship (AMS) initiatives necessitate a set of tools and abilities that health systems can use. Among them, the Essential Medicines List (EML) of the World Health Organization (WHO) divides antimicrobials into three categories: "Access," "Watch," and "Reserve" (AWaRe), based on indication, availability, and awareness. Implementation of the AWaRe tool according to national requirements and its access will reduce the antimicrobial resistance. However, on the other hand there is a significant capacity difference between industrialised and developing country health systems. For many low- and middle-income countries with inadequate laboratory resources, developing systems that can undertake laboratory-based AMR monitoring in a timely and reliable manner will entail time and long-term investments. As antimicrobial resistance (AMR) becomes a worldwide health issue, AMS programmes will require all available methods to overcome data scarcity and facilitate informed antimicrobial selection. In nations with low laboratory coverage and capability, the strong global pharmacovigilance infrastructure could be crucial. In this regard, the pharmacovigilance (PV) programme under the AMS framework has the potential to map and estimate the AMR burden in settings with limited laboratory coverage and capacity.

The scientific community continues to propose innovative antimicrobials monitoring systems. In this regard, experts have suggested pharmacovigilance data as a viable source of information for antimicrobial stewardship programmes. Pharmacovigilance is the science of activities connected to the detection, assessment, understanding, and prevention of adverse effects. A variety of unpleasant or unfavourable patient outcomes that appear to be associated with treatment are referred to as adverse effects. Recent research has highlighted pharmacovigilance's potential role in containing developing antimicrobial resistance, offering methodologies and resources that pharmacovigilance can offer to AMS programme that monitor suspected resistance or incidents of antibiotic misuse.

The WHONET programme, which was designed by WHO, is used to conduct pharmacovigilance in the form of antibiotic usage surveillance in 90 percent of the world's countries. However, the data only covers a small portion of the globe. Pharmacovigilance databases, in addition to existing AMR monitoring systems, can provide data on suspected resistance and inappropriate use. Pharmacovigilance data from around the world could be a key part of a larger multidisciplinary strategy to resistance surveillance and warning. If implemented successfully, the WHO's global action plan will significantly reduce AMR and aid in the evaluation of treatment options.

The AWaRe classification can be used as a part of the pharmacovigilance initiated tool while evaluating antibiotic-targeting efforts. A list of antimicrobials using the AWaRe (Access, Watch, and Reserve) list and the WHO Priority Pathogens List, and then searching the VigiBase using VigiAccessg for ADR reports with Preferred Terms (PTs) that contained AMR-relevant information would be one way of tapping in to the pharmacovigilance database to help AMS activities. The codes from the Medical Dictionary for Regulatory Activities should match the identified terms (MedDRA Version 21.1).

Pharmacovigilance databases are a one-of-a-kind source of information on the possible misuse of drugs (including antimicrobials) as well as other data that could be relevant to AMR. At least one study found a set of 17 MedDRA preferred phrases (PTs) that can be used to generate data on concepts like resistance, off-label use, ineffectiveness, and medication mistakes. These pharmaco-vigilance data may indicate use-

related concerns, which can be used to give prescribers a more complete picture during each consultation. Reports on off-label use or drug use in contraindicated indications can be communicated with entities in charge of national antimicrobial policies in order to provide timely information to decision-makers. The pharmacovigilance data also revealed reports of antibiotics on the Reserve and Watch lists, which is of particular significance in terms of AMR. Depending on the indications and available formulations, analysis of these data may reveal how and why certain Watch and Reserve antibiotics are potentially abused or used off-label. A surge in reports could potentially indicate that something about the medicine has changed. It is feasible to discover if there are changes in how a medicine is taken by evaluating a reporting spike.

Manufacturers should consider using AMR-relevant MedDRA terms in collecting data to inform their risk management plans if the drug safety community agrees that resistance or ineffectiveness are undesirable clinical outcomes following the use of antimicrobials with the intent to prevent or treat a disease. Reports of adverse reactions may be derived from a variety of sources, including spontaneous data sources, and may be linked to scenarios such as off-label usage and medication errors, according to the Guideline on Good Pharmacovigilance Practices. If the medical product in question is antimicrobial, responsible authorities should assess the danger of off-label use and medication in the context of antimicrobial stewardship.

Promoting the existence of AMR-relevant MedDRA keywords and emphasising their importance in antimicrobial resistance surveillance could result in more prescribers and patients submitting such reports. If pharmacovigilance is included in the antimicrobial stewardship programme package, public health will benefit from a variety of perspectives. Pharmacovigilance centres at the national level should be encouraged to promote these AMR-relevant PTs and invite reporters to gather and communicate this information to the appropriate agencies. This procedure will assist in the following ways:

1). More spontaneous reports will be received by pharmacovigilance centres, and their work will be more visible and appreciated by other public health stakeholders; and

2). Suspected AMR could be discovered quickly, possible clusters could be identified, and ad-hoc microbiological testing could be performed if necessary.

Incorporating pharmacovigilance into the Anti-Microbial Stewardship programmes could result in a win-win situation for many scientific disciplines confronting AMR from usually separate perspectives. Pharmacovigilance is already a multifaceted science with the potential to grow even more. Using existing pharmacovigilance methodologies to address AMR problems will allow pharmacovigilance to advance further as a field, and governments will see greater value in investing in their pharmacovigilance systems. Methods usually utilised in post-marketing drug safety monitoring have the potential to act as surveillance strategies for antimicrobial stewardship programmes as technology progresses in the field of pharmacovigilance.

National pharmacovigilance centres could play a proactive role in encouraging the reporting of AMR-relevant adverse drug reactions (ADRs), which could be used to trigger resistance suspect warnings. More research is needed on the narrative and other clinical pharmacology aspects in ADR reports.

References:

1. Habarugira, J.M.V., Figueras, A. Antimicrobial stewardship: can we add pharmacovigilance networks to the toolbox? Eur J Clin Pharmacol 2021;77:787–790.

Asciminib is a tyrosine kinase inhibitor approved for the treatment of patients with Philadelphia chromosome-positive chronic myeloid leukaemia (Ph+ CML). The recommended dose is 80 -100 mg orally per day.

Vosoritide is a C type natriuretic peptide (CNP) analogue approved to increase linear growth in paediatric patients with achondroplasia. The recommended dose is s 15 µg/kg body weight.
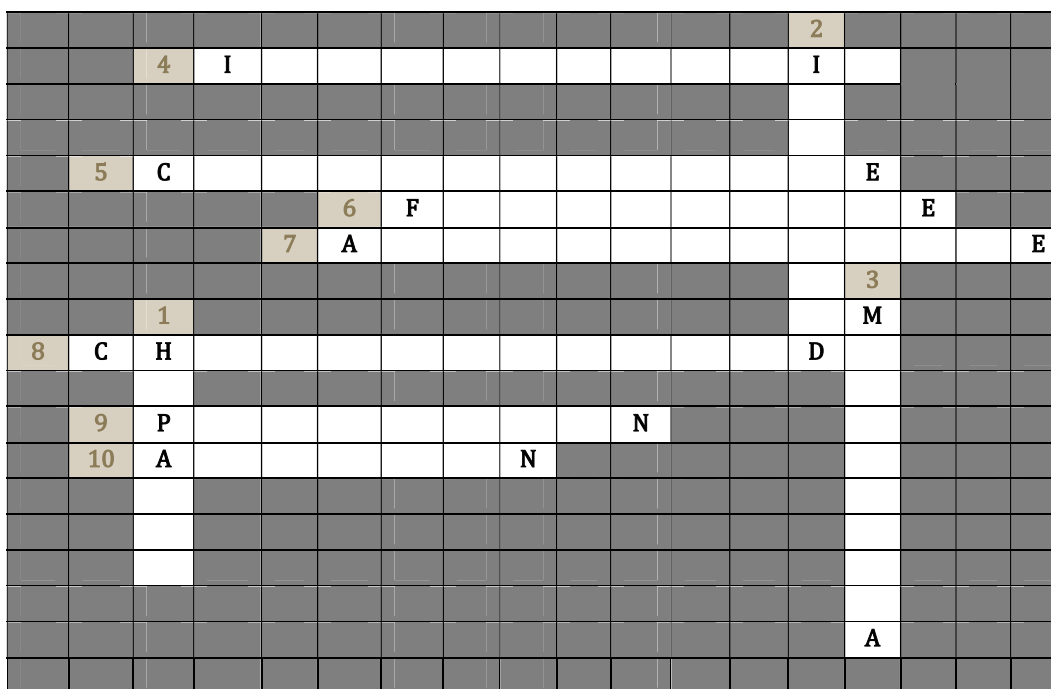
Ropeginterferon alfa-2b- is an interferon alfa-2b approved for the treatment of adults with polycythemia vera. The recommended dose is 100-500 mcg every 2 weeks.

Maribavir is a cytomegalovirus (CMV) pUL97 kinase inhibitor approved for the treatment of post-transplant CMV infection/disease. The recommended dose is 400 mg- 1200 mg BID orally.

Pafolacianine is a fluorescent imaging agent targets folate receptor approved as an adjunct for the intraoperative identification of malignant lesions in patients with ovarian cancer. The recommended dose is 0.025 mg/kg administered intravenously over 60 minutes, 1 to 9 hours before surgery.

	Downward		Across
1.	Parenteral anticoagulant that indirectly inhibits thrombin (7)	4.	NSAID which is associated with frontal headache (*12*)
2.	First line anti-tubercular drug that can also cause Peripheral Neuropathy as an adverse effect (*9*)	5.	Anti-seizure drug associated with dilutional hyponatremia (*13*)
		6.	High ceiling diuretic acts by inhibiting the Na+-K+-2Cl⁻ Cotransport (*10*)
		7.	*Carbonic anhydrase* inhibitor (*13*)
3.	Anti-hypertensive drug safe in pregnancy (*10*)	8.	Oral hypoglycemic which is a K_{ATP} Channel blocker (*14*)
		9.	Anti-seizure drug associated with gum hypertrophy (*9*)
		10.	NSAID which has dose dependent actions and indications (*7*)

Answers: