

Antimicrobial stewardship a way forward to curb rising antimicrobial resistance!

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Introduction

The present scenario of antimicrobial resistance across the globe and its anticipated future has urged various health organizations like, World Health Organization [WHO], Centre for Disease Control [CDC], Infectious disease society of America [IDSA], Society for health care & epidemiology of America [SHEA] and Indian council of medical research [ICMR] and many more to contemplate and suggest possible operational measures for its control.

Over the decades antimicrobial resistance has emerged as a major public health concern. Transmission of resistant pathogens is neither confined by geographical boundaries nor restricted to one species. At present the whole world is under the impact of its baneful effects.

Influence of Resistant Microorganisms on Health

Infections caused by resistant microbes do not respond to available antibiotics, because of limited choice. And as a result of treatment failure, infection will be prolonged and may even lead to the death of the affected individual. When such an infected person with treatment failure stay for longer periods in the community there is risk of transmission of infection to healthy contacts. The prohibiting cost of second line drugs add to the woes of treatment failure. The burden of antimicrobial resistance [AMR] is very high all over the world, according to CDC estimates every year in United States at least 2 million people acquire serious infections with bacteria that are resistant to one or more of the antibiotics available for the particular condition. And almost 23,000 people die every year of infection with these resistant microorganisms.

AMR status in India

An estimated 4,10,000 children under five years of age die of pneumonia every year in India. The crude mortality rate from infectious diseases is 417/1,00,000 population. The impact is high due to injudicious use of antimicrobials both in humans and animals. In 2010 India stood first amongst the largest consumers of antibiotics for human health 12.9 x 10⁹ units [10.7 units per capita]. As per the WHO country office India, resistance rates to most of the antibiotics of clinical use is as follows shown below in table 1.

Table 1:

Pathogens	2005	2015
Methicillin resistant Staphylococcus aureus MRSA	29%	47%
Carbapenem resistant Escherichia coli	10%	13%
Carbapenem resistant Klebsiella pneumoniae	29%	57%

Salmonella typhi resistant to fluoroquinolones	8%	28%
Shigella resistant to nalidixic acid fluoroquinolones and ampicillin	30%	>50%
Pseudomonas spp. resistant to Piperacillin and Tazobactam	30%	42%
Pseudomonas spp. resistant to meropenem	24%	50%
Acinetobacter spp. carrying NDM-1 gene	-	13%
Acinetobacter spp. resistant to meropenem	50%	70%
Klebsiella pneumoniae resistant to colistin	-	4-10%

AMR in Animals

It is seen that antimicrobials are administered to live stock to promote and enhance their growth for extended periods of time which has indirect consequences on global health. There is no system to monitor its use in India. Moreover, regulations are limited. And it is observed that India is the 4th largest consumer of antimicrobials in livestock. As a result, resistant pathogens are isolated from animals and poultry which through food chain are transmitted to humans. The Various resistance patterns isolated from livestock are as follows:

1. Vancomycin resistant enterococci [VRE] from cow and goat milk
2. Milk from cow with mastitis has Escherichia coli carrying NDM-1 [New Delhi Metallo betalactamase-1]
3. Resistance to streptomycin 70% and erythromycin 57 % in poultry
4. Resistance to several classes of antibiotics in back yard poultry is observed for example chloramphenicol, fluoroquinolones, oxytetracycline in *Staphylococcus aureus*, *Esch.coli*, *Salmonella spp.*, *Aeromonas spp.*
5. MDR isolates from 250 aqua culture samples
6. NDM -1 in water samples from community and hospital settings

Further it is observed that most of the prescriptions are unnecessary or redundant. As per the WHO estimates about 50% of antimicrobial use all over the world is inappropriate. The 30% rule is applicable in all our health care settings which is as follows:

1. 30% of all the hospitalized inpatients at any given time receive antibiotics
2. Over 30% of the antibiotics prescribed in the community are in appropriate
3. Up to 30% of all surgical prophylaxis are in appropriate
4. 30% of hospital pharmacy cost is due to antibiotic use
5. 10-30% antimicrobial cost can be saved by antimicrobial stewardship program [AMSP]

Moreover, a big difference is noticed in therapeutic vs. non therapeutic use of antimicrobials in human and animals which is alarming, as depicted in Fig. 1. below.

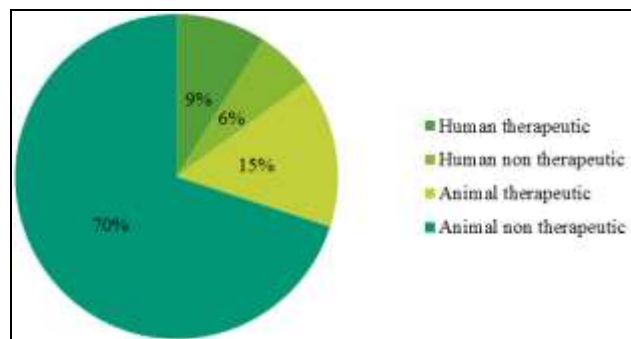


Fig. 1: Pie Diagram depicting use of antimicrobials in various sectors

The figure above precisely describes the amount of irrationality in antimicrobial use. Therefore, regulations have to be brought into practice at the earliest to contain AMR. Otherwise, antimicrobials once which were considered as “MAGIC BULLETS” for treatment of infectious diseases will no longer be effective. And the day is not far when we are going to lead to “POST ANTIBIOTIC ERA” where we don’t have any antimicrobial left to treat deadly infections caused by myriad of resistant microbes like multidrug resistant microorganisms [MDR], extensively drug resistant microorganisms [XDR] and pan drug resistant microorganisms.¹ Moreover, it is anticipated by experts in the field that in near future many patients may suffer and die of over whelming infections caused by these microorganism’s due lack of effective antimicrobials. Therefore, judicious and responsible use of antimicrobials forms the key to control rising antimicrobial resistance.

Who is responsible for the present status of AMR?

The situation of antimicrobial resistance for a long period of time remained overlooked due to reasons unknown. And I would say almost everyone who is involved in delivering health care to the patient both in governmental and non-governmental organizations are equally responsible for it. The onus is on all; the policy makers, treating physicians, quacks, the allied health care professionals practicing allopathy and the pharmacist responsible for over the counter sale of most of the antimicrobials.

Hence, investigating into who and to what extent is responsible for rising AMR is just mere waste of time and resources instead of which the same can be directed for implementing immediate remedial measures. It is better not to look back, what has happened over the years, but to look forward and tackle the issue, as rightly mentioned in “Chennai Declaration a roadmap to tackle AMR in India”.²

Why do we need AMSP? is it Really Required?

Rational use of antimicrobials can be brought about by stewardship which here is called as antimicrobial stewardship program [AMSP]. In view of the above

findings it becomes crucial to have AMSP in every health care setting. Therefore, the answer to the question is ‘YES’. Growing antimicrobial resistance across the globe, increasing misuse and over use of antibiotics, widespread use of antimicrobials in other sectors and poor research and development of new antimicrobials are some of the reasons. Hence, CDC in 2006 declared that the only way to curb the growing antimicrobial resistance problem is by “Judicious use of Antibiotics”. Therefore WHO, CDC and many more health care organization came up with the containment measures and even methods to monitor its effectiveness. AMSP has to be established in every health care facility right from primary to tertiary care hospitals. Primary health care centers are the first level of care and here the general practitioner plays a pivotal role in tackling AMR by reducing unnecessary antibiotic use. Hence, in India the department of health [DH] at public level has rolled out a program called “Antimicrobial stewardship programme in primary care” to optimise antibiotic use. Further, post prescription feedback will help more to stop, modify, continue and to assess the appropriateness of therapy.

What is AMSP?

It is defined as an interprofessional effort across the continuum of care³ and includes:

1. Optimizing the use of antimicrobials by timely selection of right drug, dose and for right duration
2. To obtain best outcome of the treatment or prevention of infection
3. To minimize toxicity to the patient
4. To minimize impact on resistance and other adverse events like *Clostridium difficile* infection [CDI] rates

The CDC definition of AMSP is much more simplified which says, use of right antibiotic, for the right patient, at the right time, with right dose, route and frequency causing least harm to the patient and future patients.

What is the goal of AMSP?

The primary goal of AMSP is to combat antimicrobial resistance while the secondary goal is to improve patient outcome and safety and even reduce health care cost.

Who all are the members of AMSP team?

The AMSP team is a multidisciplinary committee comprising of:

1. Infectious disease physician [Antimicrobial steward]
2. Infection control officer
3. Clinical microbiologist with ID training
4. AMSP nurse with ID training
5. Clinical pharmacist with ID training
6. Pharmacy in charge

The antimicrobial steward is the central driving force behind the program He/She can be either:

1. ID physician trained in clinical microbiology
2. Clinical microbiologist trained in ID
3. Infection control officer trained in ID & microbiology

AMSP team is responsible for framing, implementing and monitoring the compliance to the antimicrobial policy of the hospital

What are its Components?

The various components of the stewardship program are as follows:

1. Laboratory stewardship
2. Support from Hospital information system
3. Infection control stewardship
4. Antimicrobial stewardship
5. Framing of antimicrobial policy

Who is to plan, implement and monitor the program?

The policy makers in health care, both at the international and national level with significant inputs from administrators, directors, epidemiologist and experts in the field play a major role in planning out policies and regulations. Whereas, implementation and monitoring of the program, is the liability of all the stake holders involved in patient care. All must participate equally to achieve the desired goal [STOP AMR].

What are the steps in implementation of AMSP?

The first and most important step in the program is building up of leadership i.e. administrative support. Here the management or the medical director of the hospital must show commitment to the program by providing necessary funding and infrastructure to the program.

1. He /She must formally state the administrative support
2. Appoint essential staff for implementation of program with assigned duties and review performance annually
3. Constitute AMSP team
4. Frame antibiotic policy
5. Ensure that relevant departments of the hospital contribute to the program and they must get proper time to do so
6. Develop and implement standard treatment guidelines [STG] and antibiotic policy
7. Implement appropriate antimicrobial therapy using [STG] and see antimicrobial order forms are in place
8. Implement appropriate use of antimicrobials for surgical prophylaxis based on STG
9. Conduct prospective audit and feedback and timely intervention to streamline the antibiotic prescription
10. Place formulary restriction and preauthorization
11. Improve antimicrobial prescribing by education and administrative means

How to implement AMSP?

The three important corner stones of AMSP are antimicrobial, laboratory and Hospital infection control stewardship without which the program is incomplete and inefficient.

Antimicrobial stewardship can be implemented based on whether the intervention is applied before or after prescription of the antimicrobials. The two different

strategies available are front end strategy and back end strategy.

In Front end strategy the intervention is applied before prescription of antimicrobials with formulary restriction, preauthorization and antibiotic cycling as main tools. All three are important interventions to reduce the use and cost of antimicrobials. Formulary restriction and preauthorization [FRP] offers early and significant reduction in use of higher end antibiotics and cost without any negative impact on the patient outcome. Most significant advantage of it is reduction in antimicrobial resistance particularly in Gram negatives pathogens. It is an effective means of controlling and limiting the use of specific antibiotics. Moreover, it improves inappropriate empirical use of antibiotics. Amongst its disadvantages, snatching of clinician's prescription autonomy, potential for clinician subverting from the system, skills & availability of the approval team is a question, shift to other classes of antimicrobials which does not need approval which again brings in irrationality and lastly patient safety caused by delay in taking approval are the important ones to be considered.

Practically FRP has been found to be efficient, several Cochrane studies have shown both reduction in antimicrobial prescription and drug resistance using this tool. A survey of 22 institutions has shown implementation of restriction on use of carbapenem resulted in significant reduction in use of carbapenem and emergence of *Pseudomonas aeruginosa* resistant to carbapenem. Further there was reduction in CDI rates as well. In another study it was shown that there was a 41% reduction in antibiotic use and 71% reduction in nosocomial infection [CDI] over 5 years. Further outbreaks caused by drug resistant pathogens were also controlled.

Monitoring of frontend strategy is possible using following parameters like number of times restricted antibiotics were used appropriately, percentage of reduction in antimicrobial use or cost pertaining to restricted antimicrobial and time from initial prescription to patient receiving antibiotic.

Antibiotic Cycling

It involves withdrawal of antibiotic or class of antibiotics from use for a designated period of time and substitution with antibiotics from different class having comparable spectrum of activity. Available data suggest, it as a labour intensive, difficult & almost impossible to achieve. Instead of it, antibiotic mixing looks more useful.

Back end Strategy

In back end strategy the intervention is applied after prescription of antibiotic. it includes prospective audit and feedback [PAF]. It is the core component of AMSP. It ensures proper drug selection, dose, duration & route of administration. It involves concurrent review of patients receiving antimicrobials. It looks most effective means of intervention than FRP; as, it is a mutually agreed discussion between AMSP team and clinicians on prescription

practices. Here compliance to antibiotic policy is checked by taking AMSP clinical rounds and observing appropriateness of antibiotic used, dosage with renal adjustment, adherence to susceptibility report. There are two different ways to implement it either one step or two step method. The two-step strategy is better applicable. Some of the advantages of PAF are it is more widely acceptable, though the impact is delayed but long lasting, can lead to slow but sustainable reduction in antimicrobial use and provides higher opportunity for education through the feedback mechanism. The attached disadvantage is it is time consuming and labour intensive.

Evidences have proved PAF to be an excellent tool of AMSP. Cochrane data base of systemic reviews has shown a decrease in days of therapy [DOT] using this intervention. Further, it resulted in 22% decrease in use of broad-spectrum antimicrobials despite increased inpatient acuity over a seven-year period. Moreover, there was reduction in CDI rates and infections caused by MDR GNB. Similarly, in another Cochrane review and 14 RCT's it was seen that the duration of therapy was also significantly reduced from 11 days to 1.9 days. Hence it has been proved to be a highly effective tool to optimize appropriate use of antimicrobials and reduce duration of usage and associated complications because of infections with drug resistant microbes.

Customization of the PAF together with education to the point of patient group has further reduced the use of broad-spectrum antimicrobials. And interventions to streamline or discontinue the drug has brought a 28% decrease in the use of broad-spectrum antimicrobials. In some studies, it has also been shown to reduce the cost of treatment of about \$2602 per intervention

Laboratory Stewardship

The central component of AMSP is laboratory stewardship. Microbiology laboratory offers definitive microbiological diagnosis of patient infectious disease. It ensures quality specimen collection, timely processing and reporting of infectious agent along with antimicrobial susceptibility test results.

In order to provide accurate and timely results which is crucial for implementation of AMSP; availability of rapid and accurate microbiology diagnostic facilities is essential. Therefore, the administrators must realize the fact and allot additional required budget to upgrade microbiology laboratory with automation. Any delay in identification and susceptibility testing of pathogen, indirectly affects the patient management and outcome. The cost of switching from conventional to automation will be definitely less when compared to the cost spend on antimicrobial use and managing patient related complications.

Focus should be on improving the turnaround time [TAT] for culture, identification and antimicrobial susceptibility testing. Moreover, facilities to rule out bacterial infections using rapid viral testing, nonculture based fungal markers and biomarkers for sepsis must be available. In majority of the situations except for few, estimating serum levels of biomarkers of sepsis helps one to avoid undue delays in, arriving at microbiological diagnosis, initiating antimicrobial therapy and unnecessary use of broad-spectrum antibiotics. Procalcitonin an important sepsis biomarker and a prohormone released from thyroid gland medullary cells has shown promising results in decision making on treatment of infectious diseases. It has got both diagnostic and prognostic significance, especially in bacterial infections as shown below in the figure.

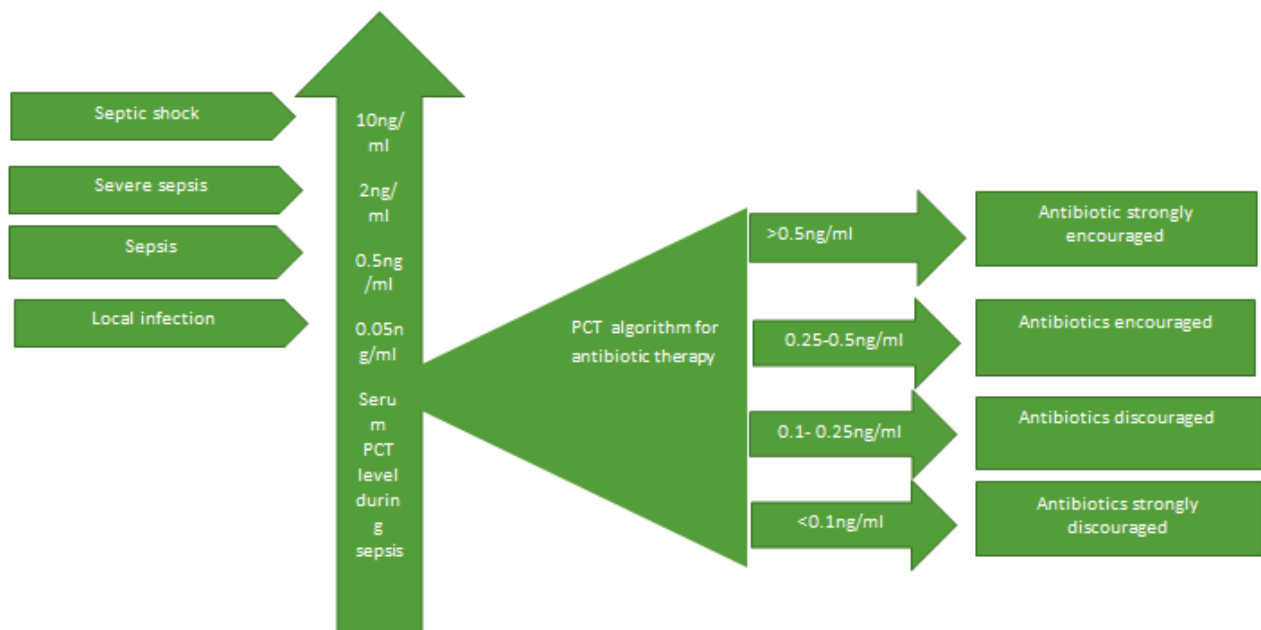


Fig. 2: PCT a guide in antibiotic therapy in sepsis

Besides this IL 6, CRP can also be used as biomarkers of infection but the attached significance is less compared to PCT [procalcitonin] due to their role more in inflammation than in infection. Undoubtedly molecular methods using nucleic acid detection and amplification test [NAAT] improves the laboratory turnaround time for diagnosis of infectious diseases from days to hours, especially in case of difficult to grow or non-cultivable microbes. The only drawback is the affordability of the patient, if possible should be the test of choice to save the patient from life threatening infections.

A key element for successful implementation of AMSP is therapeutic drug monitoring. If not all, at least the referral laboratories in every region must be equipped with facilities to monitor the antimicrobial concentrations in host serum and tissues for patients who are critically ill and in intensive care areas with compromised organ function. It also allows one to check whether sufficient antimicrobial concentrations are achieved or not, to decide the therapeutic efficacy, to minimize the risk of toxicity and finally to prevent emergence of drug resistant pathogens [suboptimal dose is known to induce drug resistance]

Hospital Infection Control Stewardship

Hospital Infection control committee [HICC] and microbiology laboratory are important pillars of AMSP. For successful implementation of AMSP the HICC has to be in place and functional. All its parameters like hand hygiene, HAI surveillance, appropriate use of PPE [personal protective equipment], TBP [transmission-based precautions] adherence to universal precautions are to be observed and monitored in order to avoid infections across the hospital.

Framing of Antimicrobial Policy

Irrespective of whether it is a primary or secondary health care facility all are supposed to have their own antimicrobial policy not a perfect one, but tailored to once needs. The main component of it is Standard treatment guidelines [STG] i.e. system wise or syndrome wise indications of antimicrobials of choice, the dosage for both adult and children. In order to ensure high quality care standard treatment guidelines are to be developed based on cumulative antibiogram of the microorganisms, antibiotic policy, surveillance of antimicrobial resistance, antibiotic consumption data and data on hospital acquired infection. The policy should be prepared after several discussions with its core members, which should be intra unit, inter unit and inter departmental so that all end users are involved equally. The policy should be compliant to international and national standards like IDSA, ICMR and local antibiogram. More relevant is common consensus to be arrived at, between all clinicians to ensure maximum compliance. It can be facility specific or patient specific.

Facility specific clinical practice guidelines for common infectious disease syndromes

This strategy when used appropriately will standardize the prescribing habits based on local epidemiology. For

example, management of community acquired pneumonia, childhood pneumonia and hospital acquired pneumonia. There is evidence to show that this intervention has helped in improving the likelihood of adequate initial therapy, use of narrow spectrum antibiotics, earlier switch from IV to oral therapy and shorter duration of therapy without any adverse events on outcome' but monitoring of adherence to guidelines and expected outcome becomes essential over the time

Patient specific clinical practice guidelines for common infectious disease syndromes

AMSP interventions for patient specific infectious disease can be effective way to improve prescribing habits. For example, an intervention developed to treat uncomplicated SSTI in adults reduced not only the use of broad-spectrum antibiotics but also shortened the duration of therapy. A study using 169 patients has shown significant reduction in the duration of therapy to 3 days, 30% reduction in use of broad-spectrum antibiotics and 0.3% reduction in clinical failure. In another study for treatment of CAP it is observed that this intervention helped in improving patient acceptance rate of therapy from 59.4% to 93.4%.

STG must be available to all the members of AMSP team in electronic form or hand book, preferably in electronic form as compliance improves when it is in electronic form rather than as hand book. The most often noted hurdles in implementation of STG are:

1. Clinician not aware of STG
2. Clinician aware of STG but unfamiliar with specific intervention
3. Not agree with specific recommendations
4. Guidelines not convenient for clinician and other AMSP team to use
5. Unable to reconcile guidelines with patient preferences
6. Clinician have no control on some changes
7. Clinician doubts about performance of STG
8. Recommendations unsuccessful
9. Clinician not motivated to change previous practices

Education and Training

AMSP like any other program requires continuous education, training, motivation and assessment of health care workers. Educational strategies include meetings, didactic lectures, distribution of resource material & periodic assessment of knowledge. It must include all the stakeholders. Trainings can be delivered on induction and then annually. Assessments must be periodic and both formal and informal.

Role of Hospital Information System [HIS]

HIS along with laboratory information system [LIS] are essential prerequisites of AMSP. They are valuable tools for generating patient database. A common source of information about a patient health history, treatment offered, investigation requested and the results of the test performed, all will be available at the click of the mouse. It ensures accurate data entry, ease of tracing laboratory reports,

instant sending of reports, no risk of loss of data, generates statistics, gives critical alerts, offers bidirectional interfacing and online access to reports.

CPOE/ COPE

Is another intervention using software stands for Computer physician order entry form which offers the physicians the facility to fill the patient medication form electronically via computer application and sends to pharmacy instead of using paper charts. It reduces the task of the clinician and provides patient treatment details to the health care system at any moment of time.

CDSS

Computer decision support system is an added feather in the cap of hospital information system, where the computer application is so designed to aid clinicians in making diagnostic and therapeutic decisions in patient care thereby improving antimicrobial use, selection of more appropriate antibiotic & dosing, reduces antibiotic resistance, adverse effects, antibiotic cost, length of stay and mortality & use of broad-spectrum antimicrobials, moreover, fewer prescribing errors will be noted, and higher opportunity for prospective audit and feedback is possible.

Other AMSP strategies that can be used are antibiotic time outs, drug optimization, automatic alerts, time sensitive automatic stop orders, intravenous to oral conversion, batching of antimicrobials, low hanging fruits, avoid redundant antimicrobials, pharmacy driven interventions, Start smart – then focus and MINDME.

How to Monitor AMSP?

Evaluation of AMSP is necessary to monitor the adherence of hospital to antibiotic policy. Most commonly used indicators are process and outcome indicators.

Process Indicators Include

1. De-escalation adherence rate
2. Culture of culture
3. Timely cessation of surgical prophylaxis
4. Policy compliance
5. 48hour antibiotic review
6. Switch from IV to oral
7. Renal adjustment
8. Administrative errors
9. Hangover time

Antimicrobials Usage Indicators Include

1. Defined Daily Dose [DDD]- WHO assigned DDD
2. Days of therapy [DOT]

DDD is the average maintenance dose per day for a drug used for its indication in adults. It helps to examine changes in utilization of antibiotic over time, make interhospital comparisons, evaluate effect of an intervention on drug use, determine antimicrobials prescription behaviour of clinician and evaluate regulatory effects and effects of intervention on prescribing patterns. But on the other side it has some

lacunas like is not available for all antibiotics and cannot be used to measure DDD for patient with adjusted renal & hepatic dosage and for children in general.

Days of therapy [DOT]

It is the number of days the patient receives at least one dose of antibiotic is summed for each antibiotic. Is the most recommended way of monitoring antimicrobials used by IDSA, WHO and CDC.

Other means of estimating antibiotic usage are ABC Calc – is a computer tool to measure antibiotic usage across the hospital. It transforms the aggregated data from the whole hospital provided by the pharmacist into a meaningful data on antimicrobial utilization rates. Pareto charts are useful charts to measure antibiotic use at the level of wards and identify wards that have high total usage or high use of restricted antimicrobials

Outcome Indicators

Includes antimicrobial resistance [AMR] surveillance, mortality and morbidity ratios.

AMR Surveillance

The primary and long -term goal of AMSP is to prevent emergence of AMR over a period of time. This is achieved by conducting AMR surveillance. Some of the desired objectives are to generate annual local antibiogram and hospital antibiogram which can be used to monitor trends in AMR. The generated data should be communicated to clinicians biannually.

Hospital antibiogram is the overall profile of the antimicrobial susceptibility testing results of a specific microorganism to a battery of antimicrobials. The various types of hospital antibiogram are routine cumulative antibiogram, enhanced antibiogram & subtraction antibiogram. Following points to be kept in mind while preparing hospital antibiogram

1. Minimum number of isolates must be 30 for each microorganism to get meaningful statistics
2. Only the first isolate per patient for any specimen type is taken for analysis
3. Should be prepared annually
4. Exclude non clinical isolates i.e. Resulting from infection not ones isolated for surveillance, water sampling or colonization

Hospital antibiogram serves several purposes, its guide clinician and pharmacist in choosing best antimicrobial for empirical therapy, helps monitoring and detecting trends in AMR within the hospital, compare susceptibility rates across the institutions, track resistance trends and contribute to national AMR surveillance data base and in last for analysing resistant strains like MRSA, VRE, CRE and KPC

The associated limitations are MIC creep, minimum Inhibitory concentrations values are not included in the antibiogram. Therefore, subtle changes below the resistance threshold are not reflected. Patient factors like age, past history of antibiotic usage, infections and underlying medical conditions are not taken care off. Cross resistance

or synergy between antimicrobials cannot be appreciated and lastly it is non generalizable, cannot be applied to the whole population

Clinical Outcome Indicators

Measures infection related morbidity and mortality. Some of the morbidity related indicators are: Length of stay, surgical site infection rate, rate of occurrence of complications due to sepsis, rate of readmission within 30 days, ward to ICU transfer rate, antibiotic related toxicity rate and finally rate of *Clostridium difficile* infection CDI

Mortality indicators are death due to sepsis and standardized mortality rates [SMR]

Financial outcome indicators include - Antibiotic cost per patient day, antibiotic cost per year and antibiotic cost per admission.

AMR Surveillance

AMR surveillance is essential to assess the burden of AMR and to implement corrective measures at local, national and international level to combat AMR. There are various international and national networks established to conduct AMR. One such example of International network is Global AMR surveillance system [GLASS]. It was launched in May 2015 by WHO to support standardized approach for AMR data collection analysis and sharing at a global level to inform the decision-making authorities and to drive local, regional and national action and provide the evidence base for action and advocacy. The main aim is to combine clinical, laboratory and epidemiological data on pathogens that pose greatest threat to global health.

WHO in 2017 published the first list of antibiotic resistant priority pathogens in a bid to promote research and development of new antibiotics and in an effort to control global AMR. They are divided into 3 different categories [4]

WHO Priority Pathogens

Critical pathogens include: Carbapenem resistant, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacteriaceae* with coproduction of ESBL

High priority pathogens include – VRE, MRSA, VISA & VRSA, Clarithromycin resistant *H. pylori*, fluoroquinolone resistant *Campylobacter* spp. Fluoroquinolone resistant *Salmonella* spp., Cephalosporin and fluoroquinolone resistant *N.gonorrhoeae*

Medium priority pathogens include – penicillin resistant *Streptococcus pneumoniae* [PRSP], Ampicillin resistant *H. influenza* and fluoroquinolone resistant *Shigella* spp.

National AMR Surveillance Network [India]

Government of India also has taken initiatives to establish national AMR surveillance system like for example:

National Program for the Containment of Antimicrobial Resistance under the banner of [NCDC]

This program was launched in 12th national five-year plan 2012- 2017. The key points of this program are to establish a laboratory-based AMR surveillance system of 30 network

laboratories across the country and generate high quality data on AMR for pathogens of public health importance, strengthen infection control guidelines and practices with promotion of rationale use of antimicrobials, raise awareness among HCP's and community about rational use of antimicrobials.

The first network involved only 10 surveillance centers, targeting basic problems of public health like infections caused by *Enterococcus* spp. *Salmonella typhi* and *paratyphi*, *P.aeruginosa* and *Acinetobacter* spp. The goal is to Establish AMR surveillance in various geographic regions of India, promote rationale use of antibiotics, develop and implement infection control guidelines, disseminate information about rational use of antibiotics and monitoring quality control checks, audits, feedback to advisory body and annual review of action plan

Antimicrobial Resistance Surveillance Research Network – [ICMR]

This network is under the control of ICMR and was established to streamline data collection on AMR at all levels of health care in order to compile the data and understand mechanisms of resistance, clonality, transmission dynamics and genetic molecular analysis.

National and regional nodal centers were established to meet the requirements, four tertiary care hospitals across the country are included under the project to cover six pathogens and 90% of WHO priority pathogens as enlisted below in table 2

Table 3:

Priority pathogen	National nodal center
Diarrheogenic bacterial pathogens	CMC Vellore
Enteric fever pathogens	AIMS New Delhi
Enterobacteriaceae causing sepsis	PGIMER Chandigarh
Gram positive pathogens including MRSA	JIPMER Puducherry
Fungal pathogens	PGIMER Chandigarh

As regional nodal centers about 20-25 medical colleges were proposed and of which 16 have already started reporting to ICMR. CLSI guidelines were adopted for performing AST and creating antibiogram. The data on AST is entered using special web services developed by ICMR. The whole data collected from various centers is analysed by ICMR to create national antibiogram. The isolates collected from regional centers are submitted to national centers for further higher research on the underlying mechanisms of resistance, clonality, transmission and genetic molecular analysis. The aim of this program is:

1. To collect a national representative data on drug resistance and monitor its trends across the country
2. To generate evidence on mechanisms of resistance in different pathogens
3. To guide antimicrobial policies for both treatment and prophylaxis

4. To direct hospital infection control efforts that facilitates prevention of the spread of resistant pathogens
5. To formulate standard operating procedures for bacteriology and mycology to create uniformity and harmonization of the clinical microbiological processes and procedures across the centers to overcome methodological limitations

There are different methods for collecting data on AMR either manual where data is entered into Excel sheets or by using specialized Software like WHONET.

WHONET is a free web-based software developed by WHOCC for surveillance of AMR. The goal of the software is to enhance local use of laboratory data and to promote national and international collaboration through the sharing of data. The software can be customized to the needs of the laboratory. The configuration allows information in the data field for list of antimicrobials, organisms isolated, susceptibility report with provision to enter the zone diameter or MIC values, patient care areas, specimen type, microbiological alerts of unusual pathogens and resistance phenotypes.

The other added features are data entry and clinical reporting, it allows the routine entry and reporting of AST results as well the retrieval, correction and printing of clinical records. During entry it provides immediate feedback on important phenotypes. For data analysis the program has user friendly interface permitting many types of analysis. Isolate line listing, summaries of frequency of isolates over the time, AST statistics, zone diameter and MIC histograms, antibiotics scatterplots and regression curves and antibiotic resistance profile line listing and summaries. It also has many alert features which permit the detection of unlikely or important pathogens, and hospital or community outbreaks of bacterial and nonbacterial species.

bacLink - Is another software provided by WHONET to those laboratories entering data manually in excel sheet. It acts as bridge between WHONET and excel and obviates the need to re-enter data in WHONET i.e. it automatically converts the data from excel sheet into the format of WHONET and helps in multicenter collaboration for AMR surveillance by facilitating standardization of data from many incompatible data sources into one common structure that can be analysed.

What is Being Done so far to Contain AMR?

Some of the strategies being adopted and followed are, CDC in 2009 launched Get smart for health care campaign to improve antimicrobial use in inpatient settings. The white house in its national action plan 2015 added component for combating antimicrobial resistance with five important goals

1. Curb antimicrobial resistance
2. Strengthen antimicrobial resistance surveillance
3. Advance development of rapid diagnostic test
4. Accelerate research targeting novel therapeutics

5. Collaborate with other countries to strengthen prevention development and surveillance of antimicrobial resistance

ASAT is an antimicrobial self-assessment tool kit. A program developed by pharmacist an advisory non departmental public body on AMR and HAI [ARHAI] in conjunction with DH. It helps organizations to fulfil the obligations with regard to antimicrobial national guidelines and regulations. It includes TARGET [treat antibiotics responsibly, guidance, education, tools] for primary health care facilities and Start Smart then focus [SSTF] for secondary health care systems launched by NHS United Kingdom

Start Smart then Focus [SSTF]

In 2011 SSTF was published by ARHAI. The aim of this program is to provide NHS hospital an outline on evidence based AMS. It has two sections. The program helps organizations to adhere to the Health and Social Care Act 2008. Which states that registered practitioners should demonstrate system to manage and monitor the prevention and control of infection and ensure appropriate antimicrobial use to optimize patient outcome and to reduce risk of adverse events and AMR.

Start Smart Advices

1. Do not start antibiotics in absence of clinical evidence of bacterial infection
2. If any evidence of bacterial infection is there use local guidelines to initiate prompt and effective antimicrobial therapy
3. Document on drug chart and in medical notes clinical indication, duration review date, route and dose
4. Obtain cultures first
5. Prescribe single dose antibiotics for surgical prophylaxis where antibiotics have been shown to be effective

Then Focus

1. Review the clinical diagnosis and continuing need for antibiotics by 48 hrs and make a clear plan of action – “the antimicrobial prescribing decision”
2. The five antimicrobial prescribing decisions are Stop, Switch IV to oral, Change, Continue and Outpatient parenteral antibiotic therapy [OPAT]
3. It is essential to document the review and subsequent decisions in medical records

The SSTF publication has suite of tools which could be used to evaluate or audit antimicrobial prescribing. Some of the tools are hospital antimicrobial prudent prescribing indicators, audit tool and antibiotic review bundle. These guidelines primarily focus on antibiotic prescribing behaviour.

MINDME strategy was launched by Australian government as a useful reminder tool for all prescribers of antimicrobials. The guidelines include:

1. Use microbiology guided therapy wherever possible

2. Indications for antimicrobial therapy to be evidence based
3. Use narrow spectrum antimicrobials
4. Dosage individualized to the patient, site and type of infection
5. Minimize duration of therapy
6. Use oral therapy wherever appropriate

Gap AMR and nap AMR⁶

In 2015 WHO at international level has initiated global action plan to combat AMR and India at national level has initiated National AMR action plan in 2017. The goal is to ensure successful treatment and prevention of infectious diseases with effective and safe medicines that are quality assured, used in a responsible way, and accessible to all in need of them. The main objectives are to improve awareness and understanding of AMR, strengthen knowledge through surveillance and research, reduce the incidence of infection, optimize the use of antimicrobials in health, animal and food sectors and develop the economic case for sustainable investment that takes into account the need of all countries and increase investment in developing new medicines, vaccines and diagnostic tools

National Networks

At present there are 4 major networks constructed by GOI as an initiative to implement various strategies like AMR surveillance, infection control and AMSP. The goal being fight for prevention of emergence of AMR. The first two projects are CDC/ICMR project on infection control and ICMR project on AMSP.

The details of the project and responsibilities are mentioned below in table 3.

Table 3:

National network	Responsibility	Objective
National program for containment of AMR	NCDC	AMR surveillance
AMR surveillance research	ICMR	AMR surveillance and research
Capacity building and strengthening of hospital infection control to detect and prevent AMR in india	ICMR /CDC India	HAI surveillance
Initiating AMSP in hospitals in India	ICMR	AMSP

CDC/ICMR Project on Infection Control

Is for strengthening and capacity building of hospital infection control team to detect and prevent AMR in India. This program was initiated by ICMR in 2016-17 to implement HICP in India with the aim & objectives to:

1. Create centre of excellence for training, detection and surveillance of AMR and hospital acquired infections in India
2. Establish and implement a sustainable process for external validation of AMR laboratory capabilities for

organisms of importance to health care system and public health

3. Link AMR infection control and data systems assessments to systematic strengthening of laboratory capacity which will include ongoing quality assurance process to ensure and maximize sustainability
4. Develop a uniform system of HAI surveillance in India
5. Initiate and support the expansion of prospective surveillance for HAI's that is linked to infection control assessments and quality assured AMR laboratory data
6. Create a trained workforce in India to curtail the threat of HAI's, AMR and outbreaks

ICMR project on AMSP

This program was initiated by ICMR in 2018 to facilitate health care institutions across India for implementing AMSP. Currently the project is being undertaken by 20 health care institutes 12 government and 8 private from various states and union territories. The Aim and objectives are as follows:

1. Creating antibiograms for hospitals
2. Creating antibiotic policy based on the hospital antibiogram including surgical prophylaxis
3. Carry out culture of cultures point prevalence studies 1 day in 3 months
4. Carry out antibiotic consumption in ICU's using ICMR tool DOT/DDD
5. Initiate audit for carbapenems and polymyxin prescription in ICU
6. Carry out workshops for education

Jaipur Declaration of AMR⁵

The health ministers of all the states of the WHO South East Asia region [SEAR] adopted Jaipur declaration on AMR at the 28th meeting on 6th Sep. 2011. Key points of which are, the countries should show holistic and multidisciplinary approach towards prevention and containment of AMR to improve public health. The national government must accord utmost priority to the problem to preserve the efficacy of antimicrobials in the fight against microbial disease

Chennai- Roadmap to tackle Challenge of AMR²

A joint meeting held on 24th august 2012 by various medical societies of India to formulate a roadmap to tackle AMR from Indian perspective was conducted

Key points of which are, the representatives from several medical societies of India, eminent policy makers from central and state governments, representatives from WHO, national accreditation board of hospitals [NABH], Medical Council of India [MCI], Drug controller general of India [DGCI] and Indian council of medical research ICMR along with six international experts attended the meeting. The meeting aimed at not to look back but rather to look forward and make joint efforts to tackle the menace of AMR

Future of AMSP in India

The ministry of health MOH is responsible for taking urgent initiatives to implement and monitor control rising AMR. Following are the requirements for the same:

1. Tailored AMSP- we need an implementable AMSP not a perfect policy. Best is to introduce step by step regulations on antibiotic usage, concentrate on high end antibiotics first then slowly extend to second- and first-line drugs
2. DGCI – the drug control general of India need to formulate and implement a policy on rational use of antimicrobials in the country both in hospitals and over the counters after consultation with stake holders and experts in the field
3. H1 drugs – The union health ministry has launched regulations on use of H1 drugs as a measure towards awareness campaign. Drugs with REDLINE on the strip the sale has to be strictly monitored to avoid over the counter sale
4. HICC- structured and fully functional HICC must be mandatory in all hospitals. Regulatory authorities and accreditation boards to insist on it during the licensing and accreditation process. State government should initiate organizing state and regional HICC's.
5. National task force has to be appointed to oversee implementation – the officers appointed for the purpose to be trained to improvise and bring uniformity
6. Fund – the central and state government must provide funds for manpower, improved diagnostics and information technology
7. Answerability – there should be a chain of unidirectional monitoring of implementation of activities so that everyone in the chain will compile to the policy and produce maximum outcome
8. NGOS- national and international organizations play a pivotal role in disseminating public information and come forward to fund research in infectious diseases
9. NABH – to insist on implementation of HICC and AMSP in all hospitals otherwise the licensing to be cancelled
10. ICMR – must broaden the scope from public sector to even private institutions for AMR. HAI and AMSP surveillance networks. Provide funds for research on AMR
11. WHO India – the Indian division should setup interaction with the government related to drug resistance, antibiotic policy and infection control
12. MCI – need to make necessary curriculum changes and implement structured training on AMSP at UG and PG level
13. Improved laboratory stewardship – there is an urgent need to upgrade microbiology laboratory across the country. Hospitals should have a good quality microbiology laboratory and willing to outsource in

case of absence. Emergency microbiology laboratory to be made compulsory

14. Increased awareness and education through medical journals and educational forums to focus more on AMR & AMSP
15. Public awareness through electronic and print mass media
16. Animal use – control of antibiotic use in animals and poultry through appropriate legislation
17. Research – GOI should look for promotion of research on new antimicrobials and AMSP

Therefore, with so many strategies in place, planned and implemented by experts to curb AMR, the only task left is to adherence to the strategies and monitor from time to time both implementation and outcome of AMSP. Analyse the data generated and modify the strategies as per the need.

Note – readers interested in further details, please follow the links mentioned below in references

Conflict of Interest: None.

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