Review Article

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INFLUENCE OF WHO/INRUD PRESCRIBING INDICATORS IN ANTIBIOTIC RESISTANCE PATTERN- A REVIEW

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ABSTRACT Antibiotics are crucial drugs in treating infections. India is the world's largest consumer of antibiotics and it is the place of origin for many multidrug-resistant organisms. Massive and irrational use of it has resulted in the evolution of microbes at a faster stride. The rising rate of resistance is a significant problem in every field including oncology and surgery. Treating multidrug-resistant infection poses a critical clinical challenge to physicians. Institutional variabilities in the resistance pattern made it more difficult. Resistance to one antibiotic lead to immense use of others resulting in collateral damage. Alternatives in our hand are very limited and we should be very vigilant. Infection control and Antimicrobial stewardship programs are the keystones in controlling the situation. Prescribers also must be made aware of reasonable prescribing habit as per WHO program on rational drug use. In this review, we focused on antibiotic resistance pattern in India at the field of surgery and oncology.

KEYWORDS : : Cancer, Infection, Antimicrobial Resistance, Multi-drug Resistance, Surgical Prophylaxis, Neutropenia, Antibiotics.

INTRODUCTION

Antibiotics are medicines used to prevent and treat bacterial infections[1]. It saved millions of life and played a crucial role in the development of modern medicine for decades. The growing rate of resistance and no new discoveries of antibiotics have created a crisis in the field of medicine. India is the world's largest consumer of antibiotics[2] . It is estimated that more than 50% antimicrobial use in hospitals are irrational, and by 2050, about 2 million people in India may die of Antimicrobial Resistance (AMR)[3].

Even with the existence of many national, international and individual institutional guidelines, the consumption of antibiotics are increasing tremendously for both therapeutic and non-therapeutic purposes. According to a study conducted by Sakthivel Selvaraj and others[4], 19 million antibiotic prescriptions were dispensed in the private sector. Majority of the antibiotic prescriptions were dispensed for acute upper respiratory infections, cough, acute nasopharyngitis and acute pharyngitis. Sadly these are mostly viral in origin and treating these self-limited diseases with antibiotic is absurd according to standard guidelines[5]

The World Health Organisation (WHO) defines appropriate antimicrobial use as the "cost effective use of antimicrobials which maximises clinical therapeutic effect whilst minimising drug-related toxicity and development of antimicrobial resistance"[6]. But the scenario in India is very opposite and is the place of origin for many multi drug-resistant infections (ex: carbapenem-resistant gram-negative Enterobacteriaceae)[2]

Emergence of resistance to antimicrobials has become a major challenge in many areas including oncology and surgery. Development of resistance to Beta-lactam antibiotics increased the consumption of carbapenem and other combinations, which in turn is facing consequential damages. Colistin resistance also is reported from many parts of India which is a significant concern[7, 8, 9, 10]. Our choice in hand is diminishing and we should be very vigilant. Discovery of novel antibiotic wouldn't even help if the irrational habit prevails.

AMR is inevitable[11] and irreversible[12] but its rate can be controlled, thereby reducing mortality, length of hospital stay and out of pocket spending.

In this review, we studied the most recent articles on the antimicrobial resistance pattern in the field of surgery and oncology. We conducted a comprehensive search of the literature in Google Scholar and PubMed using the following keywords: Cancer, Infection, Antimicrobial Resistance, Multidrug Resistance, Susceptibility, Surgical Prophylaxis, Neutropenia, Antibiotics, and WHO/INRUD etc.

SURGICAL PROPHYLAXIS

Surgical site infection (SSI) is a most common cause of post-surgical complication accounting to a high morbidity and mortality rates[13]. Antimicrobial prophylaxis plays an important role in controlling SSI, but the fear of developing one lead to its overuse. Another major false belief is that multiple antibiotics for a longer duration produce better results. It was observed that many surgeons prefer to use a single antibiotic for clean wounds and a combination of 2 or 3 for contaminated ones at a longer duration than recommended by standard guidelines[14]. In many Indian studies, it was observed that antibiotics were prescribed not in accordance with international, Indian or even institutional guidelines[15]. Appropriate use of prophylaxis is crucial to prevent SSI, but irrational use in fear of infection also causes catastrophic damages. This area is less considered in antimicrobial stewardship and hence mostly misused.

Guidelines On Antibiotic Prophylaxis In Surgery

A. Type of Wound : Antimicrobial prophylaxis is not recommended for some clean surgical procedures[16].

B. Selection of Antibiotic[16,17]

Antibiotic must be selected considering the following;

1. Surgical procedure
2. Probable microorganism involved
3. Local antimicrobial resistance pattern
4. Allergies of patient
5. Safety

C. Pre-Operative Screening and Decolonisation[16,18]

- Screening for Staphylococcus aureus (S.aureus) prior to surgery and decolonising it has shown a reduction in rate of SSI. Swabs collected from nasal, wounds, groins, pharynx can be used for the surveillance.
- This technique can be used to identify Methicillin-resistant Staphylococcus aureus (MRSA)
- Carriers of MRSA can be treated with intranasal mupirocin ointment (especially for cardiothoracic surgery), considering the susceptibility of organism to it.

D. Pre-Operative Antibiotic Prophylaxis

- Administer Surgical antimicrobial prophylaxis (SAP) prior to the surgical incision when indicated (depending on the type of

operation) within 60 or 120 min considering the half-life of the antibiotic.[16,17,18]

- Drugs with short half-life must be administered near to the time of incision.[18]
- Administration of antibiotic more than an hour prior to surgery should be dissuaded.[19]
- Antimicrobials must also be given to those who already receiving it for any remote infections to avoid sub therapeutic serum and tissue levels throughout the surgery.
- If an appropriate antibiotic is given, a single dose prior to 60 minutes of incision would be sufficient[16].
- For patients with indwelling tubes or drains, prophylactic agents should cover for the organism found in these tubes[16].

E. Intra-Operative Prophylaxis

- If the duration of the procedure exceeds 2 half-lives of the drug or if excessive blood loss (>1500ml) are observed during the procedure, intraoperative re-dosing can be considered.[17]
- Re-Dosing must not be considered in the presence of any factors prolonging half-life of the drug (ex: renal insufficiency)[16].

F. Post-Operative Prophylaxis

- Do not prolong surgical antibiotic prophylaxis after completion of the Operation[17,18]
- if necessary, extra dosing should be considered only after twice the half-life of the antibiotic has passed, since the initial preoperative dose[18].
- Duration of antimicrobial prophylaxis should be <24 h (within 48 h for cardiothoracic surgery) for surgical procedures[17]

G. Dosing

- Weight based dosing has to be done for paediatric patients but is not preferred for adults.[16]
- In obese adult patients. the weight has to be taken into consideration.[20]
- In obese patients weighing above 20% of their ideal body weight(IBW), the dose of aminoglycoside must be calculated using the formula;

IBW+ 40% (actual body weight-IBW)[20]

Table 1: Antibiotic Resistance Pattern In Post - Surgery Patients From Different Indian Studies Since – 2010

	[21] Sahu M K et al	[22] Ranjan K P et al	[23] Pramila M et al	[24] Rizvi M et al	[25] Bhardwaj N et al	[26] Govinda Swami et al	[27] Malakar A et al
Study Period	2013 – 2014	2010 – 2013	2018	2013	2013 – 2016	2013-2017	2018 - 2019
Region	New Delhi	Madhya Pradesh	Tamil Nadu	Uttar Pradesh	New Delhi	New Delhi	Andaman & Nicobar
Type of Surgery	Cardiovascular Surgery	All Surgeries	All Surgeries	All Surgeries	All Surgeries	Craniotomy	Obstetrics & Gynaecology
Resistance To:							
Gram Positive							
MRSA	NM	27.96 %	NM	40 %	NM	60 %	44.86 %
Vancomycin	0 %	0 %	0 %	0 %	NM	0 %	0 %
Linezolid	71 %	0 %	0 %	NM	NM	0%	0 %
Gram Negative							
Colistin							
Acinetobacter	18.3 %	NM	NM	NM	NM	0 %	NM
Klebsiella	4 %	NM	NM	NM	NM	0 %	NM
Pseudomonas	2 %	NM	NM	NM	NM	0 %	NM
E. Coli	28%	NM	NM	NM	NM	0 %	NM
Tigecycline							
Acinetobacter	64.2 %	NM	NM	NM	22 %	12 %	NM
Klebsiella	10 %	NM	NM	NM	12 %	6 %	NM
Pseudomonas	7 %	NM	NM	NM	66 %	21 %	NM
E.coli	25 %	NM	NM	NM	7 %	NM	NM
Piperacillin/ Tazobactam							
Acinetobacter	62.9 %	NM	NM	NM	95 %	97 %	NM
Klebsiella	77 %	NM	NM	NM	76 %	94 %	12.5 %
Pseudomonas	36 %	NM	NM	NM	1 %	45 %	0 %
E.coli	52 %	NM	NM	NM	57 %	50 %	8.43 %
Carbapenem (I/M)							
Acinetobacter	86.1 / 81.9	NM	NM	NM	92 / NM	85/83	NM
Klebsiella	90 / 86	NM	40 / NM	NM	54 / NM	57 / 62	25 /NM
Pseudomonas	96 / 84	NM	25 / NM	NM	53 / NM	53 / 49	22.83 / NM
E.coli	85 / 72	NM	NM	NM	19 / NM	29 / 33	0 / NM

* NM : NOT MENTIONED *I/M : IMIPENEM / MEROPENEM

Developments of resistant organisms are very clear from the table 1. Multidrug-resistant (MDR) Acinetobacter is a major concern as treatment substitutes for the organism are few. Resistance to Escherichia coli (E.coli) is far greater compared to global studies. Another major concern is MRSA as it is resistant to methicillin and other alternatives as well. Measures for institutional Surveillance of Surgical site infection is necessary to assess its severity and to take appropriate preventive measures[15].

ANTIBIOTICS IN CANCER

Chemotherapy-induced neutropenia and febrile neutropenia is common complications seen in patients receiving cytotoxic drugs. Such patients are more prone to infections[28]. On an estimate 1 in every 5 cancer patients require antibiotics. Antibiotic resistance hence will threaten the survival of cancer patient to a greater extent. It will push the oncology advancements back to decades and will drastically affect prognosis in cancer patients.

Antibiotic Susceptibility studies carried out on febrile neutropenia patients in India since 2010 is portrayed in the table 2.

Table 2: Antibiotic Resistance Pattern In Cancer Patients From Different Indian Studies Since – 2010

	[29] Bhat V et al	[30] Nazneen et al	[31] Babu KG et al	[32] Rani DR et al	[33] Garg VK et al	[34] Singhal T et al	[35] Singh R et al
Study Period	2013	2016	2012 - 2014	2016	2016-2017	2009 - 2014	2013
Region	Mumbai	Mumbai	Bengaluru	Hyderabad	Mumbai	Maharashtra	Delhi
Resistance To							
Gram Positive							
MRSA	41.67 %	17.64 %	31 %	15 %	NM	50 %	35%
Vancomycin	0 %	0 %	0 %	NM	26 % Enterococci	0 %	Enterococci : Respiratory Isolates – 25% Blood -15% Staphylococci -0%
Gram Negative							
Colistin	Positive in Acinetobacter, Klebsiella	NM	A.baumanii-30% P.aeruginosa-30%	0 %	0 %	0 %	0 %
Carbapenem Resistant							
Pseudomonas	NM	25 %	NM	23 %	55 %	30 %	35%
Klebsiella	> 50%	25 %	40 %	45 %	60 %	30 %	6 %
Acinetobacter	NM	22 %	40 %	28 %	35 %	30 %	80 %
E. Coli	NM	NM	NM	34 %	45 %	30%	2 %

Growing resistance to carbapenem severely limits antibiotic options and is a key concern. Colistin is the last resort and its resistance is not

very distant. These resistance patterns do definitely call for rational and judicious use of antibiotic. Comparing these results to international studies [36, 37, 38, 39, 40, 41, 42] reveals that India is at a faster pace towards resistance.

CHOOSING EMPIRICAL ANTIBIOTIC THERAPY

According to published literatures, antimicrobial sensitivity pattern varies substantially over many decades. Early initiation of empiric antibiotic is very important in febrile neutropenia and the choice of antibiotic is crucial at this era of high resistance.

Despite international guidelines[43,44] recommends using fluoroquinolone, it is not applicable in Indian scenario due to its resistance. Indian guidelines recommend using a combination of aminoglycoside and anti-pseudomonal beta-lactams as an empirical choice[45]. Adoption of these guidelines for an individual cancer unit poses many challenges. So a preferred method is to carry out antimicrobial susceptibility study in that institution and to prepare an institutional guideline.

The following factors have to be considered to choose an appropriate empirical antibiotic;

- Patient history
- Signs and symptoms
- Probable microorganism involved
- Allergies
- Recent antibiotic used
- Microbiological and resistance pattern in the locality.

WHO/INRUD PRESCRIBING INDICATORS

Vital step to restrict irrational drug use is to identify the type, volume and the reasons for irrational use of drugs. A set of indicators to measure the performance of healthcare professionals with respect to drug utilization is given out by WHO in coalition with International Network of rational use of drug(INRUD)[46]. These indicators are categorized into prescribing, patient care and facility-specific indicators referred to as core drug use indicators (Table 3).

Table 3: WHO / Inrud Core Indicators

CORE DRUG INDICATORS	PURPOSE	CALCULATION
A. PRESCRIBING INDICATORS		
Average number of drugs prescribed	To evaluate polypharmacy	Total number of drugs prescribed ÷ Number of encounters surveyed
Percentage of drugs prescribed by generic name	To compute the tendency to prescribe In generic name	(Number of drugs prescribed in generic name ÷ Total number of drugs prescribed.) X 100
Percentage of encounters with an Antibiotic prescribed	To measure the degree of use	(Number of patient prescribed with an antibiotic or injection ÷ Total number of encounters surveyed) x 100
Percentage of encounters with an injection Prescribed	To measure the degree of use	(Number of patient prescribed with an antibiotic or injection ÷ Total number of encounters surveyed) x 100
Percentage of drugs prescribed from Essential Drug List or formulary	To measure degree of practices in accordance national drug policy	(Number of products prescribed from EDL Or formulary ÷ Total products prescribed) × 100
B. PATIENT CARE INDICATORS		
Average consultation time	To measure to time spend by health Professional with patient	Total time for a series of consultation ÷ Number of consultation
Average dispensing time	To measure the amount of time the person Dispensing drug spends with the patient.	Total time spend for dispensing to a series of Patients ÷ Total number of patients
Percentage of drugs actually dispensed	To measure the extent to which health facilities are able to provide drugs prescribed	(Number of drugs dispensed at the health Facility ÷ Total number of drugs prescribed) ×100
Percentage of drugs adequately labelled	To measure the extent to which the dispenser records the necessary Information on the dispensed drug packages.	(Number of drug packets with at least patient Name, drug name, and when to take the Medicine ÷ total prescriptions dispensed) ×100
Patient knowledge of correct dosage	To measure the effectiveness of dosage schedule information given to patient.	(Number of patients who can adequately report The dosage schedule ÷ total interviews) × 100
C. HEALTH FACILITY INDICATOR		
Availability of copy of essential drug list	To indicate the availability of copies of National essential drugs list or formulary at Health facilities	YES/NO per facility
Availability of key drug	To measure the availability of key drugs for the treatment of some common Health Problems.	(Actual number of specified product in stock ÷ Total number of drugs on check list) × 100

WHO/INRUD indicators are used in many published literatures to evaluate good prescribing and dispensing qualities of Antibiotics. Polypharmacy was a major issue in majority of Indian studies.[47,48,49,50,51] Many reported the prescription of Fixed dose combination (FDC) of antibiotics having the same antimicrobial spectrum which cannot be justified (ex; amoxicillin and cloxacillin) and it can be a significant reason for developing resistance[52,47,53]

It is also observed that standard practice of enforcing institutional guidelines and essential drug list is rarely practiced after implementing it[52, 47, 48, 49, 54, 55] . A guideline recommends stopping the surgical prophylaxis within 24 hours after surgery except for cardiothoracic surgery where it must be 48 hours. But in contradiction, antibiotics are prescribed 2 to 5 days after surgery [55,56,2]Administering antibiotic more than 24 hours before surgery also was not uncommon[56].

Another major concern is usage of parenteral antibiotics[48, 49, 50, 51, 53, 57, 58] Injectable upswings patients morbidity and contradicts WHO recommended prescribing policies. WHO 2002 also states that it may increase the risk of blood borne diseases[55].

Broad-spectrum antibiotics were extensively misused in immunocompromised and surgery patients [47, 48, 53, 58]. More than one broad spectrum antibiotic having similar spectrum was found to be prescribed for prophylaxis.

Evidence suggests that most common infections can be successfully treated with a single antibiotic. Combinations are recommended for longer duration only for severe complicated infections. But literature points out that multiple combinations of antibiotics have been prescribed for the purpose of prophylaxis rather than definitive treatment without any evidence.[49, 50, 51, 53, 57]. Irrational use of multiple antibiotics is associated with increased risk of development of super infections and augmented toxicity and high cost

CONCLUSION

An alarming increase in antimicrobial resistance is seen in cancer and surgery patients. Choosing an empiric antibiotic in both surgery and cancer patients must be based on many factors including the patient's status and regional resistance pattern. Treating infections due to multidrug-resistant organism is difficult since the options are minimal. Development of resistance to Colistin is a serious concern. Over prescribing, using parental over oral and irrational FDC were major threats. Enforcing a precisely regulated antimicrobial stewardship and infection control programs are the need for the hour. Misusers must be strictly punished and a notion of the importance of antibiotics must be instilled in every health professionals. Prescribers must be made aware of reasonable prescribing habit as per WHO program on rational drug use. Occasional surveillance using WHO/INRUD indicators are of help to assess the institutional scenario and may provide a scope of improvement. The idea of the post-antibiotic era is not too far if the present condition continues.

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