

Antimicrobials Overuse in COVID-19: A Silent Pandemic of Antimicrobial Resistance

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Abstract

The COVID-19 epidemic has presented many treatment challenges to physicians due to the lack of specific effective medicines. The COVID-19 pandemic is also witnessing irrational antibiotic use. The aggressive use of several antibiotics for treatment of COVID-19, and its complications may lead to another pandemic of Antimicrobial Resistance (AMR). Limiting unnecessary antibiotic use in viral infections, like COVID-19, should be emphasized in antimicrobial stewardship programs.

Keywords: Antimicrobial resistance, AMR, Covid-19 pandemic, irrational prescribing, antibiotic stewardship

Introduction

COVID-19 has been the century's worst pandemic. In India, as of May 11 2021, about 2.3 crore people have been infected, 1.96 crores have recovered and 2.5 lakhs have died. The daily reported cases have been hovering around 4 lakhs.^[1] Though there has been some relief for the past few days, due to some plateauing, yet, the threat of a third wave looms large over the country. This emphasizes that, the Indian healthcare system should continue to augment its health care infrastructure, be vigilant about mutations through enhanced genomic surveillance, intensify research in developing new drugs and ensure that the vaccine reaches every part of the country to immunize each eligible citizen.

The situation warrants a multifaceted approach for dealing with the pandemic. Continued efforts on creating awareness, ensuring complete adherence of COVID appropriate behaviour by every citizen, and a need for physicians, policy makers and regulators to maintain strict compliance and rational use of drugs in the management of mild, moderate and severe COVID cases.

COVID-19 is a disease caused by a new Coronavirus called the SARS-CoV-2. Since WHO first learned of this on 31st Dec 2019, following a report of cluster viral pneumonia in Wuhan, China, the disease has been named as Coronavirus Disease 19 (COVID-19). Initially, it was found to mainly affect the elderly and those with co-morbidities like diabetes, respirato-

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ry diseases, cardiovascular diseases, etc. but of late, a large number of young adults and adolescents are also getting affected.^[2]

Though RT-PCR is the gold standard test, as a testing strategy, ICMR recommends increased use of rapid antigen test (RATs), for screening of COVID-19 while the confirmatory diagnosis of a negative RAT in a symptomatic person is based on RT-PCR. Despite innovations and development of indigenous antigen detection kits, and RT-PCR methods, only a fraction of the mildly symptomatic and asymptomatic population actually gets tested.

The initially described cardinal symptoms of COVID-19, i.e., fever, sore throat, dry cough, loss of smell/taste, fatigue and difficulty in breathing, soon widened its canvass to manifest a diverse symptomatology including nasal congestion, red-eye, headache, muscle or joint pain, skin rashes, nausea, vomiting, diarrhoea, irritability, and neurological symptoms. One of the major issues encountered by physicians is the lack of effective and safe treatment options against COVID-19.^[3]

Irrational Antibiotic Prescribing in COVID-19 - a Dangerous Syndrome for Anti-Microbial Resistance

In COVID-19, there is primary involvement of the respiratory system, slowly incapacitating the lungs. The pneumonia is a cause of severe morbidity and mortality. While the second common cause of deaths are cardiovascular events.^[4]

Indian patients, due to low literacy in many parts of the country, and hesitant treatment seeking behaviour, avoid consulting qualified medical practitioners. Instead, they resort to self-medication or consultation from easily accessible chemists. Sometimes they consult friends/ relatives or neighbours who have recently suffered and recovered from COVID-19 infection and behave as self-proclaimed COVID experts.

Easy availability of medicines, without prescription, including, antimicrobial agents is a common phenomenon in rural as well as urban India. Because of hesitancy in declaring oneself as suffering from COVID-19, many patients, go to these chemists rather than consulting a doctor. Most of the times, the chemist readily obliges the patient with a set of drugs which invariably has antipyretic, steroid, proton pump inhibitor and one or two antibiotics.

Anti-microbial agents being very important as life-saving drugs in all infections is a common myth with

many doctors. This arises from a belief that there is a negligible risk from antibiotics, which leads to an unreasonable dependence on antibiotics for the treatment of viral illnesses like COVID-19. The lay man often demands and the wise physician resorts to prescribing empirical antimicrobial agents to almost all COVID-19 patients.

Antimicrobials are justified to treat a secondary infection. However, ironically, most of the times they are prescribed prophylactically. Most commonly prescribed antimicrobial agents in COVID-19 are azithromycin, doxycycline, amoxicillin-clavulanic acid, cephalosporins and fluoroquinolones. In some cases, a higher class of anti-microbial agents are also prescribed empirically such as carbapenems, clindamycin, kanamycin, piperacillin/tazobactam, and meropenem.^[5,6] There is a need to generate data on antimicrobial prescribing trends in COVID-19 in India.

The WHO in its list of essential medicines 2019, has classified antibiotics in three categories, termed as AWaRe (A. Access; B. Watch, and C. Reserve). Category A, 'Access' drugs: these antimicrobials have activity against a wide range of commonly encountered susceptible pathogens. They exhibit lower resistance potential than antibiotics in the other groups. This group includes antibiotics like: amikacin, amoxicillin, amoxicillin + clavulanic acid, ampicillin, benzathine benzylpenicillin, benzylpenicillin, cefazolin, clindamycin, cloxacillin, doxycycline, gentamicin, metronidazole, nitrofurantoin, phenoxymethylpenicillin, procaine benzylpenicillin and sulfamethoxazole + trimethoprim.

Category B, 'Watch' drugs have higher resistance potential and include the highest priority agents among the Critically Important Antimicrobials (CIA) for human use and carry a relatively high risk of bacterial resistance. The list includes antibiotics like: azithromycin, cefixime, cefotaxime, ceftriaxone, cefuroxime, ciprofloxacin, clarithromycin, piperacillin + tazobactam, vancomycin, ceftazidime and meropenem.

The third category C, 'Reserve' drugs are drugs to be used as the last options, for the treatment of multi-drug-resistant organisms. They have a favourable risk-benefit profile and proven activity against "critical pathogens" such as carbapenem resistant Enterobacteriaceae. These pathogens are identified by the WHO as priority pathogen list. The examples are, fosfomycin and linezolid.^[7]

In COVID patients, all categories of drugs A, B or C

are often prescribed irrationally. No antibiotic should be prescribed in COVID-19 patients without strong justification. Category B and C drugs will certainly promote AMR. Without strong justification, if B & C category drugs are prescribed in any situation, it will not only promote AMR, but will also render these precious antibiotics ineffective. Thus, they should be prioritized as key targets of antibiotic stewardship programs and monitoring to preserve their effectiveness. A similar philosophy has been applied in drafting the National List of Essential Medicine (NLEM 2021).

An increase in tele-consultations during the pandemic, has also contributed to irrational and excessive prescribing of antibiotics. With such inappropriate antibiotic prescribing and their unsupervised consumption, there is a high possibility of adverse drug effects and drug interactions.^[8] At the backdrop of empirical management of COVID-19, by irrational use of antimicrobial agents, another deadly pandemic of AMR may get precipitated.

Antimicrobial Resistance: A Growing Menace

Today, AMR is a ticking bomb which is fast assuming the form of a silent pandemic. Alarming figures are showing that, certain bacteria have already achieved a high resistance level to certain antibiotics. Data from WHO guidance document 2017, and 2019 Global Antimicrobial Resistance and Use Surveillance System (GLASS), shows more than 50% resistance to carbapenem (in *Acinetobacter baumannii*); 31% to 50% (in *Pseudomonas aeruginosa*); 8.4% to 92.9% for ciprofloxacin (in *Escherichia coli*), and 4.1% to 79.4% (for *Klebsiella pneumoniae*) in the Indian subcontinent.^[9,10] In another study conducted at a tertiary care hospital in Southern India, 55% of *Enterobacteriaceae* were found to be resistant to 3rd generation cephalosporins due to extended-spectrum beta-lactamases (ESBL), and 53% of *Staph. aureus* were Methicillin-resistant.^[11]

In India, respiratory pathogens have reported high resistance to third-generation cephalosporins (up to 84%) and carbapenems (up to 81%). The majority of the pathogenic organisms reported in patients with COVID-19 are found to be multidrug-resistant (MDR) nosocomial organisms. In a study at a tertiary care hospital in northern India, MDR was found in 60% of isolates. The overall resistance ranged from 9% to 84% amongst all organisms. The highest resistance observed was to amoxicillin / clavulanic acid (84%), followed by levofloxacin (83%), ciprofloxacin (79%), piperacillin / tazobactam (77%), and trimethoprim / sulfamethoxazole (75%). Overall resistance

to third-generation cephalosporins and carbapenems was found to be 64%–69%.^[12] These are worrying figures that need instant action.

Strategies for Combating AMR During COVID-19

Immediate intervention and mitigation strategies should be implemented to ensure strict compliance to clinical treatment guidelines of COVID-19 to limit unnecessary antimicrobial usage, thereby limiting AMR. Enforcement of prohibition of the sale of over-the-counter (OTC) can substantiate this process, ensuring the effectiveness of antimicrobials at the time of need.

Other strategies could be the use of both 'push and pull' mechanisms amongst practitioners for reducing antimicrobial use. The physicians prescribing minimally prescribing antimicrobials should be academically rewarded and recognised. The hospitals needing and using lesser antimicrobial agents should be suitably rewarded in the hospital accreditation system. The physicians irrationally prescribing, misusing, using a short cut therapy or obliging patients illegitimate request should be sent for compulsory antibiotic stewardship programme.

In India, the guideline on clinical management of COVID-19 should also include a specific recommendation about rational antibiotic use. Antibiotic therapy or prophylaxis for patients with mild or moderate COVID-19 is not recommended, unless there is a concurrent bacterial infection. In severe hospitalized patients, intravenous antibiotics can be justified due to immunosuppression resulting from the disease itself and steroid use, which are high-risk factors for secondary bacterial infections.^[13]

The WHO guidelines recommends empiric antibiotic treatment on clinical diagnosis in certain conditions like, Community-acquired pneumonia (CAP), Hospital-acquired (nosocomial) pneumonia (HAP), Sepsis in COVID-19 with pneumonia and Severe pneumonia (SARI).^[14,15] No routine prophylactic use of antibiotics should be practiced, and a strict regimen should be followed when prescribing antimicrobials, to avoid rampant usage.

Conclusion

We are passing through a critical stage of the COVID-19 pandemic, for which the scientific community is still struggling to develop clinically effective medications. Increased prescribing of antimicrobials, without first validating their effectiveness in treating COVID-19 cases, might flare up antimicrobial re-

sistance (AMR).

Let us not end up with another dreadful pandemic, where no effective antibiotic will be available for the treatment of even common bacterial infections and we will be in a more helpless state than what we are in today. Concerted efforts on multiple fronts will save us from another possible catastrophe of AMR, while we are still battling with COVID-19.

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