

Antimicrobial Agent Utilization Pattern among Footballers in Eastern India: Classifying Using Access, Watch, and Reserve

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ABSTRACT

Background: Vigorous training, practice-related injuries coupled with inadequate resting time puts athletes at risk of bacterial infections, which begets the use of antimicrobial agents. The present study was planned to observe and assess the antimicrobial utilization among footballers from various professional clubs in Eastern India.

Materials and methods: A cross-sectional observational study was conducted to probe the professional footballers regarding the information on their AMA usage during the last 6 months. Data like name of AMAs, whether prescribed by physicians or taken up as over-the-counter (OTC) drugs, indications for consuming AMAs and consuming AMA for the recommended duration or not were taken into consideration. To assess the AMA utilization pattern, prescriptions and medical records available in respective clubs were thoroughly studied. Antimicrobial agent utilization was assessed based on AWaRe classification as laid down by the WHO.

Results: Azithromycin (19.1%), ofloxacin plus ornidazole fixed-dose combination (17.3%) and amoxicillin plus clavulanic acid fixed-dose combination (11.1%) were the top three antibiotics consumed by them. Access, Watch, and Reserve (AWaRe) classification conferred 74% to be under "Watch" group, 22% "Access" and 4% "Reserve." 62% ($n = 68$) of the total AMA consumers were prescribed an AMA, with a sore throat, upper and lower respiratory tract infection, effusion in the joint, cellulitis, prophylactic use in case of cut injury, loose motion, enteric fever, and skin infections being the common indications. And 71% of the AMA users were found not completing the AMA therapy as per the recommended/ advised dosage schedule and duration.

Conclusion: The knowledge on completing the recommended AMA course requires effective information dissemination. Antimicrobial agent prescribing pattern seen in this study revealed a high chance of development of resistance. Application of knowledge and principles of AWaRe classification thus need to be followed strictly by practitioners.

Keywords: Antimicrobial agents, AWaRe classification, Eastern India, Footballers.

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INTRODUCTION

Antimicrobial agents (AMAs) are defined as natural or synthetic products, which inhibit the growth and multiplication or produce a killing effect on living microorganisms. They act as a ligand to specific protein structures present in microorganisms.¹ The development of AMA represents an important advancement in the field of therapeutics. Overuse of antibiotics, irrational prescribing, ease of availability of over-the-counter (OTC) AMA, and excessive agricultural and animal use have endangered us with the threat of antimicrobial resistance.² Multidrug-resistant acinetobacter, drug-resistant *Campylobacter*, fluconazole-resistant *Candida*, extended spectrum beta-lactamase-producing enterobacteriaceae (ESBLs), vancomycin-resistant enterococci (VRE), multidrug-resistant *Pseudomonas aeruginosa*, drug-resistant nontyphoidal *Salmonella*, drug-resistant *Salmonella typhimurium*, drug-resistant *Shigella*, methicillin-resistant *Staphylococcus aureus* (MRSA), drug-resistant *Streptococcus pneumoniae* and drug-resistant tuberculosis appear as serious threats to humanity.³ This problem is aggravated by challenges like a smaller number of new antibiotic developments in recent years. In this background, it is really important to understand the pattern of AMAs in community.

Drug utilization studies have the objective to understand the marketing, distribution, prescription, and the use of drugs in society, with special importance given to consequences in medical, social, and economic sectors.⁴ It is very important to

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know the utilization pattern of AMAs as this would guide us regarding the execution of necessary future steps. Access, Watch, and Reserve classifies antibiotics into three stewardship groups: Access, Watch, and Reserve, to emphasize the importance of their optimal uses and potential for antimicrobial resistance.

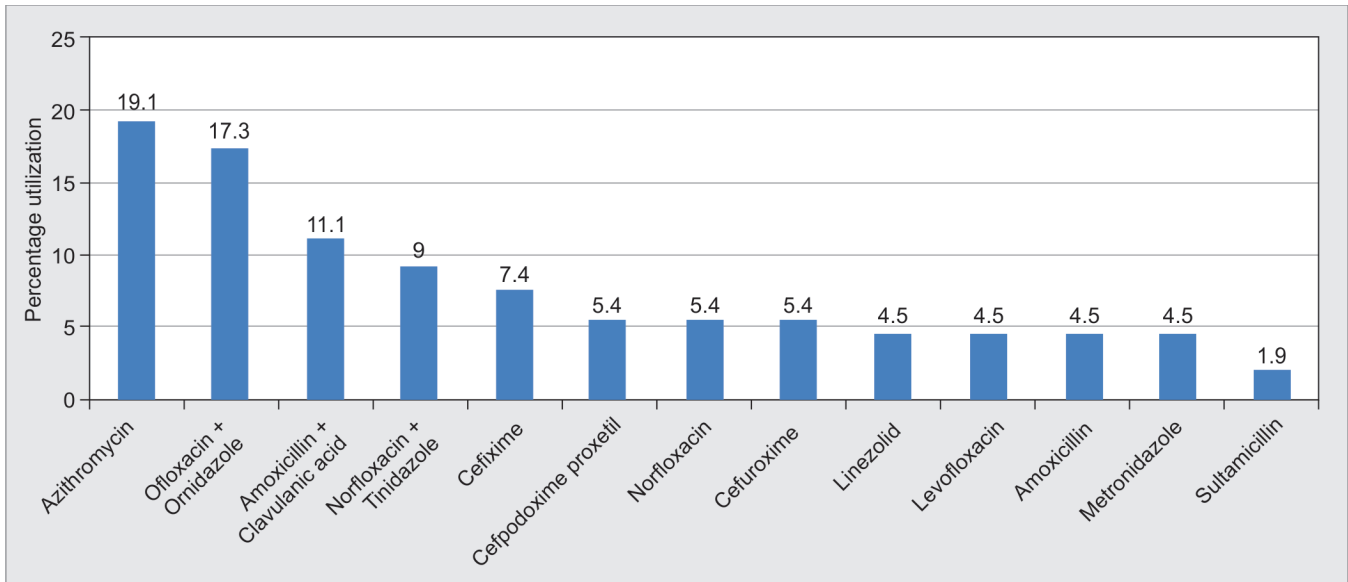


Fig. 1: Antimicrobial utilization spectra among the AMA users

This classification is intended to be used as a tool for countries to better support antibiotic monitoring and stewardship activities. Antibiotics need to be used for bacterial infections in athletes. As athletes need vigorous training, and resting time in them is often quite inadequate, they are at risk of bacterial infections. There is also a high chance of transmission of infection among athletes as they often need to stay in a group. Travel to different places and exposure to different sources of food due to their professional activities, which would render them more vulnerable to infections. Injuries during practices and games may require prescription of antibiotics. Antibiotic usage may result in adverse effects, such as tendon injuries, cardiac arrhythmias, diarrhea, photosensitivity, cartilage issues, and decreased performance.⁵ The present study was planned to observe and assess the antimicrobial utilization among footballers from various professional clubs in Eastern India.

MATERIALS AND METHODS

A cross-sectional observational study was done among footballers from 28 different professional clubs in Eastern India. Permission from the Institutional Ethics Committee was obtained before the commencement of the study. Relevant permission was sought from the professional football clubs for conducting the study on their players. From October 2023 to January 2024, the study was conducted among 650 footballers, who gave consent for participation. Among them, 110 were taking AMAs, and were asked for the information on their AMA usage during the last 6 months. Data like the name of AMAs, whether prescribed by physicians or taken up as OTC drugs, indication for consuming AMAs and consuming AMA for the recommended duration or not were taken into considerations. To assess AMA utilization pattern prescriptions and medical records available in respective clubs were thoroughly studied. Antimicrobial agent utilization was assessed based on AWARe classification as laid down by WHO.

Data collected was checked for completeness and then statistically analyzed. Descriptive data was represented as mean or percentages wherever applicable. All statistical analysis for various measures was performed using Microsoft Excel.

Access	Watch	Reserve
<ul style="list-style-type: none"> • Amoxicillin plus clavulanic acid (12) • Amoxicillin (5) • Metronidazole (5) • Sultamicillin (2) 	<ul style="list-style-type: none"> • Azithromycin (21) • Ofloxacin plus ornidazole (19) • Norfloxacin plus tinidazole (10) • Cefixime (8) • Cefuroxime proxetil (6) • Norfloxacin (6) • Cefuroxime (6) • Levofloxacin (5) 	<ul style="list-style-type: none"> • Linezolid (5)

Fig. 2: AWARe classification of the AMA used

RESULTS

Total study population consisted of 650 male footballers from different professional clubs in Eastern India. And 110 footballers were exposed to antibiotics. Azithromycin (19.1%), ofloxacin plus ornidazole fixed-dose combination (17.3%), and amoxicillin plus clavulanic acid fixed-dose combination (11.1%) were the top three antibiotics consumed by them (Fig. 1).

Classifying AMA as per AWARe classification, it was observed that 74% were taking “Watch” Category AMA, while “Access” category AMA was being consumed by 22% of users and 4% were on “Reserve” Category AMA (Fig. 2).

About 62% (n = 68) of the total AMA consumers were prescribed an AMA, while 38% got it OTC. Among the antibiotics prescribed by physicians, sore throat, upper and lower respiratory tract infection, effusion in joints, cellulitis, prophylactic use in case of cut injury, loose motion, enteric fever, and skin infections were the common indications. A few footballers have prescribed azithromycin (3 in number) and amoxicillin plus clavulanic acid fixed-dose combination (6 in number) due to fever without diagnosing the etiology. The various indications necessitating AMA use have been tabulated in Table 1.

However, non-adherence to the recommended dosage schedule and duration with regard to AMA therapy has been a cause of concern in fighting antimicrobial resistance worldwide.

Table 1: Indications necessitating AMA usage

AMA	Indication	Number of patients prescribed (N = 68)
Azithromycin	Sore throat	7
	Enteric fever	3
	Undiagnosed fever	3
Ofloxacin plus Ornidazole	Loose motion	2
	Acute bacillary dysentery	2
Levofloxacin	Sore throat, cough	3
	Lower respiratory tract infection (CAP)	2
Amoxicillin + Clavulanic acid	Undiagnosed fever	6
	Prophylaxis for cut injury (after suture)	4
Norfloxacin + Tinidazole	Loose motion	2
	Acute bacillary dysentery	2
Cefixime	Upper respiratory tract infection	6
	Lower respiratory tract infection	2
Amoxicillin	Upper respiratory tract infection	5
Cefuroxime	Effusion in knee joint following injury	6
Sultamicillin	Skin infection	2
Linezolid	Cellulitis	5
Cefpodoxime proxetil	Lower respiratory tract infection	6

Table 2: Non-compliance to AMA therapy

Category of AMA	AMA users who did not complete the therapy [n (%)]
Fluoroquinolone	40 (36.4)
Beta-lactam	39 (36)
Macrolide	21 (19.1)
Oxazolidinones	05 (4.5)
Imidazoles	34 (30.9)

In our study population, 71% ($n = 78$) of the AMA users were found not completing the AMA therapy as per the recommended/advised dosage schedule and duration (Table 2). Fluoroquinolone (36.4%) and beta-lactam (36%) AMAs were most commonly taken by them followed by macrolide (19.1%).

DISCUSSION

Unfortunately, it is true that AMAs are vastly overprescribed. Getting these antibiotics OTC facilitates the development of resistance. There are a few important considerations that need to be emphasized before initiation of an AMA. Clinical findings are important tools to start antibiotics and sometimes it is also important to consider whether we can wait until there is positive clinical or laboratory evidence. It is always appropriate to collect clinical specimens for further investigations to establish microbiologic evidence which would guide AMA selection in the future. Time and cost burden could be an issue against this step many times, but before initiating AMA it is really important to identify the likely etiologic microorganism for the patient's disease.

Also, it is our responsibility to take appropriate protective measures for prevention of exposures from index cases and to limiting secondary cases. Timely diagnosis, isolation, and targeted therapy would help in this regard and limit unnecessary overuse of AMA in other individuals. It is also important to consider evidence-based medicine while choosing an AMA for a specific patient population.⁶

In our study, it was shown that AMAs like azithromycin, amoxicillin–clavulanic acid fixed-dose combination, ofloxacin–ornidazole fixed-dose combination drugs were used frequently without compelling indications. Over-the-counter AMAs were available and consumed by more than one-third of the study population. This information is very challenging, which requires urgent attention and regulatory involvement. It is the responsibility of the management of professional football teams to educate footballers regarding this important information that AMA should not be considered for consumption without any doctor's advices.

As it has been seen that the fluoroquinolone group of AMAs was used mostly by footballers followed by beta-lactams and imidazoles, it is very important to educate them regarding adverse impact of fluoroquinolone on the tendon, cartilage, bone, and muscle health. Reports are suggestive of tendinitis, tendinosis, tendon rupture, cartilage, and bone damage-related adverse impacts, such as arthralgia, impaired fracture healing, and cartilage lesions, which are related to fluoroquinolone group of antibiotics. This group of AMA also could produce an adverse impact on muscle producing myalgia and rhabdomyolysis rarely. It is important to recommend that it is better to avoid the athlete subpopulation unless no alternative AMA is available. Athletes and team management should be aware of this toxicity. Fluoroquinolone requires informed prescribing focusing the potential adverse impacts and advices regarding not using oral or injectable corticosteroids concomitantly as it may enhance the risk of tendon rupture. In case of no contraindications, supplementation with magnesium and/or antioxidants would be done. Need vigilant monitoring of athletes who were on fluoroquinolone, any potential signs and symptoms of adverse drug reaction need to be dealt with extreme cautions and rational de-prescribing.⁷ Antibiotic-associated diarrhea is an important consideration as this adversely impacts on footballers' professional activities and quality of life. Azithromycin and amoxicillin–clavulanic acid fixed-dose combination had evidence to produce antibiotic-associated diarrhea. The pediatric studies on antibiotic-associated diarrhea had shown 23% prevalence with amoxicillin–clavulanic acid fixed-dose combination and a prevalence of 25% with macrolides.⁸ Prolongation of QTc is an important concern with AMAs like macrolide and fluoroquinolone. As we had seen a good number of footballers on these two AMAs in our study, it is also a matter of concern. There are a few evidences in the field of football where we have noticed sudden cardiac death. Arrhythmia related to AMAs should be taken into consideration for prescribing antibiotics such as macrolides and fluoroquinolones. They are associated with an increased risk of torsades pointes, ventricular arrhythmia, and cardiac arrest.⁹ Informed prescribing is extremely crucial in this regard to prevent unwanted atrocities. AMAs, such as tetracyclines, fluoroquinolones, and sulfonamide are potential photosensitizers.¹⁰ Footballers are exposed to sunlight often so photosensitizers like fluoroquinolone could evoke skin reactions in them. While prescribing these agents they should be informed on photosensitivity to patients is extremely important to prevent untoward event-related anxiety and stress among footballers. Preventive cream with well-defined sun protection factor could be used in high-risk subjects where fluoroquinolone usage

is compelled. There are no absolute safe AMAs. Photosensitivity may aggravate anxiety and irritability, tendon injuries, and antibiotic-associated diarrhea may decrease professional performances but the prolongation of the QT interval may be more detrimental. There are potential risks with antibiotic therapy. Intended indications should justify the use of antibiotics after considering risk versus benefit.

Maximum footballers were not following the recommended dose schedules and duration of therapy. More than two-thirds of the study population had terminated AMA therapy prematurely. Informed medication use would address this issue holistically. Not completing the course of antibiotics could be responsible for an epidemic of resistant infections which could threaten the whole community as a whole. Antimicrobial-resistant organisms are responsible for around 7,00,000 deaths per year and the number is rising day by day. This is one of the biggest public health threats at present.¹¹ Antibiotics should be considered as *non-renewable* precious resource of our time. While advising our patients to finish the course of AMA, doctors should consider two important concepts: (1) Antimicrobial agent would be less effective and (2) Resistance against AMA would be developed. Findings of our study emphasize the importance of counseling in this regard along with spreading awareness in the community. The slogan prepared by WHO "Antimicrobials: Handle with Care" need to be spread.¹²

To control the epidemic of inappropriate use of antibiotics, WHO in 2017 updated the list of essential medicine list (EML) and categorized the antibiotics into three groups – Access, watch and reserve (AWaRe).¹³ "The Right Antibiotic at the Right Time" – this message should be percolated in every related sectors and need to increase awareness. Unfortunately, in our study, it was found that a good number of antibiotic from "Watch" and "Reserve" groups were consumed by footballers. "Access" group contains first and second choice antibiotics for most common infectious syndromes as the empiric treatment. Globally, they are widely available at appropriate quality, dose, duration, formulation, and price consistently and examples from this group are amoxicillin, amoxicillin plus clavulanic acid, metronidazole, doxycycline, clindamycin, nitrofurantoin, sulfamethoxazole plus trimethoprim, gentamicin, and amikacin. "Watch" group consists of higher resistance potential antibiotics. Prescription of this group should be restricted to a small number of syndromes or patient groups. Examples of "Watch" group are macrolides, fluoroquinolone, piperacillin plus tazobactam, and 3rd generation cephalosporin. This group of antibiotics has higher toxicity issues and resistance development potential. Assisting in the development of tools for stewardship at local, national, and global levels is extremely important here. "Reserve" group of antibiotics are the "last resort" therapeutics. Efforts should be made to protect and prioritize this group as a key target of high-intensity national and international stewardship programs involving central monitoring and reporting. Objectives of this program should emphasize prevention of developing resistance and preserving effectiveness of AMAs from "Reserve" group. A few examples of this group are linezolid, aztreonam, 3rd and 4th generation cephalosporin, fosfomycin, tigecycline, and polymyxin B.¹⁴ While choosing an antibiotic, it is extremely important to follow "AWaRe" classification of AMA.

CONCLUSION

Over-the-counter purchases of AMAs should be regulated, and awareness regarding the harm of OTC AMA use needs to be

spread in the footballers' community. Health literacy is extremely crucial for the healthy life of footballers. Knowledge of completing the recommended AMA course requires effective information dissemination. Antimicrobial agent prescribing pattern seen in this study revealed a high chance of development of resistance. Application of knowledge and principles of AWaRe classification thus need to be followed strictly by practitioners. Achilles tendon rupture or tendinitis, tendinopathy, arrhythmia, photosensitivity, and antibiotic-associated diarrhea are recognized adverse effects of different prescribed AMAs. Extremely cautious prescribing is warranted while advocating AMAs such as fluoroquinolone, macrolide, etc. To get detailed data on the potential adverse impacts of AMAs, we need to conduct a prospective observational study with a larger sample size.

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