Original Article

TRENDS IN ANTIMICROBIAL RESISTANCE PATTERN AND AN OVERVIEW ON ITS CONTRIBUTING FACTORS & PREVENTIVE MEASURES

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Abstract

The World Health Organization has highlighted antimicrobial resistance as a major concern to community health, henceit is crucial to understand the types of primarily isolated pathogens from various biological samples such as blood, urine, sputum, pus, stool, ear discharge& etc, and their corresponding antimicrobial resistance pattern in a particular region for the better clinical services, among the isolated gram-negative & gram-positive pathogens, such as Escherichia coli,Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella, Enterobacteriaceae, salmonella, shigella, proteus species andStaphylococcus aureus & streptococcus species respectively were involved in the development ofnumerous infectious diseases, in which these above mentioned pathogens were highly resistance to majority of the conventional antibiotics, especially to 3rd generation cephalosporins, while Aminoglycosides and Carbapenem class of antibiotics was found to be highly effective towards most of the pathogens specified. Inappropriate antibiotics use, poor infection control, poor hygiene, self-medication and prolonged use of antibiotics are considered to be the significant driving factors for emergence of antimicrobial resistance (AMR). It is necessary to stop antibiotics misuse and OTC antibiotics to prevent AMR.Rational use of antibiotics and surveillance plays a major role in AMR prevention. By following recommended practice guidelines and infection control protocols AMR can be managed. The key factors associated with AMR treatment is reduction of antimicrobial use and prevention of AMR emergence.This review provides a detailed study on the antimicrobial resistance pattern of various pathogens& prevention, treatment and factors associated with AMR.

KEY WORDS: Antimicrobial resistance, Microbiological culture, antimicrobial stewardship, Gram-negative species, Infection prevention & control.

INTRODUCTION:

Antimicrobial resistance is a condition whereby, previously susceptible microbes develop resistance to antimicrobial treatments, in which a unique adaptive push to create a retaliation response to an antibiotic or group of antibiotics led to the fundamental cause of resistance[1]. Antimicrobial resistance has attained a tipping phase and has become a world concern to population health on a global scale. The World Health Organization

(WHO) recently identified antimicrobial resistance as a global health concern and advised various nations to develop a strategy to address the issue [2]. Microbial strains from clinical samples are evaluated for their sensitivity to antimicrobials in order to identify potential antibiotic resistance in prevalent microorganisms and confirm their sensitivity to the recommended antibiotics for a given infection. Since sensitivity might differ significantly among the organism, they are carried out to assess which drug will best manage the infections caused by bacterial species in vivo [3]. Numerous pathological disorders, including urinary tract infection, bacteremia, pneumonia, healthcare associated infections, opportunistic & other infections are brought on by gram-negative bacteria in comparison with gram-positive species [4][6]. Bloodstream infections are identified by the existence of active pathogenic microorganisms, which cause an immune process and frequently change medical, biochemical, and physiological variables and are the main source of morbidity and mortality in individuals of all ages, especially in patients with impaired immune systems[5][7]. Urinary tract infection (UTI) refers to the bacterial invasion and inflammation of parts associated with urinary system such as pyelonephritis, cystitis and urethritis, which are the major types of UTI's that can be characterised as complicated & uncomplicated UTI's [10]. To a Minimum UTI affects greater than 50% of women at a certain point over their lifetime & most will experience relapses [9] and this may be due to several biological and anatomical aspects of humans, such as the fact that women's urethras are shorter than men's, partial bladder emptying and the vesicoureteral reflux commonly seen in pregnant women enhance the likelihood of developing a UTI [8]. Acute & chronic bronchitis, pneumonia are the most prevalent lower respiratory tract infections (LRTIs) and are linked to severe morbidity, mortality, and enormous medical expenditures [12] and are accompanied with lung abscess, pleural effusion preceded by respiratory distress, sepsis and multi-organ failure [13]. Injury, cell waste, and dead tissues are created as the outcome of pyogenic organisms infecting human skin and soft tissue during or post trauma, skin burns, and surgical treatments[16] usually marked by many localised inflammations, typically with pus development as a result of immune responses, which are sent to the site of infection as part of the body's defence strategy to combat pyogenic microbes [15] , while orthopaedic patients frequently experience skin infections in comparison to normal population, which can be brought on by both gram-positive and gram-negative bacteria [14]. According to the World Health Organization (WHO), diarrhoea is described as passing three or more watery or loose stools per day, with a rise in water composition, quantity, and regularity of bowel movements and also associated with other symptoms like nausea & vomiting, fever and cramping [18], however it is primary contributor to morbidity and mortality especially in children and teenage adulthood notably in places where resources are scarce and where hygiene standards are not properly observed[17]. Chronic suppurative otitis media (CSOM) is described as a middle ear inflammation that remains for more than six weeks with a ruptured tympanic membrane discharging effluent and which frequently coexists with cholesteatoma [19]& are primarily triggered by microbial infection which are generally associated with hearing impairment and intracranial consequences [20].Inappropriate use of broad-spectrum antibiotics leads to development of Multidrug resistant (MDR) organisms [32]. Antimicrobial resistance (AMR) development can be provoked by antibiotics misuse [25]. Overuse/misuse of antibiotics, poor hygiene, self-medication are the major driving factors for the development and spread of AMR [29][31][42].

ANTIMICROBIAL RESISTANCE PATTERN OF BACTERIAL ISOLATES FROM CULTURES:

a) Blood culture:

According to Alka Hasani et al. [5] Staphylococcus aureus, Escherichia coli, Acinetobacter baumannii, Pseudomonas aeruginosa, Coagulase negative Staphylococcus, Klebsiella pneumonia, Enterobacter species were prominently identified microorganisms responsible for blood stream infections, in which these organisms are majorly resistant against gentamycin, ofloxacin. Cefotaxime, ceftazidime, ceftriaxone and co-trimoxazole in an increasing manner and moderately resistant against fluoroquinolones, and majorly sensitive towards amikacin and imipenem.

According to the study conducted by Tamanna Zerin et al. [6] The most prevalent pathogen was E. coli, preceded by Staphylococcus aureus, Klebsiella pneumoniae, Staphylococcus epidermidis, Salmonella species,

Streptococcus viridans & Pseudomonas aeruginosa, in which the resistance pattern of cloxacillin for Streptococcus viridans, gentamycin for Staphylococcus epidermidis, azithromycin and linezolid for Staphylococcus aureus, ciprofloxacin & co-trimoxazole for Salmonella species, ceftriaxone & moxifloxacin for Klebsiella pneumoniae, aztreonam & colistin for Pseudomonas aeruginosa, ceftriaxone, cefuroxime for E.coli were discovered. Whereas, all the identified bacteria were sensitive towards cefepime & meropenem, while imipenem and nitrofurantoin are effective towards gram-negative & gram-positive microbes respectively.

Similarly in a study initiated by John Gameli Deku et al. [7] Demonstrated that the development or synthesis of the extended-spectrum beta-lactamase (ESBL) enzyme is linked to the rising resistance to second- and third-generation cephalosporins, notably cefuroxime and cefotaxime.

b) Urine culture:

According to Syed Suhail Ahmed et al. [8] Gram-negative organisms such as Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterococcus faecalis and Enterobacter cloacae are the prominent microbes responsible for developing urinary tract infections, which possess an broad range of resistance to ampicillin, piperacillin, amoxicillin-clavulanic, nitrofurantoin, co-trimoxazole & cefuroxime, also the intermediate range of resistance to ciprofloxacin, cefoxitin, norfloxacin, piperacillin-tazobactam and 3rd generation cephalosporins, whereas these microbes are highly sensitivity to cefepime, tobramycin, gentamycin, amikacin and meropenem.

A study by Jamaan Al-Zahrani et al. [9] Escherichia coli, Klebsiella, Enterobacter, proteus & pseudomonas species are the unique pathogens identified from the patient urine cultures known to cause uncomplicated cystitis, in which these microbes show an ascending spectrum of resistance to aztreonam, nitrofurantoin, piperacillin, co-trimoxazole, cephalothin and ampicillin with a sensitivity sequence to ciprofloxacin and levofloxacin.

Similar results have been proposed in the study conducted by Harshkumar B. Patel et al. [10]& according to this study, it may be advised to use nitrofurantoin as an empiric antibiotic therapy in place of cotrimoxazole and ciprofloxacin for uncomplicated cystitis. Aminoglycosides and carbapenems are recommended over fluoroquinolones and cephalosporins for treating mild to severe pyelonephritis.

c) Sputum culture:

According to Zaharaddin Muhammad Kalgo et al. [11] Staphylococcus aureus, Klebsiella pneumoniae, Klebsiella oxytoca, Escherichia coli, Pseudomonas aeruginosa, Aeromonas hydrophila are the majorly detected bacterial species of Lower respiratory tract infections with a greater sensitivity profile descending from gentamycin, ciprofloxacin, azithromycin, co-trimoxazole & piperacillin. Whereas, Staphylococcus aureus, Klebsiella species and Escherichia coli exhibited a broad scope & intermediate scope of resistance especially for 3rd generation cephalosporins respectively, while Pseudomonas aeruginosa & Aeromonas hydrophila exhibited resistance to nearly all of the examined antibacterial agents.

According to Biagio Santella et al. [12] Pseudomonas aeruginosa, Klebsiella pneumoniae, Staphylococcus aureus and Acinetobacter baumannii are the principal microbes responsible for lower respiratory tract infections (LRTI's) and illustrates extended level of sensitivity to colistin, vancomycin & linezolid. Whereas these microbes exhibited broad scope of resistance to penicillin, fluoroquinolones and cephalosporins type of agents with an intermediate level of sensitivity to ertapenem, gentamycin, tetracycline and co-trimoxazole.

Likewise in the study initiated by Sadia Batool et al. [13] stated that Streptococcus pneumoniae, Staphylococcus aureus and Haemophilus influenzae are the importantly identified microbes responsible for LRTI's. Streptococcus pneumoniae showed greater sensitivity for macrolide antibiotics, Haemophilus influenzae and Staphylococcus aureus showed high sensitivity for ceftriaxone, levofloxacin. Amoxicillin-sulbactam, ciprofloxacin, ceftazidime, azithromycin and amikacin respectively with a poor scope of sensitivity to ampicillin & trimethoprim-sulfamethoxazole.

d) Pus culture:

According to Lee Kapalisya Mwakalinga et al. [14] Staphylococcus aureus and Pseudomonas aeruginosa, Escherichia coli are the most typically identified gram positive & gram-negative bacterial species respectively, and shows greater level of sensitivity against amoxicillin-clavulanic acid, clindamycin, amikacin, ciprofloxacin & gentamycin. Whereas ceftriaxone and ampicillin resistance are common in gram-negative bacteria's and erythromycin, vancomycin & trimethoprim-sulfamethoxazole resistance in common among gram-positive organism.

According to Dayavanti Kumari et al. [15] Staphylococcus aureus, Coagulase negative Staphylococcus, Enterococcus faecalis, Pseudomonas aeruginosa, Klebsiella pneumoniae & Escherichia coli are the majorly identified bacterial species, in which Staphylococcus aureus, Enterococcus faecalis & Coagulase negative Staphylococcus exhibited extremely high level of susceptibility to vancomycin & linezolid, and Escherichia coli, Klebsiella pneumoniae & Pseudomonas aeruginosa exhibited the same to tigecycline & colistin. Whereas, other antibacterial agents such as, tetracycline, gentamycin, teicoplanin, clindamycin, erythromycin, ciprofloxacin, cotrimoxazole & meropenem were also found to be considerably effective.

In the study conducted by Krishna Kumar Patel et al. [16] Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa, Citrobacter species, Acinobacter baumannii, Proteus mirabilis & Streptococcus species, Gram-negative bacteria predominated among the isolates from wound samples in contrast to Gram-positive bacteria. High level of resistance to cephalosporins, amoxicillin/clavulanic acid and azithromycin, ciprofloxacin, ampicillin, amoxicillin/clavulanic acid was exhibited by E. coli and S. aureus respectively. While meropenem, linezolid, imipenem, vancomycin was effective against S. aureus. P. aeruginosa, P. mirabilis & Streptococcus species showed little resistance and were sensitive to the majority of anti-bacterial agents.

e) Stool culture:

In the study conducted by A. Samie et al. [17] proposed that Campylobacter species, Aeromonas species, and Salmonella species appeared as the most typically identified bacterial species. These pathogenic agents were found to be considerably attributed with diarrhoea, with expanding resistance to antibacterial drugs such as erythromycin in case of Campylobacter species, tetracycline in case of Shigella, and ampicillin in case of Salmonella species. The sensitivity trend of diarrhoea-causing microbial species, which include Yersinia enterocolitica, Shigella, E. coli, and Salmonella were highly sensitive to polymyxin B, norfloxacin, gentamicin and nalidixic acid. It was also discovered that ampicillin was ineffective towards the majority of the organisms tested, whereas gentamicin was successfully effective towards the majority of the species examined.

According to Achenef Melaku Beyene et al. [18] shigella species, salmonella enterica, E. coli and campylobacter species appeared as the most typically identified gram negative intestinal bacterial species which serves crucial role in the onset or extent of diarrhoea. Among these pathogenic agents shigella and salmonella species shows greater extent of resistance to ampicillin & amoxicillin, with a lower extent of resistance to ciprofloxacin & ceftriaxone. Whereas E. coli and campylobacter species exhibited greater level of resistance towards tetracycline, trimethoprim-sulphamethoxazole & ampicillin. On the other hand, erythromycin and chloramphenicol were ineffective towards campylobacter species.

f) Ear discharge:

According to Rahel Molla et al. [19] P. mirabilis and S. aureus emerged as the most frequently found bacterial species. P. vulgaris, Pseudomonas, Providencia species, Citrobacter species, Klebsiella species, Enterobacter species have also been identified. This study also sheds light on the resistance pattern of identified bacteria from ear infections and revealed that chloramphenicol, nalidixic acid, ciprofloxacin, gentamicin, and norfloxacin are active towards Gram-negative bacterial species, while cefixime, cefuroxime, and cefepime have a considerable spectrum of sensitivity against Gram-negative bacteria. Amoxicillin-clavulanic acid, gentamicin, chloramphenicol, clarithromycin, and tobramycin, on the other hand, were reasonably effective towards Gram-positive bacteria.

In the study conducted by Jianghong Xu et al. [20] stated that Staphylococcus aureus and P aeruginosa emerged as the most frequently found bacterial species. Cephalosporins and fluoroquinolones are the most commonly given oral antibiotics for CSOM in China. The Staphylococcus aureus species discovered in this investigation were significantly resistant to penicillin and erythromycin. Likewise, vancomycin, gentamicin, rifampicin, moxifloxacin, sulfamethoxazole and trimethoprim were extremely effective against S aureus species. Also, Piperacillin, piperacillin/tazobactam, and meropenem were all effective against isolated Pseudomonas aeruginosa, whereas, Levofloxacin, ciprofloxacin, and ceftriaxone are all extremely resistant to Pseudomonas aeruginosa cultures.

IMPACT OF EMPIRICAL THERAPY IN THE DEVELOPMENT OF ANTIMICROBIAL RESISTANCE:

Antimicrobial resistance is the major public health concern. The major drug resistance is identified mostly among MDR Pseudomonas aeruginosa, Methicillin resistant staphylococcus aureus (MRSA), Vancomycin resistant enterococci (VRE) and Enterobacteriaceae producing extended spectrum beta lactamases (ESBL's) [21]. All these resistant bacteria are mostly resistant to carbapenems and quinolones [22]. Carbapenems are the one and only drug in beta lactamases which maintains its potential activity against MDR Enterobacteriaceae producing ESBL's. It is also indicated by clinical data's that carbapenems are the only drug of choice for the management of chronic infection induced by similar strains [21].

In a study conducted by Department of Infectious Disease, University of Verona in government hospital of Trieste, Italy shows that by reducing the use of piperacillin-tazobactam, they obtained decreased resistance to Aeruginosa by 57% to this drug, at the same time they also noted increased resistance to the drug imipenem. In hospital acquired pneumonia; as an empirical therapy imipenem was replaced with piperacillin-tazobactam [22]. The use of high dose beta lactam antibiotics and macrolides was suggested by the American Thoracic Society and Infectious Disease society of America for the empiric treatment of community acquired pneumonia. This empirical treatment shows less resistance against streptococcus pneumoniae [28].

It is stated that uncomplicated urinary tract infections (UTI's) should be managed empirically with the use of Trimethoprim and Sulfamethoxazole by Infectious Disease Society of America Guidelines. If the community resistance exceeds 10-20% among uropathogens, then it must be treated with fluoroquinolones [23]. Fusidic acid acts mainly against gram positive bacteria with a potential invitro activity against S. aureus. Its resistance is very low due to its advanced penetration in damaged skin [24]. In therapy of infectious wounds, mupirocin acts as a narrow spectrum anti-staphylococcal topical drug, prescribed empirically due to its low resistance [24].

Development of antibacterial resistance can be provoked by antibiotics misuse. Follow appropriate antimicrobial use in order to prevent the development of AMR and to improve clinical benefit [25]. Unpropitious mortality rate can occur in co-morbid patients due to inappropriate empiric use of antimicrobials [26]. Without any indication of bacterial infection, fluoroquinolones and Piperacillin/tazobactam were repeatedly prescribed in Covid-19 patients as an empirical therapy. Inappropriate use of broad-spectrum antibiotics leads to development of multidrug resistant organisms [32].

FACTORS ASSOCIATED WITH ANTIMICROBIAL RESISTANCE

Factors promoting the spread of AMR-bacteria are:

- Inappropriate use of antibiotics in clinical practice [29] [31].
- Overcrowding in hospitals
- Infection control failure
- Poor hand / personal hygiene
- Self-medication [29] [31].

- Misuse of antibiotics/antimicrobials [29] [38] [42] [43] [44] [45].
- In E. coli, K. pneumoniae and P. aeruginosa; the risk factor for the ciprofloxacin resistant bacteria is the use of fluoroquinolones [30].
- Improper prescribing patterns [38] [42].
- Insufficient new novel antibiotics [38].
- Healthcare facilities and Pharma industries releases antibiotics and its residues into the environment that results in the frequent development and spread of antimicrobial resistant organisms in environment [27] [31] [42].
- Multidrug resistant gram-negative bacteria, MRSA, VRE are primarily transmitted by direct or indirect contact from one person to another [29].
- Long term hospitalization / use of antibiotics [29] [42].
- Frequent use of broad-spectrum antibiotics (e.g., cephalosporin, fluoroquinolone) [29][31].
- Urinary catheterization, abundant antibiotic use, humidifiers and nebuliser contamination are the major driving factors for the spread of gram-negative resistant bacteria [29] [30].
- Overuse of Penicillin, overcrowding, tracheostomies are the factors for the spread of penicillin resistant pneumococci (PRP) [29].
- Delayed diagnosis, poor ventilation, poor isolation facilities are the driving factors for the transmission of multidrug resistant Mycobacterium tuberculosis (MDR-Tb) [29].

PREVENTIVE STRATEGIES TO COMBAT ANTIMICROBIAL RESISTANCE:

The worldwide difficulty of antimicrobial resistance is increasing. The strategies to combat AMR are;

- Prevention of unnecessary overuse or misuse of antibiotics [34] [35] [38].
- Antibiotics should be prescribed rationally [34] [43] [45] [41].
- Prevention and control of infection [33] [35] [38] [41].
- Cessation of OTC antibiotics [34].
- Maintain hand and personal hygiene [33] [34] [35] [36].
- Surveillance of antimicrobial resistance [34] [37].
- Follow guidelines for standard treatment [34].
- Initiation of advanced AMR programmes [33] [34].
- Since it is important to reduce the emergence of antimicrobial resistance during treatment; it is essential to stop the antibiotics that motivates the transfer of genes [34].
- Evaluate the impact of various driving factors of antibiotics resistance in population [35].
- Before hospital admission always pre-screen for any carrier status [36].
- Hospital rooms must be disinfected regularly [36].
- A low rate of antimicrobial resistance will be achieved by reducing the antibiotics consumption [45] [36].
- Antimicrobial prescribing should be monitored carefully [36].

TREATMENT RECOMMENDATIONS TO COMBAT ANTIMICRIBIAL RESISTANCE:

Misuse of antibiotics has resulted in emergence of various antibiotics resistance and formation of superbugs. In order to combat AMR, practice guidelines implementation would result in increased appropriateness of AMR

management and improved therapy success; but AMR cannot be controlled if additional measures aren't reinforced. In AMR treatment; it is important to prevent the spreading of resistant bacteria. In hospital, practice guidelines for precaution of isolation were introduced by centres for disease control and prevention (CDC) in the period of 1996 in which it indicates hand hygiene as a major essential measure to decrease the probability of spreading organisms from person to person [37][39].

- For the surveillance of antimicrobial resistance and antimicrobial use; it is mandatory to develop an effective system[37][40].
- In order to control the cross-transmitting of resistant microbe; it is essential to reinforce appropriate infection control measure[37][39].
- Inappropriate use of antibiotics should be stopped, if not, it would result in multi-drug resistant bacteria (MDR-Bacteria) and superbugs[37][39].

For the management of AMR; various suggestions were listed as follows:

1. Suggestion for clinicians in managing AMR:

a) For prescribing antibiotics; always follow recommended guidelines strictly[38].
b) In order to prevent infection, infection control guidelines and protocols are to be practiced[38].
c) The patient or their care taker must be counselled about the antibiotic use / consequence of antibiotic misuse like developing of AMR or allergic reaction[38][44].

2. Suggestion for patient / care taker:

a) Patient / caretaker must be notified about AMR.
b) Patient / caretaker must be accepting counselling from physician about
i. Treatment plan
ii. Duration of therapy
iii. Contraindication
iv. Indication
v. ADR of drug.
c) Proper personal / hand hygiene must be practiced.
d) Avoid public contact if he / she is sick.
e) Periodic vaccination must be obtained[38].

3. Suggestion for health care organizations:

a) In order to identify the source of misuse, prescribing patters in clinics, community hospitals and nursing home are to be monitored regularly[38].
b) Organize educational programmes for physicians and public about antibiotics use and consequences of its misuse[38].
c) For diagnosing and managing infections disease; establish an effective practice guideline[38].
d) Support the researchers in developing advanced technologies and drugs to promote optimal antimicrobial use[38][39].
e) Prevent antibiotics resistance and develop new novel antibiotics[38][43].
f) AMR surveillance is an important aspect in AMR treatment which provides adequate information to develop,
i. Therapy guidelines for monitoring AMR
ii. Antibiotics formularies
iii. Antibiotics stewardship programmes
iv. Public health intervention
v. Infection control strategies
vi. Novel antibiotics and vaccines[40][44].
g) To treat resistance microbes; it is essential to develop new antimicrobial therapies[44].

h) The key factors in reducing the emergence of AMR are reduced antimicrobial use and prevention of development of antimicrobial resistance[44].

CONCLUSION:

From the above retrieved study, we come to know about the predominance of numerous gram-negative & gram-positive microorganisms and their pattern of antimicrobial resistance, which are involved in the development of various infectious diseases associated with blood, urine, sputum, pus, stool & ear discharge, which aids in the decision of empirical treatment. In order to prevent AMR and to combat AMR it is important to prevent overuse / misuse of antibiotics. Implementation of rational use of antibiotics plays a major role in preventing antimicrobial resistance. In AMR treatment it is essential to prevent the spread of resistant bacteria. To combat antimicrobial resistance, antibiotics must be prescribed according to recommended guidelines and follow infection control protocols.However, the antimicrobial resistance monitoring framework must be built to comprehend the pattern of antibiotic resistance across harmful bacteria and to prepare and carry out preventive measures including adequate prevention and control of contagious diseases and antimicrobial stewardship schemes. Although even more research is required to fully comprehend the pattern of antimicrobial resistance from multiple biological samples for further conclusion.

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