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A Study on Extensive Drug Resistance in Enterobacteriaceae

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Abstract:

Introduction: *Bacterial infections involving antibiotic resistant Gram negative bacilli (GNB) have emerged as major threats to human communities worldwide. The emergence of multidrug resistant GNB, as well as new mechanisms of resistance, is worsening the situation. Currently, some GNB show extreme or complete resistance to all 1st and 2nd line drugs available for treatment and are referred to as extreme or extensively drug resistant pathogens (XDR). No comprehensive data about prevalence of XDR GNB, worldwide or in India are available. Studies from various centers from India and the rest of the world give figures ranging from 12% to 45% at their specific centers of study.*

Objectives: *To study the occurrence of extensive drug resistance in MDR isolates of Enterobacteriaceae*

Materials and Methods: *80 consecutive, non repetitive MDR Enterobacteriaceae isolated from clinical samples were tested in the Department of Microbiology, MMCRI, Mysore, to identify extensive drug resistance. Antimicrobial susceptibility testing was done by Kirby Bauer disc diffusion method as per CLSI guidelines. Isolates were defined as extensively drug resistant (XDR) when there was non-susceptibility to at least 1 agent in all but 2 or fewer antimicrobial categories.*

Results: *Of the 80 MDR (n=80) isolates studied, 39(48.75%) were E.coli, 32(40%) were Klebsiella spp, 6(7.5%) were Citrobacter spp and 3(3.75%) were Enterobacter spp. A total of 35 isolates were found to be XDR, of which 13 isolates exhibited resistance to all groups of antimicrobials except one group, rest 22 isolates exhibited resistance to all groups except two groups.*

Conclusion: *A high occurrence of extensive drug resistance (XDR) among MDR Enterobacteriaceae was found. Antibiotic recycling, implementation of infection control programmes, administration of appropriate antibiotics based on culture and sensitivity are all essential to decrease the incidence of extensive drug resistance.*

Keywords: *Enterobacteriaceae, Extensive drug resistance, extensively drug resistant, gram negative bacilli, GNB, XDR, Multi drug resistant, MDR.*

1. INTRODUCTION

Bacterial infections involving antibiotic resistant Gram negative bacilli (GNB) have emerged as major threats to human communities worldwide.[1]The emergence of multidrug resistant GNB, as well as new mechanisms of resistance, is worsening the situation.[2, 3]

Antibiotic resistance, a global concern, is particularly pressing in developing nations like India, where the burden of infectious diseases is high and healthcare spending is low.[4]

The bacterial disease burden in India is among the highest in the world; consequently, antibiotics play a critical role in limiting morbidity and mortality. Many of these deaths occur because patients do not have access to life-saving antibiotics and at the other extreme, antibiotics are used in situations where they cannot improve the patient's condition, as in treatment for common cold and uncomplicated diarrhea.

Although drug resistance is primarily a medical problem, the factors that influence the spread of resistance are ecological, epidemiological, cultural, social, and economic.[4] With few new antibiotics in the pipeline, the emphasis has been on prevention and control of the spread of resistant gram negative bacilli.

Currently, some GNB show extreme or complete resistance to all 1st and 2nd line drugs available for treatment and are referred to as extreme or extensively drug resistant pathogens (XDR).[5]

No comprehensive data about prevalence of XDR GNB especially Enterobacteriaceae, worldwide or in India are available. Studies from various centers from India and the rest of the world have reported XDR GNB ranging from 12% to 45%.[6,7,8]

This prompted us to study the occurrence of extensive drug resistance in Enterobacteriaceae.

2. MATERIALS AND METHODS

80 consecutive, non repetitive isolates of multidrug resistant Enterobacteriaceae isolated from clinical samples between December 2013 to May 2014 in the Department of Microbiology, MMCRI, Mysore, were reviewed for XDR status. Antimicrobial susceptibility testing was done by Kirby Bauer disc diffusion method to the following antibiotics- amoxicillin clavulinic acid, cotrimoxazole, ciprofloxacin, cefoxitin, ceftriaxone, cefotaxim, ceftazidime, cefaperazone sulbactum, gentamycin, imipenem, amikacin, piperacillin tazobactum, aztreonam, netilmycin , tigecycline and colistin as per CLSI guidelines.[9]

Isolates were defined as Multidrug resistant when they were non-susceptible to at least 1 agent in 3 or more antimicrobial categories and extensively drug resistant (XDR) when they were non-susceptible to at least 1 agent in all but 2 or fewer antimicrobial categories.[10]

3. RESULTS AND DISCUSSION

3.1. Results

Of the 80(n=80) MDR isolates studied, 39(48.75%) were *E.coli*, 32(40%) were *Klebsiella* spp, 6(7.5%) were *Citrobacter* spp and 3(3.75%) were *Enterobacter* spp.

All the MDR isolates (100%) – *E.coli* (39), *Klebsiella* spp (32), *Citrobacter* spp (6), *Enterobacter* spp (3) were resistant to amoxicillin clavulinic acid, ciprofloxacin, cefoxitin, ceftriaxone, cefotaxim, ceftazidime, cefaperazone sulbactum, piperacillin tazobactum, aztreonam, netilmycin and tigecycline.

All the 80 MDR isolates (100%) were sensitive to Colistin. 5 (6.2%) isolates were sensitive to cotrimoxazole, 2(5.1%) isolates were sensitive to gentamycin, 7 (8.75%) were sensitive to imipenem and 4(5%) isolates were sensitive to amikacin. Colistin appeared to be most effective (100%) against the isolates. (Table 1)

Table1. *Showing resistance of the isolates to various antibiotics*

	E.coli	**Klebsiella spp**	**Citrobacter spp**	**Enterobacter spp**
Total isolates	39	32	06	03
Amoxicillin – clavulinic acid	39(100%)	32(100%)	06(100%)	03(100%)
Cotrimoxazole	36(92.3%)	30(93.7%)	06(100%)	03(100%)
Ciprofloxacin	39(100%)	32(100%)	06(100%)	03(100%)
Gentamycin	37(94.8%)	32(100%)	06(100%)	03(100%)
Cefoxitin	39(100%)	32(100%)	06(100%)	03(100%)
Ceftriaxone	39(100%)	32(100%)	06(100%)	03(100%)
Cefotaxim	39(100%)	32(100%)	06(100%)	03(100%)
Ceftazidime	39(100%)	32(100%)	06(100%)	03(100%)
Cefaperazone sulbactum	39(100%)	32(100%)	06(100%)	03(100%)
Imipenem	35(89.7%)	30(93.7%)	05(83.3%)	03(100%)
Piperacillin tazobactum	39(100%)	32(100%)	06(100%)	03(100%)
Amikacin	38(97.4%)	30(93.7%)	05(83.3%)	03(100%)
Aztreonam	39(100%)	32(100%)	06(100%)	03(100%)
Netilmycin	39(100%)	32(100%)	06(100%)	03(100%)
Tigecycline	39(100%)	32(100%)	06(100%)	03(100%)
Colistin	0(0%)	0	0	0

A total of 35 (44%) isolates were found to be XDR. All 3(100%) isolates of *Enterobacter* were XDR and were susceptible only to Colistin.

13 (37 %) isolates -3 (7.69%) *E.coli* and 10 (31.25%) *Klebsiella* exhibited sensitivity to only 1 group of antibiotics, rest 22 (63%) isolates -11(28.2%) *E.coli* and 07(21.8%) *Klebsiella* exhibited sensitivity to 2 groups of antibiotics. (Table 2)

Table2. *Showing XDR, sensitivity to 1 and 2 groups of antibiotics*

	E.coli	Klebsiella spp	Citrobacter spp	Enterobacter spp
XDR	14	17	01	03
Sensitive to only 1 group	03	10	0	0
Sensitive to 2 group	11	07	01	03
Total	39	32	06	03

3.2. Discussion

Presence of XDR and reduced susceptibility to third generation of cephalosporins, carbapenems fluoroquinolones, aminoglycosides, and Trimethoprim-sulfamethoxazole is considered a serious clinical problem. Presently, data on XDR GNB in India is lacking.

Most studies have reported resistance in non fermenters and *Klebsiella*. *Enterobacteriaceae* are commonly encountered pathogens in clinical samples and their presence in environmental samples make them more prone for acquiring and disseminating resistance.

In our study, a total of 35 (44 %) of the 80 MDR isolates were found to be XDR, of which 13 (37 % of XDR) isolates exhibited sensitivity to only 1 group, rest 22 (63% of XDR) isolates exhibited sensitivity to 2 groups.

Very similar findings were noted in a recent study conducted in a tertiary care centre in Delhi. 81 of 383 GNB isolates were found to be MDR (21%). Of these 81 MDR isolates 36 were found to be XDR (44.4% of MDR, and 9.3% of total GNB isolates).[11]

In a study conducted in South India, of 45 isolates of *E.coli* studied, 42% *E.coli* were resistant to atleast one antibiotic, 8% were resistant to 3 or more antibiotics.[12]

In a study conducted in an ICU in a tertiary care hospital in North India, among the ESBL producers (195), XDR organisms were most frequent, followed by MDR and PDR organisms - 14 (5.6%), 113 (45.2%) and 68 (27.2%) respectively.[13]

The decreasing effectiveness of antibiotics in treating common infections has quickened in recent years, and with the arrival of untreatable strains of carbapenem resistant Enterobacteriaceae, we are at the dawn of a postantibiotic era. [14]

NDM (New Delhi metallo-beta-lactamase) enzymes, first reported in 2008, are now found worldwide.The distribution of resistance genes, such as Enterobacteriaceae-producing extended-spectrum β-lactamase (ESBL), NDM-1, and *Klebsiella pneumonia* carbapenemase (KPC), indicates the ease with which resistance can spread.[15] Hyper-production of chromosomal AmpC beta-lactamases as well as the production of extended-spectrum beta-lactamases (ESBLs) confers a MDR phenotype in Enterobacteriaceae.[16]

An XDR phenotype in Enterobacteriaceae is undoubtedly represented by carbapenem resistance which is mainly mediated by metallo betalactamases (MBLs) of VIM and IMP-type. The vast majority of MBL genes are carried on plasmids as gene cassettes inserted into class 1integrons and are usually associated with aminoglycoside resistance genes. [17]

The key driver of resistance is a combination of antimicrobial overuse, misuse and underuse. Several other factors contributing to XDR include poor infection control measures, poor sanitation and infrastructure, decreased access to clinical microbiology laboratory, increased immunocompromised states, globalization and increased travellers. [18]

While approaching the “end of antibiotics” a concerted action by industry, government, and academia is urgently required. “Hand hygiene” is considered worldwide to be the cornerstone of nosocomial infection prevention [16]

Decreasing antibiotic overconsumption resulted in decreased resistance rates of MDR Gram-negative bacteria in US and European hospitals. It is also evident that in order to escape resistance, under-dosing should be avoided and the duration of therapy should be limited. To avoid empiricism the appropriate cultures should be taken and the relationship between pharmacokinetics and pharmacodynamics should be exploited. De-escalation of the administered antibiotics as soon as culture results are ready should remain a quality indicator. [16, 19, 20]

4. CONCLUSION

In conclusion, this study has yielded high rates of extensive drug resistance among MDR Enterobacteriaceae from our centre. Overall resistance rates were nil with colistin and low with imipenem, followed by cotrimoxazole and amikacin.

However, the current condition is probably the result of ineffective hospital infection control and antibiotic policies, which may result in increasing rates of resistance to all antibiotics.

Priority needs to be given to

- National surveillance of antibiotic resistance and antibiotic use - better information to underpin decisions on standard treatment guidelines, education and other actions, as well as to monitor changes over time
- Increasing the use of diagnostic tests, which necessitate improvements in microbiology laboratory capacity
- Setting up and/or strengthening infection control committees in hospitals
- Restricting the use of antibiotics for non-therapeutic uses in agriculture.

These interventions would help to reduce the spread of antibiotic resistance, improve public health, benefit the populace and reduce pressure on the healthcare system. [4]

The role of the infectious diseases physician is now enhanced since (s)he is a vital resource in the implementation and promotion of the above strategies against drug resistant pathogens.[16]

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