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Carbapenemase producing enterobacteriaceae from chronic hemo-dialysis and renal transplant patients from a tertiary care centre in Chennai, South India

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Background: Carbapenemase producing *Enterobacteriaceae* (CPE) is on the rise worldwide. They are currently reported from all the continents in a variety of environmental settings. Different carbapenemases have geographical preponderance with the bla_{NDM} and $bla_{OXA48\,like}$ being prevalent in the Indian sub continent. Although many Indian studies have reported their prevalence in the hospital settings, systematic studies on their prevalence in the community are lacking. Chronic Hemo Dialysis (CHD) patients and renal transplant (RT) patients are a unique group with constant interaction with both the community and hospital settings. Hence, the current study was designed to find the prevalence of CPE and their associated resistant genes from Chronic Hemo Dialysis and renal transplant patients from a tertiary care centre in Chennai, South India.

Methods & Materials: A total of 315 non-repetitive enterobacterial isolates from CHD and RT patients were included in this study. They were screened for carbapenem resistance and carbapenemase production by antibiotic sensitivity testing and Modified Hodge Test respectively. The isolates were identified by conventional biochemical methods. The carbapenem resistant isolates were screened for the presence of genes encoding carbapenemases, Extended Spectrum Beta Lactamases, plasmid AMPCs, 16S rRNA methlylases and PMQR genes by PCR using published methods.

Results: 32/315 (10%) isolates were found to be CPE isolates of which 23 were *K.pneumoniae* and 9 isolates were *E.coli*. 20/32 (62%) isolates were from renal transplant patients and 12/32 (38%) were from CHD patients. 28/32 (87.5%) isolates harboured bla_{NDM} gene with 16/28 (57%) isolates also harbouring a $bla_{OXA48lilke}$ gene. 4/32 (12.5%) isolates harboured $bla_{OXA48lilke}$ gene alone. 31/32(97%) isolates were positive for $bla_{CTXMgp1}$ gene and 9/32(28%) isolates harboured bla_{CMY} . 13/32 (40.6%) isolates were positive for the *armA* gene and 5/32 (15.6%) were positive for the *rmtB* gene. 27/32 (84.4%) isolates harboured the PMQR determinant-*aac(6′)-IB-cr* and 26/32(81.3%) isolates harboured *qnrB*.

Conclusion: The high prevalence of CPE co-expressing other clinically relevant resistant genes from CHD and renal transplant patients substantiates the need for routine surveillance of CPE among chronic haemodialysis and renal transplant patients to prevent wide-spread dissemination of carbapenemases into the community.

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Synthesis and biological evaluation of indole-based 2-Aryl-2,3-epoxy-1,4-naphthoquinones as methicillin-resistant staphylococcus aureus (MRSA) inhibitors

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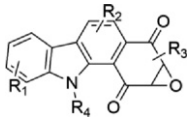
Background: Methicillin-resistant *Staphylococcus* aureus (MRSA) is one of the most successful human pathogens responsible for causing a wide range of infections ranging from Toxic shock syndrome to boils and endocarditis. MRSA has demonstrated extreme ability to resist antibiotics, thus necessitating a continuous search for new scaffolds active against it. Fosfomycin, a clinically utilized antibiotic for the treatment of MRSA infections, is known to act through covalent modification of biological thiols with its epoxide functionality. 2,3 epoxy-1,4-naphthoquinones are found to be constituents of numerous natural products. These compounds are found to be reactive with cellular thiols and generate reactive oxygen species (ROS), which can act to induce oxidative stress. Thiols, such as cysteine and glutathione are important for the maintenance of redox homeostasis in cells and hence, depletion of thiols could induce cellular stress and trigger cell death. Thus, such compounds might have therapeutic potential against MRSA infections.

Methods & Materials: We synthesized a library of indole-based 2,3 epoxy-1,4-naphthoquinones, varying the substitution on the epoxide carbons, and studied their reactivity with thiols, such as cysteine and glutathione. The synthesis of these compounds was undertaken in five steps from commercially available indole-3-carboxaldehyde.



Results: These compounds showed potent activity against drug-resistant clinical isolates of *S. aureus* including VRSA with MIC ranging from 0.06-0.12 mg/L. A good correlation was found between thiol-mediated decomposition profiles and MIC values of these compounds. The selectivity index of these compounds was >200, thus indicating specificity for bacterial cells and were found to be non-haemolytic against human RBCs. These compounds exhibited concentration dependent bactericidal activity with a ~5 log killing at 24 h in comparison to drug free control. These compounds

exhibited a potent post-antibiotic effect when compared to Vancomycin. In order to elucidate their mechanism of action, resistant mutants with a MIC of 64 mg/L were generated (frequency ~10^{-7}) and are being characterized at the molecular level to decipher mechanism of action of these compounds.

Conclusion: A series of 2-Aryl indole-based 2,3-epoxy-1,4-naphthoquinones have been synthesized with potent anti-MRSA activity. These compounds potentially deplete thiols, thus enhancing ROS in bacteria, which might help in overcoming drug resistance.

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Susceptibility pattern of healthcare-associated methicillin resistant staphylococcus aureus to Vancomycin and Daptomycin

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Background: Healthcare-associated methicillin resistant *Staphylococcus aureus* (HA-MRSA) is a major pathogen. Vancomycin is used in the treatment of serious infection caused by HA-MRSA. However, the emergence of Vancomycin intermediate *S.aureus* (VISA) and vancomycin resistant *S.aureus* (VRSA) is a matter of concern. The present study was conducted to determine minimum inhibitory concentration (MIC) of vancomycin and daptomycin among HA-MRSA in our healthcare settings.

Methods & Materials: A total of 110 HA-MRSA isolates (as defined by Centres for Disease Control and Prevention criteria) were collected over a period of seventeen months. Vancomycin MIC was determined by agar dilution method according to CLSI guidelines. Daptomycin MIC was determined by E-test (BioMerieux, France).

Results: Out of the total HA-MRSA isolated, 53.6% (59/110) had vancomycin MIC of 2μg/ml. Intermediate resistance to vancomycin was detected in 03.6% (04/110) of the HA-MRSA and these isolates had a vancomycin MIC of 4μg/ml. All HA-MRSA isolated were sensitive to daptomycin.

Conclusion: Occurrence of VISA among the HA-MRSA is a matter of concern. As these strains do not respond to vancomycin treatment hence their detection is crucial. VISA cannot be detected by routine disk diffusion method. Determination of MIC of vancomycin is necessary for the detection of VISA. Daptomycin can be effectively used in the treatment of infections caused by VISA isolates in our healthcare settings as resistance to this antibiotic has not yet been observed.

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Prevalence and antibiotic sensitivity of Staphylococcus aureus and Pseudomanas aeruginosa in middle ear fluids of chronic suppurative otitis media and chronic rhinosinusitis patients undergoing ear surgery

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Background: Chronic Suppurative Otitis Media (CSOM) and Chronic Rhinosinusitis (CRS) are strongly associated common diseases with a significant impact on people's quality of life worldwide. Emergence of antimicrobial resistance of the causative microbes poses problem in management of the disease. The present study aimed to find the microbial prevalence and compare the antibiotic sensitivity in middle ear fluid isolates of CSOM and CRS patients with CSOM in South Indian population.

Methods & Materials: 86 subjects with CSOM and 68 patients with CRS undergoing ear surgery at a MAA ENT Hospitals, Hyderabad, South India between 2009 and 2015 were included in the study. The middle ear aspirates were collected aseptically, cultured by conventional methods and tested for antibiotic sensitivity using Kirby Bauer disc diffusion method. Chi-square analysis was performed to test the difference between the two groups.

Results: The present study included 99 males and 57 females with mean age of 34.06 ± 19.215yrs. Significant difference in prevalence of bacterial isolates with respect to sex and age was seen between the two groups (table 1). The most frequent microbial isolates in CSOM subjects was Pseudomonas aeruginosa (24%) followed by Staphylococcus aureus (19%) whereas in CRS with CSOM subjects, Staphylococcus aureus was 45% and Pseudomonas aeruginosa was 20%. Antibiotic susceptibility of staphylococcus aureus was high to cefotaxime, amikacin and gentamicin in both the groups. Antibiotic resistance of staphylococcus to ciproflaxacin is 78.8% and vancomycin is 55% in CSOM subjects . High rate of antibiotic sensitivity of Pseudomonas aeroginosa was observed for imipenem, piperacillin tazobactam, cefotaxime and amikacin in both the subgorups. Antibiotic resistance of Pseudomonas aeroginosa to ciproflaxacin is 55%, Gentamicin 47.2% and Cefepime 50% in CSOM subjects. Antibiotic resistance of Pseudomonas aeroginosa was not seen in CRS with CSOM subjects (Table 2).