Hospital infection (HI) are a public health problem mainly because they increase morbidity and mortality of hospitalized patients, at the time of hospital stay (Jarvis, 1987;). Infections caused by antibiotic resistant bacteria are a growing concern in hospital, the hospital environment may play a significant role in the transmission of microorganism (Al Barrak A., et al., 1998).

Resistance to a variety of antimicrobial agents in emerging the bacterial pathogens throughout the world, the emergence of antimicrobial resistant strains of pathogenic bacteria has become a great threat to the public health, resistance to commonly prescribed antibiotics is an expanding global problem and has been observed in both developed and developing countries. (Finch R.G., 1998; Farrar EW., 1985; Rahal K, et al., 1997; Tennol F.C., et al., 1996;). Resistance has emerged even to newer, more potent antimicrobial agents (Parry MF., 1989;). A number of epidemics have recently occurred by multiple resistant organism. (Frost JA, et al., 1981; Olarle J, et al., 1976) Plasmid encoded resistance to amino-glycoside in gram negative bacilli has been a significant clinical problem in many hospitals since the middle 1970’s Epidemiological studies of

Impact of antibiotics on origin of resistance genes

We frequently refer to bacteria as being resistant to antibiotics, but rarely do we consider what that means, even the most resistant bacterium in can be Inhibited or killed by a sufficiently high concentration of antibiotics, patient, wherever would not be able to Tolerate the high concentration required in some cases bacterial species vary tremendously in these susceptibility to an antibiotic. The origins of antibiotic resistance genes are obscure because at the time that antibiotics were introduced biochemical and molecular basis of resistance was yet to be discovered bacteria collected between 1914 and 1950 (Marray Collection) were later found to be completely sensitive to antibiotics. They did however contain a range of plasmid capable of conjugative transfer (Hughes V.M., et al., 1983;) none of the Murrey Strains was resistant no sulphonamides, although there had been introduced in the mid – 1930; resistances was reported in the early 1940s in streptococci and gonococci (Davis, J.E., 1997;) Introduced
in the mid-1930s; resistance was reported in the early 1940s in Streptococci and gonococci (Davis J.E., 1997; the Introduction of streptomycin for treating tuberculosis was thwarted by the rapid development of resistance by mutation of the target genes. Mutation is now recognized as the commonest mechanism of resistance development in Mycobacterium tuberculosis, and the molecular nature of the mutation, conferring resistance to most Anti tuberculosis drugs is known (Musser J.M., 1995) favorable mutation that arise in bacteria can be mobilized via insertion sequences and transposons on an to plasmid and then transferred to different bacteria.

In considering the evolution and disseminations of antibiotic resostance gene it is important to appreciate the rapidity of bacteria multiplication and the continued exchange of bacteria among animal, human and agricultural hosts throught the world there is support for the notion that determinats of antibiotics resistance were not derived from the currently observed bacterial host in which the resistance plasmid is seen. DNA sequencing studies of β-Lactamases and aminoglycosides inactivating enzymes show that despite similarities within the protein studies of the two families, there are substantial sequence differences (Bush K. et al., 1995; Shaw K.J., et al., 1993) as the evolutionary time frame has to be less then 50 years it is not possible to derive a model in which evolution could have occurred by mutation alone from common Ancestral genes Thus must have been derived from a large and diverse gene pool presumably already occurring in environmental bacteria.
2.1 Impact of Antibiotics on Enterobacteriaceae

Klebsiella pneumoniae is a successful opportunistic pathogens and has been associated with various ailments such as urinary tract infections, septicemia, respiratory tract infections and diarrhea. (Podschun R, et al., 1998;) Resistance of this species to third generations cephalo-sporins such as Oxyimino β-Lactams was first described in 1980 since them a linear increase in resistance has occurred, Extensive use of newer generation Cephalosporin has been the strong factor for the evolution of new β-Lactamases such as ESBLs. ESBLs are encoded by Transferable Conjugative Plasmids, which after code resistance determinants to other antimicrobial agents such as Amino glycosides there conjugative plasmids are responsible for the dissemination of resistance to other member of gram negative bacteria in hospitals and in the community (Sirot D, et al., 1987; Jaloby GA, et al., 1991; Knoth H, et al., 1983; Phillippon A, et al., 1989).

Transmissibility of drug resistance and ESBL production was also studied, since Klebsiella are considered as important source of transferable drug resistance among different species of Enterobacteria (Caswell MW, et al., 1981). Extended spectrum beta-lactamase (EsBL) mediated resistance to third generations cephalosporins among pneumonia in Chennai (Subha A, et al., S, 2002).

The incidence of EsBL producing strains among clinical isolates has been steadily increasing over the past year resulting in limitation of therapeutic options (Podschun R, et al., 1998;) Microorganism responsible for UTI such as
Escherichia coli and Klebsiella is large quantities these enzymes are plasmid borne and confer multiple drug resistance, making UTI difficult to treat (Bal S. 2000) Extended spectrum β-Lactamases in urinary isolates of Escherichia coli and Klebsiella pneumonia. (Baby Padmiris, (2004)).

The most important causative agents of nosocomial infections are bacteria (Qadri SMH, et al., 1995 ;) A large number of bacteria are potential pathogen in hospitalized patients, Klebsiella, Proteus, Morganella, Enterobacteria, Citrobacter, Serratia, Acinetobacter and Pseudomonas spp. are commonly associated with the hospital environment and also be isolated from patients with underlying diseases.


Klebsiella Pneumonia is an important hospital acquired pathogen with the potential of causing severe morbidity and mortality in pediatric patients several out breaks of infections caused by K. Pneumonia isolates that are simultaneously resistant to Broad spectrum cephalosporins and aminoglycosides have been widely reported (French. G.L., et al., 1996; Gniadkowski, M. et al., 1998; Pena C., et al., 1998; Rice L.G., et al., 1996) Some of there multi resistant isolates produce extended – spectrum β-Lactamases (EsBLs) that are able to hydrolyze expended spectrum cephalosporins (e.g. Ceftriaxone, Cefotaxime, and Ceftazidime) aztreonam, and related oxyimino β-Lactamases. Most of this enzymes are TEM – or SHV – type β-Lactamases in which the substitutions of one or more amino acids has altered the configuration of the active site (Bush. K, et al., 1995; Medeirus A., 1997; Philipon R, et al., 1989) Most of the plasmids determing EsBLs are large (≥ 80 kbp) and encode multiple resistance. (Jaloby G., and A. Mederios, 1991).

The incidence of R-Plasmid mediated drug resistance in enterobacteria isolated from Patients in general practice, but some of these reports include hospital patients as well. (Harkness J.C., et al., 1975; Moller J.K., et al., 1976;
Pause M.V., and K.M. Wadhawa 1973) the presence of R-Plasmids was generally inferred in their investigations from Transmittance of resistance by conjugation.

Multiple antibiotic resistances to useful classes of antibiotics, including the Penicillin's cephalosporin aminoglycosides, and fluoroquinolones has gradually increased among a number of gram negative hospital pathogen, especially Klebsiella pneumonia. (Falkows S, 1975; Endtz H.P., et al., 1997) Enterobacter species (Chow JW., et al., 1991; De Ghaldre Y. et al., 1997) Pseudomonas aeruginosa epidemics and endemics infections caused by these multiple resistant strains followed intense antibiotics use in many hospitals, particularly in intensive care units. (Gold H.D., Noellering Re, 1996;) Chow JW., et al., 1991; Richard P., et al., 1994).

2.2 Impact of Antibiotics on Gram Positive cocci

Some reports have documented the conjugal transfer of gentamicin resistance (Gm\(^1\)) plasmids in staphylococcus aureus (Forbes B.A., and D.R. Sehaberg., 1983; Mc Donnell. Row., et al., 1983; Sehaberg D.R., et al., 1982) the proportion of staphylococcus Gm plasmid which are self transmissible (Tra\(^+\)) however and the extent to which conjugation may account for the emergence of Gm staphylococcus aureus is as yet unknown.

Aminoglycoside resistance plasmids can reside in avirulent, colonizing Staphylococcus epidermidies strains which are selected by antibiotics as the Predominant skin flora in ill patients (Archer G.L., and B. Armstrong 1983; Jaffe, H.W., et al., 1980; Weinstein R.A., et al., 1982).

Transfer of aminoglycoside resistance to more virulent S. aureus strains can then occur on human skin (Jaffe H.W., et al., 1980; Naldoo J., and W.C. Noble 1978) Aminoglycoside resistance allows staphylococci to survive in areas of the hospital where aminoglycoside usage is high.

Transfer of R-Plasmids among staphylococci traditionally has been thought to occur only by Transformation or Transduction (Jaffe H.W., et al., 1980; Lacey R.W, 1975 ;) However the rapid emergence and spread of aminoglycoside resistance among staphylococcus in hospitals and the transfer of aminoglycoside resistance plasmids among staphylococcus mixed culture (Jaffe, H.W., et al., 1980) and on human skin (Jaffe H.W., et al., 1980; Naldoo, J., and W.C. Woble 1978) Suggested that another means of Aminoglycoside resistance transfer many be involved.

Two publications appeared recently which documented conjugal transfer of aminoglycoside resistance plasmids among staphylococcus (Forber B.A., and

Staphylococcus aureus infections remains a significant problem in hospitalized patients after the introduction of each new antimicrobial effective against S.aureus, staphylococcal strains have appeared which are resistant to that antibiotic, and resistance is often mediated by R-Plasmids. It has been proposed that transfer of resistance genes from Staphylococcus epidermidies to Staphylococcus aureus – might occur where by S.epidermidies strains would serve as a reservoir for resistance plasmid (Lacey, R.W., 1975) several studies support this hypothesis. Iordanesus *et al.*, 1978; and Sjostrom J.E., *et al.*, 1979) described resistance Plasmids Isolated from S.aureus and S.epidermidies “Strains which were similar”. Jaffe H.W., *et al.*, 1980; 1982; and more recently Cohen *et al.*, 1970; described nosocomial outbreaks of infections due to an S.aureus strains with a specific resistance Phenotype. Examination of the molecular epidemiology demonstrated that S.epidermidies and S.aureus isolates contained homologous gentamicin resistance plasmids. Furthermore Jaffe *et al.*, described transfer of gentamicin resistance between S.aureus and S.epidermidies strains by Transduction. Inter generic transfer of conjugal resistance plasmid from streptococcus faealis to S.aureus has been described. (Schaberg D.R., *et al.*, 1982 ;) It was determined that the streptococcus conjugative plasmids, once in S.aureus, retained the ability to transfer resistance to other Staphylococcal recipients.
Enterococci commensal inhabitants of the Intestinal and genital tract, are rising in prominence as hospital pathogen (Falkows. S., 1975) this rise in related to their natural resistance to most commonly used antibiotics and their capacity to acquire resistance to other antibiotics either by mutation (penicillin) or by transfer of resistance genes on plasmids and transposons (Aminoglycosides and glycopeptides) (Falkow.S., 1975; Flaherty JP., and Weinsterm, 1996).

2.3 Impact of Antibiotic on Pseudomonas species

The transfer of drug resistance from Pseudomonas to Escherichia coli occurs at very low frequencies (Smith, D.H, 1967) except in a few instances (Fullbrook P.D., et al., 1970; Sykes R.B., and M.H. Richimoud, 1970). There strains of Pseudomonas aeruginosa were demonstrated to transfer double drug resistance by conjugations to a P. aeruginosa recipient at frequencies of \(10^{-4}\) to \(10^{-2}\) per recipient cell (L.V. Bryan, et al., 1972).

In the past few decades P. aeruginosa has been increasingly recognized as a pathogen in a variety of serious infections in hospitalized patients especially with impaired immune defenses. (Neu H.C., 1983). This organism is an important opportunistic pathogen with innate resistance to many antibiotics. Despite innate resistance, additional acquired resistance due to plasmids is also found in P. aeruginosa. Plasmid mediated resistance to various antimicrobial drugs have been demonstrated by various workers (Karunasagar I, et al., 1987; Kawakami, et al., 1972; ) and most of them have demonstrated it by plasmid curing experiments alone. Ten Multi drug resistant (MDR) isolates of
P. aeruginosa obtained from hospitalized burn patient and all the isolates were found to harbor R-Plasmid (Shahid M., 2004).


Pseudomonas aeruginosa, although resistant to many antibiotics, has been generally susceptible to gentamicin and Carbenicilli. Recently, description have appeared of R-factors in this organism, including reports of factors determining resistance to one or the other of these antibiotics (Bryan. L.E., *et al.*, 1973; Bryen L.E., *et al.*, 1972; Fulbrook P.D., *et al.*, 1970; Jacoby G. 1974; Knothe K., *et al.*, 1973, Lowbery E., *et al.*, 1969; Sykes R.B., and Richruond 1970; Van, Reusterg A.J, 1974; Witahitz J.L., and Y.A. Chabbert 1971) these findings prompted our search for transmissible drug resistance among clinical strains of Pseudomonas aeruginosa.