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Superbugs Spread and Problems of Multidrug-Resistant Infections during Surgery

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ABSTRACT

Surgical procedures are part of our life where normal mechanisms of cells in blood and tissues are hampered creating bacterial infections which are so far controlled by antibiotics since 1950s. Sudden increase in drug resistant pathogens has created a shadow for traditional use of antibiotics before and after surgery. The creation of diversified MDR genes in R-plasmids and integrons (~2-9 kb) is the main cause of drug resistance. However, MDR genes save the gut microbiota for vitamin synthesis whereas vitamins as coenzymes are absolutely needed for >30000 enzymatic reactions for normal human metabolosome. Continuous insult of gut microbiota with antibiotics and therefore our intestinal cells have resulted in a tight symbiotic control where creation of a new *mdr* gene against a new antibiotic will take only few days to few weeks. This has happened due to combination of R-plasmids/integrons with F'-plasmid creating MDR conjugative plasmids (50-500 kb) with a more space for 5-15 *mdr* genes, 10-20 Tra genes and 20-60 transposons or IS-elements encoding many integrases, recombinases, DNA polymerases, reverse transcriptases and DNA topoisomerases. Those enzymes are absolutely necessary for new gene creation. Thus drug companies are in fear for antibiotic market and new antibiotic discovery has stopped. However, surgical procedures are increased 50-400 fold as compared to year 2000 data indicating a huge demand of potent antibiotics that could kill superbugs and prevent infection after surgery. WHO has suggested a new direction for antimicrobial research involving heterogeneous phyto-antibiotics, enzybiotics and phage therapy. G-20 leaders are ahead to augment effective one nation research platform for superbug control. We also see gene therapeutics and nanotechnology based drug carriers are in the fore front for the treatment options of MDR infections during surgery. However, MRSA *Staphylococcus aureus*, MDR *Acinetobacter baumannii*, XDR *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* and NDM-1 *Escherichia coli* infections are deadly.

Keywords: MDR infections, Surgery, Symbiosis, Gut microbiota, Biofilm

INTRODUCTION

Human life suffers from many ailments and so far antibiotics and many other antagonistic drugs have cured the diseases since 1928 [1]. Surgery is evident in case of tumors in diverse organs, infections of intestine, blockage of artery and every day accidental fractures or burn [2]. Also in the developed countries cosmetic surgeries are increased many fold [3]. The concept to reduce the surgical infections was came from Dr. Josheph Lister in 1860s when phenol was found good disinfectant for surgical instruments reducing death rate after surgery [4]. Antibiotic were discovered by Nobel Laurates Alexander Flaming and Selman Waksman in 1930s but penicillins and tetracyclines were came to market for all in 1943 after World War II. Ampicillin, amoxicillin, tetracycline, chloramphenicol, sulfamethoxazole, azithromycin, vancomycin, colistin, ciprofloxacin, streptomycin, refampicin, norfloxacin, cefotaxime and imipenem are great antibiotics those had safely rule the drug industry for 80 years and perhaps still now if the infections

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were not drug resistant [5]. During surgery prophylactic antibiotic therapy was utilized until in recent years drug resistant *Pseudomonas aeruginosa* and *Acinteobacter baumanii*, etc., were appeared. Hundreds of Beta-lactamase genes are assembled in bacterial plasmids as well as chromosome (as in MRSA *Staphylococcus aureus* infections in burn patients) [1,6,7]. Beta-lactamase gene is *amp* gene which was discovered in 1965 in pBR322 plasmid which was also contain tet gene. Presently, amp gene was termed as bla gene which was diversified into 20 distinct isomers **(Figure 1)** with no sequence similarities [6]. Cat gene and related aacC1 or aacA1 genes acetylate many drug's -OH and -NH_2 groups or aminoglycoside drugs are phosphorylated at –OH group by strA, strB or related many APH enzymes [1]. Adenylation (aad genes) and ribosylation (arr3 gene) are other rapid mechanisms of inactivation of drugs like streptomycin and rifampicin respectively generating major drug resistant TB and Gonorrhoea [1]. Interestingly, 200 ABC transporter-like drug efflux genes (tetA/C, acrABC, mexAB/CD/EF, mcr, norA, mtrCDE, macAB) made most devastation in drug industry as all drug's MIC were increased now-a-day [8].

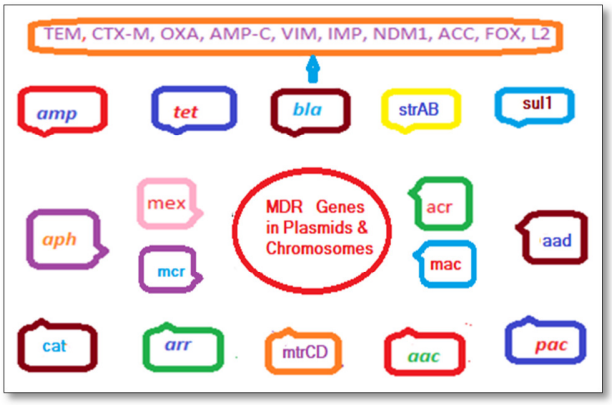

Figure 1. Too many antibiotic resistant genes were discovered in bacterial plasmids and chromosomes.

Amp gene encodes 286 aa beta-lactamase enzyme that degrades beta-lactam A ring of penicillin. Tet gene kicks out tetracycline drug from bacterial cytoplasm increasing MIC, so no binding to ribosome for inhibiting protein synthesis. *Bla* genes are blaTEM, blaCTX-M, blaOXA, blaCMY, blaAmp-C and blaNDM-1, etc. and also degrade lactam A ring of penicillin, cephalosporins and in some case carbapenems. Sul1/2 is altered enzymes give resistant to sulfamethoxazole. *Aph* gene encodes phosphotransferases and phosphorylated amikacin and phosphorylated-tabromycin no longer bind ribosome to kill bacteria. StrA/B are enzymes that phosphorylate streptomycin and aacC1/A1 are enzymes that acetylate aminoglycoside antibiotics and in some case ciprofloxacin type fluoroquinolones. mtrCD are drug efflux enzymes similar to mexAB/CD enzymes or acrAB/CD enzymes. Chromosomal macA/B genes of *N. gonorrhoeae* inactivate macrolide antibiotics. *Cat* and *Pac* genes acetylate chloramphenicol and puromycin, respectively.

Figure 2. EM structures of few gram positive and gram negative MDR microorganisms (1-1.5 µm; 6000x).

For example, we see 40% of sea, river and pond household bacteria resistant to ampicillin, amoxicillin and to lesser extent tetracycline and ciprofloxacin, drugs widely used between 1950-1990 [9]. The situation was controlled by development of cefotaxime, meropenem, lomofloxacin, amikacin, colistin and linezolid types drugs [10]. Sadly, in 2009 blaNDM-1 enzyme gave carbapenem resistant and in 2016 mcr-1 enzyme gave colistin resistant where as blaOXA and blaCTX-M new isomers (ESBLs and MBLs) enzymes were mostly resistant to all penicillin's, cephalosporins and carbapenems or related inhibitors. More generously, R-plasmids (5-15 kb) were combined with many integrons (2-4 kb) and F'-plasmid (62 kb) generating MDR conjugative plasmids (50-500 kb) which were very dangerously donating mdr genes to most Enterobacteriaceae present in water resources [11]. The point is, most trusted antibiotics are no longer safe as prophylactic therapy during surgery [4,5]. It is also evident that intestinal cells and gut microbiota are in symbiosis to exchange nutrients residing in the biofilm where microbes can withstand low dose of antibiotics but hardly withstand the repeated high doses of antibiotics [12]. Repeated high dose antibiotics is a concern as it affects kidney, liver and most importantly intestinal luminal cells being symbiosis with gut microbiota hampered lowering coenzymes concentration [13]. Such cells now secrete many interleukins and cytokines influenced by bacterial LPS, vitamins and butyrate. Thus such mechanisms demand the life of bacteria and signals to rearrange genes in bacterial plasmids containing many IS-elements, transposons, topoisomerases and integrases [14]. Such hypothesis is true as many plasmids acquired vitamin metabolizing genes and also ¼ genes are unknown but likely are required for gut microbiota protection [15]. In other words, it now only took few weeks to make a new gene to inactivate the action of a new antibiotic which cost two billion dollars for its

development requiring about ten years. This decade is sad for drug companies as no new drugs for bacterial infections but on the other hand, plenty of drugs have been developed recently for cancer, diabetes, hypertensions and AIDS. We thus have declared antibiotic void day as present before 1928.

MATERIAL AND METHODS

Purification of superbugs from Ganga river water and Digha sea water

Water from Ganga River was collected at the morning from Babu Ghat (Kolkata, 700001) and Howrah Station River [9]. About 100 µl of water was spread onto 1.5% Luria Barton-agar plate containing different concentration of antibiotics at 2-50 µg/ml. MDR bacteria were selected in agar-plate containing ampicillin, streptomycin, chloramphenicol, tetracycline or ciprofloxacin at 50, 50, 34 and 20 µg/ml, respectively. As imipenem and meropenem resistant bacteria were present low (0.08-0.2 cfu/ml water), a modified method was followed. 2 ml 5x LB media was added into 10 ml River/Sea water at 2-10 µg/ml concentration and was incubated 24 h to get drug resistant bacteria population [10]. Meropenem resistant bacteria were further selected on tetracycline, chloramphenicol and streptomycin to get the superbugs. Antibiotics were purchased from HiMedia and stored at 2-50 mg/ml at -20°C. Antibiotic papers were also purchased from HiMedia according to CLSI standard. Antibiotic papers are: A-25 (ampicillin), T-10 (tetracycline), AT-50 (aztreonam), COT-25 µg (Cotrimoxazole), Met-10 µg (methicillin), CAZ-30 µg (ceftazidime), LOM-15 µg (lomofloxacin), VA-10 µg (vancomycin), AK-10 µg (Amakacin), TGC-15 µg (tigecycline), LZ-10 µg (linezolid) and IMP-2 µg (imipenem).

Molecular biology techniques

The plasmid DNA was isolated from overnight culture using Alkaline-Lysis Method [15,16]. 16S rDNA gene colour Sanger's di-deoxy sequencing was performed by SciGenom Limited, Kerala, India [17]. PCR amplification was performed using 1 unit Taq DNA polymerase, 20 ng DNA template, 0.25 mM dXTPs, 1.5 mM $MgCl_2$, for 35 cycles at 95°C/30" (denaturation)-52°C/50" (annealing)-72°C/1.5'. The product was resolved on a 1% agarose gel in 1x TAE buffer at 50 V for 2-4 h and visualized under UV light and photograph was taken [10]. NCBI BLAST analysis was performed for bacterial specific gene analysis (http://www.ncbi.nlm.nih.gov/blast) and data was submitted to GenBank. NCBI databases were retrieved using the BLAST programmes [11]. The complete genes are sequenced in plasmids and were analyzed by Seq-2 programme of BLAST [18]. We type the same at the NCBI port (http://www.ncbi.nlm.nih.gov/nucleotide or http://www.ncbi.nlm.nih.gov/protein) and to BLAST search to type the accession number for protein or DNA into BLAST port-(https://blast.ncbi.nlm.nih.gov/Blast.cgi?PAGE_TYPE=BlastSearch) [19,20].

RESULTS

The household bacteria in river, sea, pond and rain water are drug resistant and air P10 particulate carry high concentration of MDR bacterial spores. As for example, **Figure 3** showed the drug resistant pattern of a Ganga River superbug and **Figure 4** shows how chloramphenicol resistant cat enzyme formed acetylated chloramphenicol which ran fast in a Thin Layer Chromatography and such drug derivative could not able to inhibit bacterial protein synthesis. The *Escherichia coli* KT-1_mdr was only sensitive to imipenem and linezolid but was resistant to other seven drugs (**Figure 3** and Material and Method). Interestingly, 1,3 di-OH chloramphenicol although bigger (two CH3CO- group were added in place of two hydrogen atoms) but ran first in Silica gel ascending chromatography in organic solvent (methanol, isopropanol) **(Figure 4)**.

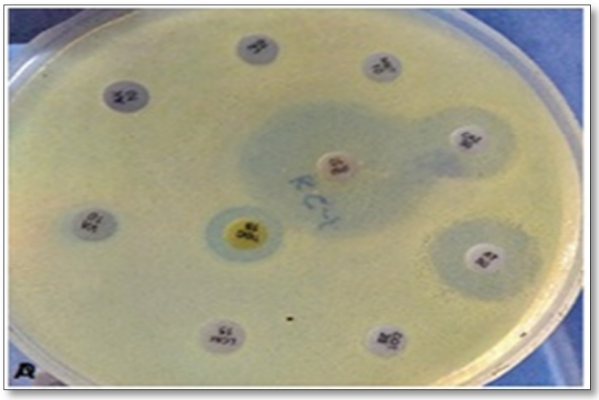

Figure 3. Drug sensitivity of *Escherichia coli* KT-1_mdr isolated from Ganga River of Kolkata.

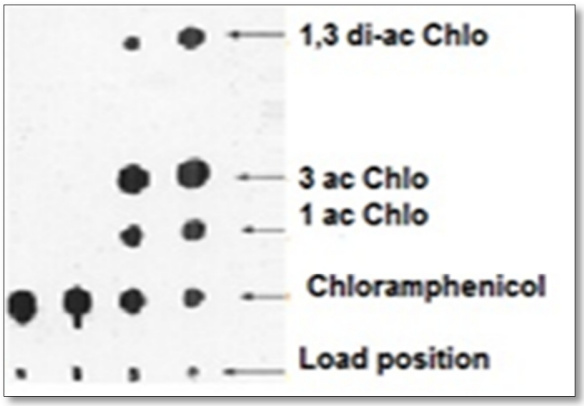

Figure 4. TLC assay of chloramphenicol showing CAT enzyme action on drug.

Such demonstration proved that during surgery antibiotic treatment is not as effective and trustworthy now as before. **Table 1** demonstrated that different cosmetic surgeries were increased in the USA. Brest augmentation in 2017 is 46%

increase as compared to 2000 and similarly Tummy tuck has increased 107% whereas upper arm lift has increased tremendously to 4235%. In 2012, 80 million surgeries were performed in the United States but now worldwide surgeries were increased to 234 million. By 2030, prosthetic joint arthroplastics are projected to increase 3.8 million per year. Surgeries of mouth, GI tract, respiratory tract require high dose cefazolin (2 g) or (+metronidazole) but now blaCTX-M-2/9/15 are expressed in most bacterial plasmids (*E. coli*, *P. aeruginosa*, *A. baumannii* and *S. aureus*). Vancomycin (15 mg/kg) and gentamycin (5 mg/kg) are advised as postoperative infections but vanA gene cluster is very much present in *Enterobacter aerogenes*, Proteus mirabilis and *Helocobacter pylori* MDR bacteria. A best pre-operative antibiotic prophylaxis is Clindamycin but aacC1/A1 type acetyl transferases very much active in most bacteria to inactivate such drugs. So Ertapenem (1 g) and Meropenem (0.5 g) are advised now but blaNDM-1 as well as blaKPC-2 is increasing in *Pseudomonas aeruginosa* and *Clostridium difficile*, etc. plasmids (accession nos. KP009590; KP735848; KP265934; KP893385; KJ748372; FJ624872). Alternately, many patients do not tolerate penicillin drugs and also there is Stevens-Johnson syndrome and toxic epidermal necrosis. Old drug colistin is used in superbug infection but recently *mcr-1* gene has discovered in *Escherichia coli* and *Pseudomonas aeruginosa* plasmids [21,22].

The worldwide surgical procedures (234×10^6) are increased tremendously. As for example, approximate reported cases are: Injuries 63×10^6, malignancies 31×10^6, congenital anomalies 14×10^6, Obstetrical complications 10×10^6, Cataract and Glaucoma 8×10^6, Perinatal conditions 7×10^6 and other like cosmetic surgeries 31×10^6 [23,24]. In Africa 15 injuries/1000 peoples/day is the highest as also in South Asia 13 injuries/1000 peoples/day [25]. Between 2009-2014, 125,378,073 surgery procedures are recorded in the United Kingdom (England, Wales, Scotland and Ireland) which means 24 procedures per 1000 peoples per year with cost of $104.4 billion. In India 31.5×10^6 of surgical procedures were reported in 2017 (**Figure 5**) of which 52.4% were obstetrical and gynecological and 25.9% ophthalmological [26,27]. The cosmetic surgeries are increasing in the United States as shown in **Table 1**. Brest reduction and Liposuction surgeries are ahead but infections are also frequent [28].

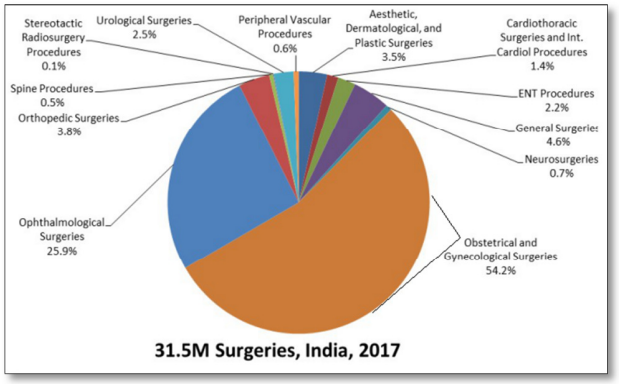

Figure 5. Statistics of invasive surgical procedures in India during 2017.

Table 1. Types of cosmetic surgeries in the US. Further, Brest implant removal (0.27×10^5), Facelift (1.25×10^5), Tummy tuck (1.29×10^5) surgeries appear increasing (https://www.plasticsurgery.org as assessed on 26.04.2018) African American has more heart attach (19.7%) than White American (10.9%) and much higher than Asian American (7.1%).

Total Cosmetic Procedures in the United States in 2017=17.5×10^6.					
Cosmetic Minimally Invasive Procedures			**Cosmetic Surgical Procedures**		
Botulinum type A	7.2×10^6	2% u	Breast Augment	0.3×10^6	3% u
Soft Tissue Fillers	2.7×10^6	3% u	Liposuction	0.24×10^6	5% u
Chemical peel	1.4×10^6	1% u	Nose Reshaping	0.2×10^6	2% d
Laser Hair Remover	1.1×10^6	2% d	Eyelid Surgery	1.3×10^6	0
Microdermabrasion	0.7×10^6	4% d	Breast Reduction	5.8×10^6	11% u

Wound infections are generally occurred by drug resistant *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumonia*, *Acinetobacter baumannii*, *Prividentia stuartii*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Morganella morganii* and *Proteus mirabilis*, etc. Gram positive and Gram negative bacteria [25,26]. Many pathogens are *ESBLs* and *blaTEM*, *blaCTX-M*, *blaNDM-1*, *aacA1*, *catB3*, *strAB*, *sul1/2*, *arr3*, *aphA2*, *aadA4* and *ermB* genes were reported in plasmids and chromosomes as recently were demonstrated by full length plasmid DNA sequencing (**Table 2**). Majorities of surgeries of intestine are greatly affected after surgeries being 2×10^{12} gut bacteria reside there and many are drug resistant [26]. The *Clostridium difficile* Infections (CDI) during colorectal surgeries has increased tremendously irrespective of hospital setting [27,28]. Inflammatory Bowl Syndromes (IBD) generally persist CDI and after surgery many patients have returned to hospital with CDI with *ermB* genes in plasmids and chromosomes giving resistant to clindamycin, erythromycin, ciprofloxacin, tobramycin and gentamycin but

sensitive to ceftizidine. *Clostridium sordelli* on the other hand has pCS1 plasmid with toxin TcsL gene as well as ermB DNA methylase gene and capable of conjugative gene transfer involving cst locus [29]. *Clostridium perfringens* carry on the other hand tetracycline resistant 45-140 kb pCW3 and pXO1/2 plasmids encoding toxin (Beta-toxin) as well as *mdr* genes. Other suggested phiCD211-like 131 kb bacteriophages genome insertion in *Clostridioides difficile* (5% prevalence) activating multidrug-resistant AcrB/D/F drug efflux genes [30]. *Enterococcus faecium* infections during surgery is also evident and such strains carry 60-100 kb plasmids like pAD1, pMG1, pPD1, pMG2201, pWZ1668, pJEG043, pS177, pE856 and pRE25 conferring gentamycin, erythromycin and or vancomycin resistance (**Table 2** for large MDR plasmids) [31].

Table 2. Generation of multidrug resistant plasmids with diversified *mdr* genes in superbugs.

Plasmids	Accession	Length	Multidrug resistant genes	Pathogens
pLW043	AE017171	59 kb	Dhfr, GNAT, aacA-aphD (6'-2"), vanR/S/H, vanA, vanB, vanY/Z, blaTEM, blaR1, blaI	*Staphylococcus aureus*
pSD107	JX566770	107 kb	aadA1, dhfr, strB, blaTEM, sul2, aph6'-1d	*Enterobacter aerogenes*
pS121-1a	CP022170	192 kb	mexC, aac6'-1b, cmlA5, ANT3"-1a, dhfr, aac6'-1b-cr, OXA1, sul1, mphE 2', floR	*Aeromonas sulmonicida*
pTW9	AB563188	85 kb	ABC, bcrD, ermB, vanY/X, vanA, vanS/R, blaTEM	*Enterococcus faecalis*
pEGY1mcr-1	CP023143	229 kb	Aac3'-IIa, EmaA, TelA/B/F, tetA, mcr-1, ANT3"-Ia, cmlA, sul1, floR	*Escherichia coli*
P1068-KPC	MF168402	146 kb	CTX-M-65, TEM-1, SHV-12, KPC-2, MerA/C, RmtB	*Klebsiella pneumoniae*
PSHE-CTX-M	CP022359	193 kb	CTX-M-15, aac3'-IIa, CusA, tetA, aph3"-1d, aph3"-1b, sul1, (Vit*)	*Shewanella bicestrii*
pECAZ155_KPC	CP019001	272 kb	KPC, mphA, sul1, aac6'-II, cmlA, aph6'-1d, CMY-2, MFS, tetB, aac6'-1a	*Escherichia coli*
pEA19081	KX976485	79.8 kb	vanH, VanA, vanBm, FosB, vanY, vanS/R, vanZ	*Enterococcus avium*
pKP13f	CP004000	295 kb	Sul1, QacE, TEM-1, OXA-9, aad3", sul2, CTX-M-2, aac6'-Ia, TerX/X/A	*Klebsiella pneumoniae*
pAUSMDU8141	CP022697	149 kb	MFS, sul1, catA2, tetD,TEM-1, aac3'-Ia	*Citrobacter farmeri*
pKN-LS6	NC_021654	246 kb	catA1, dhfr, sul1, mphA, MFS, ABC, silP/E/A/B, arsH/A, cusB/C/S	*Klebsiella pneumoniae*
pHXY0908	KM877269	249 kb	Aad, floR, aac6', aac3', blaOXA, catB, arr3, sul1, cmlA, aphA1	*Salmonella enterica*
pRJ119-NDM1	KX636095	335 kb	Ble, TEM, **cobS**, aac6', sul1, cusA,arsD, dhfr, qnr, tetA, NDM1, aph3', sul,arsH	*Klebsiella pneumoniae*
P1	NC_019375	180 kb	blaVIM, aacA7, dhfr, ANT3', blaSHV-5,	*Providencia stuartii*

			sul1, aph3'	
pOZ176	KC543497	501 kb	Ter2, OXA-10, MFS, TEM-8, ble, catB3, aac6'. IMP-9, neo	*Pseudomonas aeruginosa*
pKPx-2	AP012056	141 kb	Aac3'/6', catB4, tetA, sul2, OXA-1, CTX-M, TEM-1, strAB, qnrB	*Klebsiella pneumoniae*
pHX40908	KM877269	249 kb	Aad, floR, hph, aac6'/3', OXA-1, catB3, arr3, sul1, cmlA	*Salmonella enterica*

DISCUSSION

Bacteria present in air, water and every matters that associated with air and water [10]. We now see how it is advisable for preventing bacterial contamination during invasive surgery and burn. First, we must be aware of MRSA *Staphylococcus aureus* infections which are not only carry MDR plasmids but also "MDR Islands" in chromosome and it is almost death signal in case of burn patient's infection. Again drug cocktail is must be given which is injurious liver, kidney and intestine and more sadly many antibiotics has acquired drug induced expression of MDR genes like blaAMP-C gene induction by imipenem, a drug mostly used in MDR infections between 1985 to till date [9]. Imipenem now has replaced by potent derivatives like meropenem and dorripenem that block bacterial cell wall peptidoglycan synthesis.

Presently, we most blame *Acinetobacter baumannii*, a Gram(-) bacteria being highly resistant to disinfections and its spore can withstand in surgical instruments for months. Essentially, ampicillin, cefotaxime, imipenem, ciprofloxacin, azithromycin, streptomycin, tetracycline, chloramphenicol are useless as single plasmid could carry 10-15 mdr genes (accession nos. CP001921, CP002522, AP013357). Importantly, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* are dangerous as have acquired mexAB/CD/EF and smeDEF drug efflux genes cluster respectively as well as tetA/C drug efflux genes other than few bla gene isomers and acetyl- or phospho-transferases (accessions nos. AM743169; KC543497; HE798556). *Klebsiella pneumoniae* is another culprit that cause nosocomial infections and we see hundreds of potent MDR plasmids have been sequenced today to clarify that during surgery such bacterial infections could be deathful (accession nos. NC_021232; KT185451). In India clinical isolates of *E. coli* have blaPER, blaVIM and blaTEM where as in *P. aeruginosa* blaOXA-23, blaNDM-1, blaOXA-51 are very prevalent *mdr* genes [32]. In liver cancer surgery, a shift of gut microbiota has been observed where probiotic therapy could be beneficial and likely indicates drastic action of prophylactic antibiotics on gut microbiota population [33]. Other than *S. aureus* well characterized chromosomally encoded *mdr* determinants (SECmec), *Salmonella typhi* Asian isolates have shown to harbor both chromosomal and plasmid encoding *mdr* genes giving resistant to fluroquinolones, 3rd generation cephalosporins and aminoglycosides [34]. A Kolkata study between 1998-2012 indicated the decrease in ampicillin resistance but increase in ciprofloxacin resistance among *Salmonella enterica* clinical isolates but our recent study had demonstrated that blaTEM, blaCTX-M and aac6'-1b genes were very frequent in most environmental Enterobacteriaceae [10,35].

CONCLUSION

We conclude that surgical infections will be problem even we use antibiotics. But some reports advice ampicillin, chloramphenicol, ciprofloxacin and streptomycin as preoperative prophylaxis which totally wrong this days. Main reason is high cost of carbapenem and new aminoglycosides and peptide antibiotics (100 times) which is very hard to pay by poor patients of Asia, Africa and Latin America. Sadly, Drug Sensitivity Tests are not mandatory in India and patients are given repeated antibiotic doses which is totally devastating for health [36-40]. Doctors sometime prescribe high cost vitamins and probiotics to patients but many good drug companies have low cost such nutrients and medicines for poor countries. WHO and CDC guidelines are there but Nursing Homes hardly follow such guidelines and Government has no control of such malpractices in poor nations [37]. Medical cost drags millions peoples into poverty line each year and is very catastrophic in the light of 21st century civilization. Many surgeries in India cost much less than developed world. As for example, liposuction in the USA cost rupees 483941, in the UK cost rupees 387153 but in the India cost rupees 64000. Thus many tourists have done plastic surgeries in India. Global surgery procedures are 234 million and in India 31.5 million. So we should find alternative to antibiotics. Phyto-antibiotics, phage therapy, enzybiotics, gene therapeutics and nanotechnology are the driving forces shaping next generation antimicrobials to prevent infections during surgery [41-48].

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