OLD IS GOLD

IS IT TRUE FOR ANTIBIOTICS ?

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A new strategy to fight antimicrobial resistance: the revival of old antibiotics

INRODUCTION

- The **increasing prevalence** of hospital and community-acquired infections caused by **multidrug-resistant (MDR) bacterial** pathogens is **limiting the options for effective antibiotic therapy.**
- Moreover, this alarming spread of antimicrobial resistance has **not been paralleled** by the development of novel antimicrobials. **Resistance to the new antibiotics is also emerging.**
- In this context, the rational use of **older antibiotics could represent an alternative to the treatment of MDR bacterial AND** We will review here the successful treatment of MDR bacterial infections with the use of old antibiotics and discuss **their place in current practice.**

Introduction

- Antimicrobial resistance is **one of the greatest threats to human health worldwide** (Walker et al., 2009.

- It has been demonstrated that antimicrobial resistance prevalence can be diminished through **decreased antibiotic consumption** (Seppälä et al., 1997).

- **Old and new antibiotics** vary in their impact on the emergence and spread of resistant bacteria (Sullivan et al., 2001).

- In this context, the **reintroduction of previously used antibiotics** active against MDR bacteria represents a new alternative for the control of antimicrobial resistance (Pulcini et al., 2012).

As **old antibiotics** have rarely been subjected to contemporary drug-development procedures or compared to commonly used antibiotics, they are **less considered in practice guidelines. Therefore, their efficacy and safety must be revaluated to optimize therapy.**

"FORGOTTEN" ANTIBIOTICS

We consider the value of **"forgotten" antibiotics** for the treatment of

- **MDR Gram-negative bacterial infections** (polymyxins, fosfomycin, mecillinam, temocillin, and nitrofurantoin);

- **MDR Gram-positive infections** [trimethoprim-sulfamethoxazole (TMP/SMX), tetracyclines, chloramphenicol, pristinamycin, rifampicin, and fusidic acid]

MDR Gram-negative bacteria

Escherichia coli* and *Klebsiella pneumoniae were resistant to to third-generation cephalosporins, fluoroquinolones, and aminoglycosides (http://www.ecdc.europa.eu).

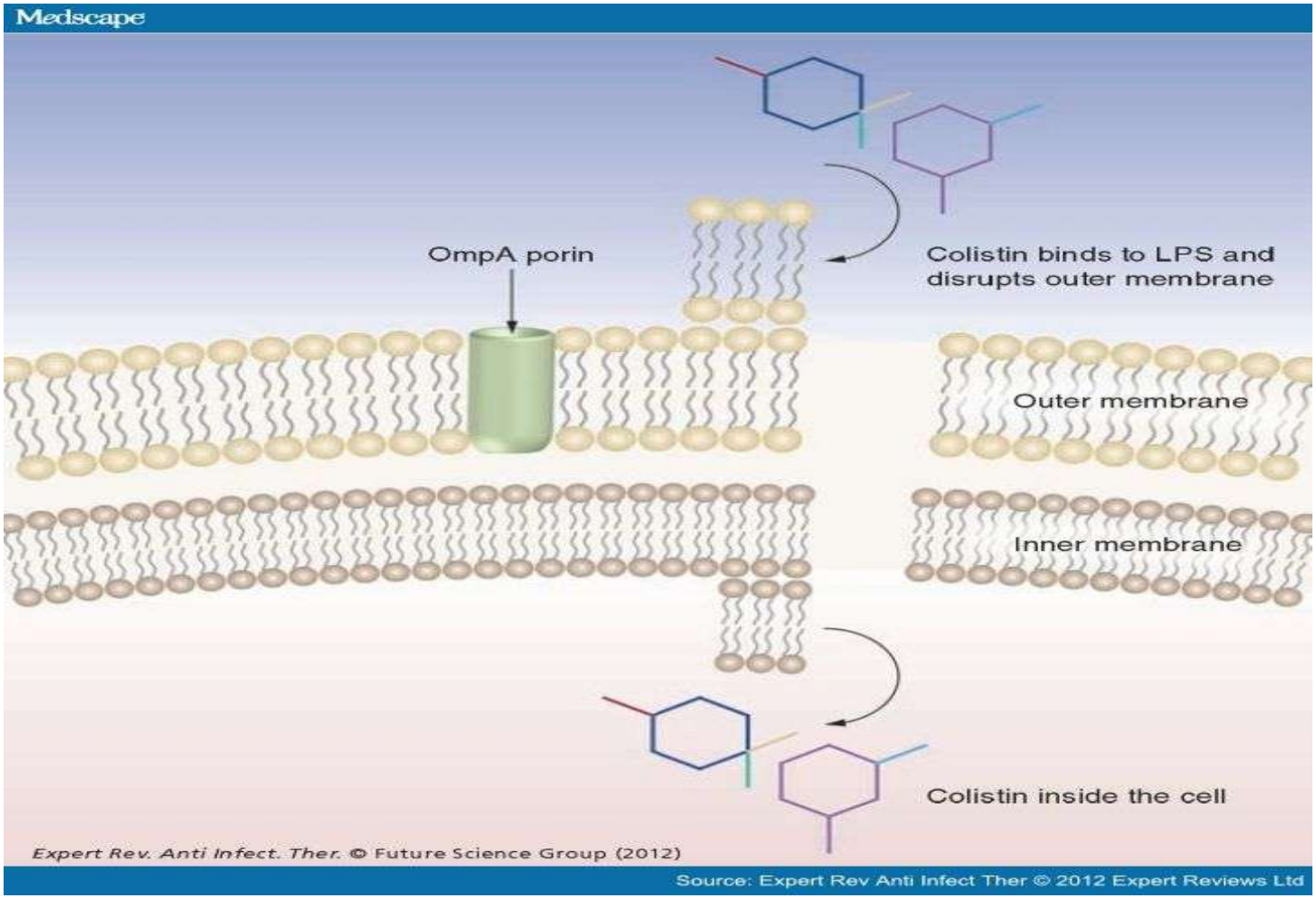
The spread **beta-lactamases with an extended spectrum(ESBL),** which confer resistance to most ß-lactams (even carbapenems) and are frequently associated with resistance to other groups of antibiotics (Pitout and Laupland, 2008; Zahar et al., 2009; Diene et al., 2013.

POLYMYXINS

- Colistin, synthesized by *Paenibacillus polymyxa* subspecies *colistinus*, was discovered in **1949** (Komura and Kurahashi, 1979).

- Polymyxin B and polymyxin E (colistin) are the 2 polymyxins used in clinical practice.

- Their mechanism of action includes **attachment to the outer cell membrane of Gram-negative bacteria, leading to membrane-permeability changes and cell death.**


Medscape
OmpA porin
Colistin binds to LPS and disrupts outer membrane
Outer membrane
Inner membrane
Colistin inside the cell
Expert Rev. Anti Infect. Ther. © Future Science Group (2012)
Source: Expert Rev Anti Infect Ther © 2012 Expert Reviews Ltd

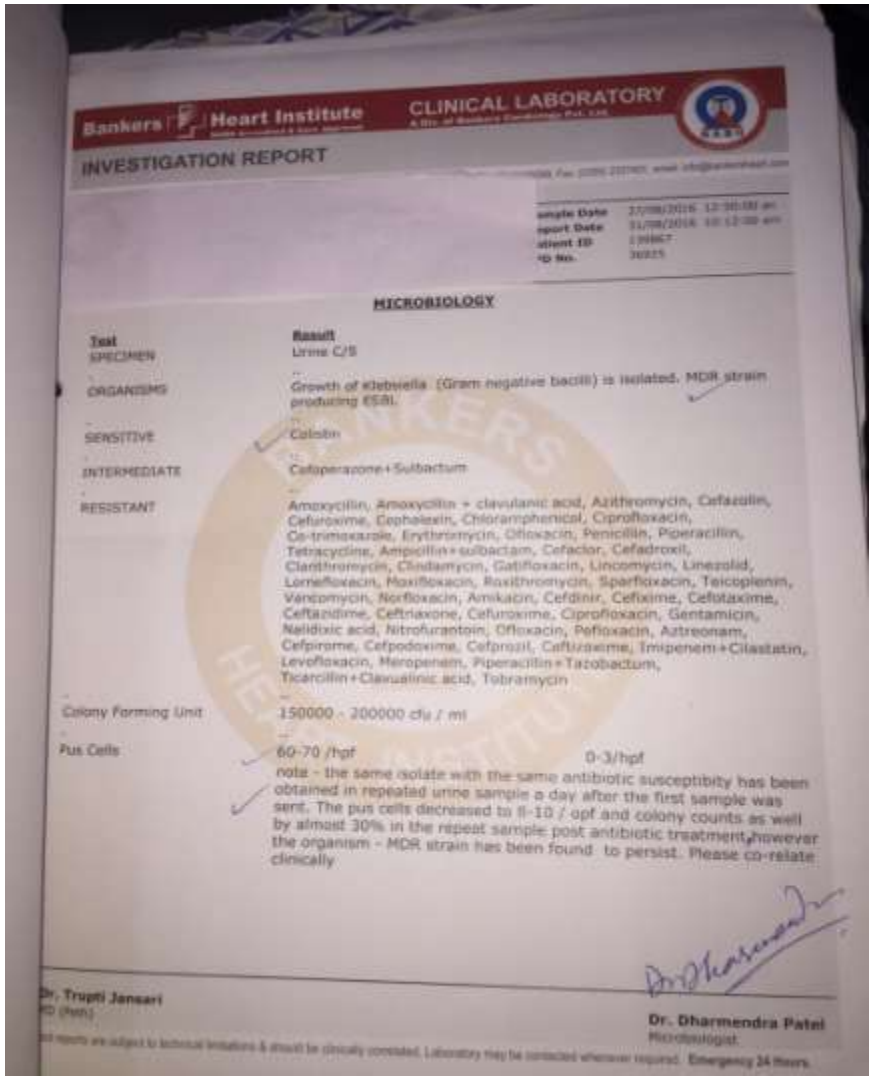
Abandoned in most parts of the world in the **early 1980s because of the reported high incidence of nephrotoxicity** (Biswas et al., 2012).

Recent studies have shown that better management of intravenous formulations led to **considerably less toxicity than was reported in old studies** (Falagas and Kasiakou, 2005).

- Colistin was recommended by the most recent American Thoracic Society Guidelines as a therapeutic option for the treatment of ventilator-associated pneumonia (**VAP) caused by MDR Gram-negative organisms** (American Thoracic Society, and Infectious Diseases Society of America, 2005).
- Intravenous polymyxins has been evaluated for the treatment of serious **MDR *Pseudomonas aeruginosa, Acinetobacter baumannii* infections** of various types, including pneumonia, bacteremia, abdominal infections, bone and joint infections (BJIs), urinary-tract infections (UTIs), and meningitis (Falagas and Kasiakou, 2005)

- One worrisome problem is the emergence of colistin resistance **in KPC(Klebsiela pneumoniae carbapenemase)-producing bacteria**, as seen in up to 20% of isolates in some countries (Kontopidou et al., 2014).
- The spread of colistin resistance may **be related to the extensive use of this drug in empirical therapy** (Oostdijk et al., 2013).
- The other most common mechanism of colistin resistance is **modification of LPS (Lipopolysaccharides)** (Park et al., 2011).

Antibiogram (only senstive to colistin)



Bankers Heart Institute — CLINICAL LABORATORY

INVESTIGATION REPORT

MICROBIOLOGY

Test	Result
SPECIMEN	Urine C/S
ORGANISMS	Growth of Klebsiella (Gram negative bacilli) is isolated. MDR strain producing ESBL
SENSITIVE	Colistin
INTERMEDIATE	Cefoperazone+Sulbactum
RESISTANT	Amoxycillin, Amoxycillin + clavulanic acid, Azithromycin, Cefazolin, Cefuroxime, Cephalexin, Chloramphenicol, Ciprofloxacin, Co-trimoxazole, Erythromycin, Ofloxacin, Penicillin, Piperacillin, Tetracycline, Ampicillin+sulbactam, Cefaclor, Cefadroxil, Clarithromycin, Clindamycin, Gatifloxacin, Lincomycin, Linezolid, Lomefloxacin, Moxifloxacin, Roxithromycin, Sparfloxacin, Teicoplenin, Vancomycin, Norfloxacin, Amikacin, Cefdinir, Cefixime, Cefotaxime, Ceftazidime, Ceftriaxone, Cefuroxime, Ciprofloxacin, Gentamicin, Nalidixic acid, Nitrofurantoin, Ofloxacin, Pefloxacin, Aztreonam, Cefpirome, Cefpodoxime, Cefprozil, Ceftizoxime, Imipenem+Cilastatin, Levofloxacin, Meropenem, Piperacillin+Tazobactum, Ticarcillin+Clavulanic acid, Tobramycin
Colony Forming Unit	150000 - 200000 cfu / ml
Pus Cells	60-70 /hpf 0-3/hpf

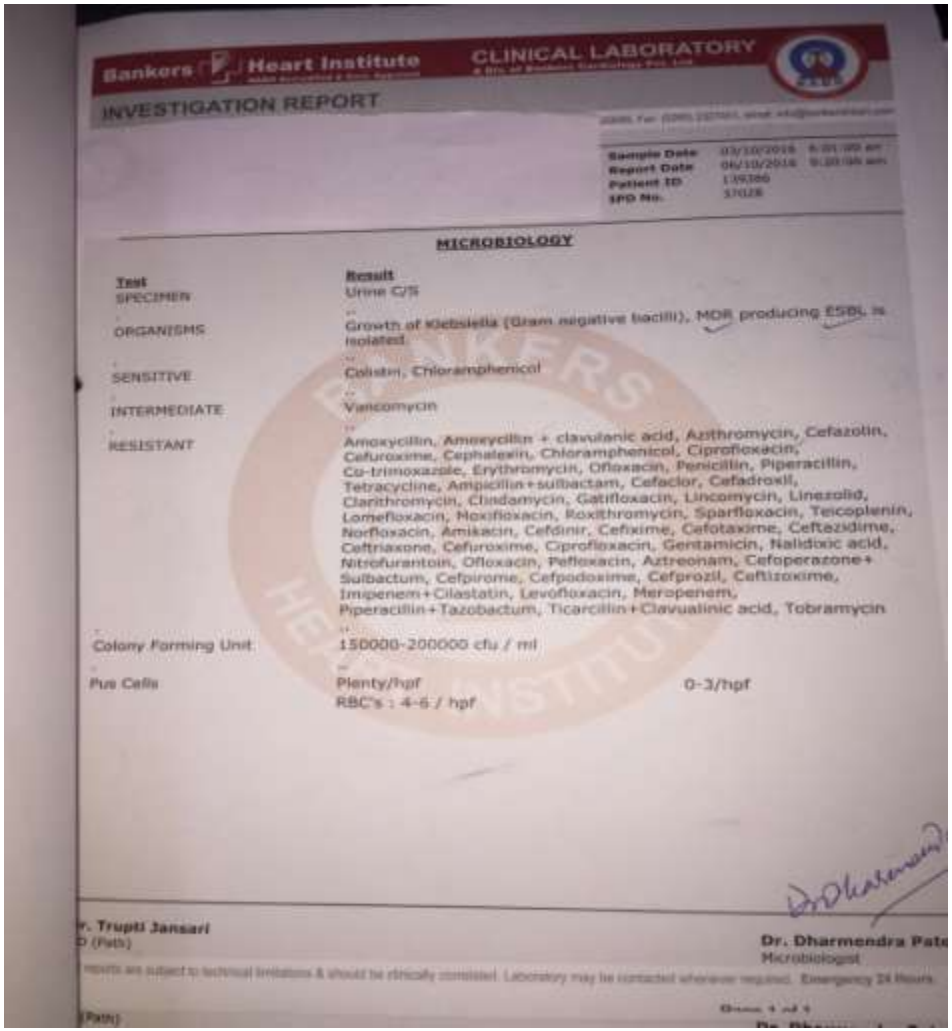
note - the same isolate with the same antibiotic susceptibity has been obtained in repeated urine sample a day after the first sample was sent. The pus cells decreased to 8-10 / opf and colony counts as well by almost 30% in the repeat sample post antibiotic treatment,however the organism - MDR strain has been found to persist. Please co-relate clinically

Dr. Trupti Jansari

Dr. Dharmendra Patel
Microbiologist

Emergency 24 Hours

URINE – KLEBSIELA ONLY SENSITIVE TO COLISTIN & CHLORAMPHENICOL (DATED:10/2016)



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MICROBIOLOGY

Test	Result
SPECIMEN	Urine C/S
ORGANISMS	Growth of Klebsiella (Gram negative bacilli), MDR producing ESBL is isolated.
SENSITIVE	Colistin, Chloramphenicol
INTERMEDIATE	Vancomycin
RESISTANT	Amoxycillin, Amoxycillin + clavulanic acid, Azithromycin, Cefazolin, Cefuroxime, Cephalexin, Chloramphenicol, Ciprofloxacin, Co-trimoxazole, Erythromycin, Ofloxacin, Penicillin, Piperacillin, Tetracycline, Ampicillin+sulbactam, Cefaclor, Cefadroxil, Clarithromycin, Clindamycin, Gatifloxacin, Lincomycin, Linezolid, Lomefloxacin, Moxifloxacin, Roxithromycin, Sparfloxacin, Teicoplenin, Norfloxacin, Amikacin, Cefdinir, Cefixime, Cefotaxime, Ceftazidime, Ceftriaxone, Cefuroxime, Ciprofloxacin, Gentamicin, Nalidixic acid, Nitrofurantoin, Ofloxacin, Pefloxacin, Aztreonam, Cefoperazone+ Sulbactum, Cefpirome, Cefpodoxime, Cefprozil, Ceftizoxime, Imipenem+Cilastatin, Levofloxacin, Meropenem, Piperacillin+Tazobactum, Ticarcillin+Clavualinic acid, Tobramycin
Colony Forming Unit	150000-200000 cfu / ml
Pus Cells	Plenty/hpf 0-3/hpf RBC's : 4-6 / hpf

Dr. Trupti Jansari
(Path)

Dr. Dharmendra Pate
Microbiologist

- Regarding ***Acinetobacter baumanii***, colistin resistance has emerged worldwide (Cai et al., 2012).
- **Combination therapy** might be the best antimicrobial strategy (Rolain et al., 2011).

COLISTIN MONOTHERAPY VS. COMBINATION THERAPY: EVIDENCE FROM MICROBIOLOGICAL, ANIMAL AND CLINICAL STUDIES

- In clinical practice, it is frequently used **as combination therapy** in order to improve its antibacterial activity,
- Most of the microbiological studies examined colistin monotherapy vs. combinations with rifampicin (nine studies) or **with carbapenems** (three studies) for *Pseudomonas aeruginosa* or *Acinetobacter baumannii* infections.
- **A synergistic effect was detected in the combination of colistin with other antibiotics** in available evidence from various studies
- **Mortality rates were significantly lower in the combination treatment arm**

ONLY CARBAPENAM

COLISTIN + CARBAPENAM

- DONOT use colistin in species which are **naturally resistant to colistin , such as *Serratia marcescens* and *Proteus mirabilis*** (Merkier et al., 2013).

FOSFOMYCIN

Fosfomycin is an **antimetabolite inhibitor** that prevents the formation of N-acetylmuramic acid, an essential precursor of peptidoglycan-chain formation in the bacterial wall.

- It was first identified in **Spain in 1969** in the fermentation broths of several strains of *Streptomyces* sp.
- Fosfomycin has a **broad spectrum of antimicrobial activity**, including a rapid **bactericidal** effect against several Gram-negative and Gram-positive aerobic bacteria (Falagas et al., 2009).
- Unlike many alternatives, fosfomycin formulations are **generally well tolerated, with minimal toxicity** (excepting thrombophlebitis when administered via peripheral venous catheter).

- The use of **intravenous fosfomycin** formulations for the treatment of infections caused by **MDR bacteria** has shown a high rate of clinical success .
- For **lower UTIs**, the successful use of **oral fosfomycin** is well documented.
- One of the first studies on the broad use of fosfomycin in Spain noted development of **resistance in 3%** of the 959 cases in total but in **10% of the 86 *P. aeruginosa* infections** (Rodríguez et al., 1977).
- These rates of emergence appear to be **stable over time** in countries where fosfomycin use has been used for decades (Falagas et al., 2008).

- Currently, **plasmid-mediated fosfomycin resistance** determinants, have been discovered and are related to fosfomycin resistance in ***Escherichia coli* (*fosA, fosA3, fosC*), *Enterobacter cloacae* (*fosA2*) , *Klebsiella pneumoniae* (*fosA, fosA3*) , *Staphylococcus* spp. (*fosB*) and *Enterococcus faecium* (*fosB3*)** (Xu et al., 2013 & Lee et al., 2012).
- This is a major concern about the potential for the selection and spread of resistance. Then, when used to treat systemic infections, **intravenous fosfomycin** may be a component of **combination therapy** administered (Pogue et al., 2011).

PIVMECILLINAM/MECILLINAM

- Pivmecillinam is the prodrug of mecillinam, a unique ß-lactam with high specificity against penicillin-binding protein 2 (PBP-2) in the **Gram-negative cell wall and therefore is highly active against Enterobacteriaceae and resistant to β-lactamases.**
- This drug for **oral use** is well tolerated and can be given in patients with impaired renal function, but its usefulness is limited by its **lack of activity against Gram-positive organisms and *Pseudomonas aeruginosa*** (Dewar et al., 2014).
- Since its introduction in the 1970s, it has been widely used for the **treatment of acute lower UTIs** (Graninger, 2003).

- Treatment with pivmecillinam was successful in a case of **relapsing pyelonephritis caused by ESBL-producing *E. coli*** where other treatments had failed (Nicolle and Mulvey, 2007).

- Currently, the use of **pivmecillinam as first-line treatment for uncomplicated UTIs** is recommended by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases (Gupta et al., 2011),

……..but not available in india

- The widespread and long-term use of pivmecillinam for UTIs in Denmark,Norvey,Sweden countries is well documented **with very low rate of mecillinam resistance** in these countries (Graninger, 2003).

- Indeed, Pivmecillinam is a **prodrug and thus has a low impact on the endogenous microflora** (Sullivan et al., 2001).

TEMOCILLIN

- Developed and first marketed in the UK in the **1980s**.
- Temocillin , **derivative of ticarcillin**, is also characterized by its resistance to beta-lactamases with an extended spectrum (Livermore et al., 2006; Rodriguez-Villalobos et al., 2006; Glupczynski et al., 2007; Adams-Haduch et al., 2009).
- Temocillin is mainly **excreted renally** and therefore requires dosage adjustment in patients with renal impairment.

TEMOCILLIN– AS MICROBIOLOGICALLY DIRECTED THERAPY

Temocillin particularly used for **the UTIs caused by confirmed ESBL(extended spectrum beta lactamase producers** as microbiologically directed therapy, so used as an alternative to carbapenems (Livermore and Tulkens, 2009).

Research in Belgium suggests that temocillin is also effective in severe infections such as **VAP** if the organism appears susceptible *in vitro* (De Jongh et al., 2008).

It is also a potential alternative treatment option for **UTIs caused by KPC (Klebsielaa pneumoniae carbapenemase)-producing Enterobacteriaceae** (Adams-Haduch et al., 2009).

……..but not available in india

NITROFURANTOIN (NFT)

- Nitrofurantoin (NFT) - synthetic antimicrobial derived from furan by the addition of a nitro group and a side chain containing hydantoin, was introduced into clinical practice in its **microcrystalline form in 1952**.
- This molecule has a broad-spectrum activity against the **main uropathogens** (i.e., *Escherichia coli*, group-B streptococci, enterococci, *Staphylococcus aureus*, *Klebsiella pneumonia*, and *Enterobacter* sp.) , also against **ESBL-producing Enterobacteriaceae and vancomycin-resistant enterococci(VRE).**
- Notably, it **lacks activity against *Pseudomonas aeruginosa, Serratia marscecens*, and *Proteus mirabilis*** (Cunha et al., 2011).

- Currently, NFT is **recommended** as **a first-line treatment for uncomplicated UTIs** by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases (Gupta et al., 2011).

- Surveys have found a persistent low prevalence of resistance to NFT **(1.9–7.7%) among urinary *E. coli* isolates**, including those resistant to TMP/SMX or ciprofloxacin; the prevalence of this resistance reaches **23.2% in ESBL-producing *E. coli*** (Tasbakan et al., 2012).

Forgotten Antibiotics for Multidrug-Resistant Gram-Positive Bacteria

- ***Staphylococcus aureus* and *Enterococcus* spp.** are two of the most common organisms causing nosocomial infections and are consistently associated with high mortality rates

- **Resistance** among these pathogens to first-line agents such as **methicillin and vancomycin** continues to rise, while isolates with reduced susceptibility to newer agents, including **linezolid, are also emerging** (Patel et al., 2013).

TRIMETHOPRIM-SULFAMETHOXAZOLE

- The combination drug TMP/SMX acts as a broad-spectrum bactericidal agent and was introduced clinically in the **early 1970s** (Grim et al., 2005).
- Trimethoprim is a **tetrahydrofolate reductase inhibitor** that, when added to sulfamethoxazole, provides a **second-step block in the folate biosynthetic pathway** (Proctor, 2008).
- According to its good oral bioavailability, high-dosage regimen of TMP/SMX represents a **suitable alternative for methicillin-resistant *S. aureus* (MRSA) infections** (Muhammed Ameen et al., 2014).

- TMP/SMX is recommended as first-line treatment for **uncomplicated UTIs, skin and soft-tissue infections (SSTIs), and community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections,** according to clinical practice guidelines (Gupta et al., 2011; Stevens et al., 2014).
- In study with a cohort of 328 patients with infections due to MRSA , **TMP/SMX alone compared favorably to linezolid and daptomycin in terms of treatment efficacy, mortality, and reduced antibiotic costs** (Campbell et al., 2012).

- **Long-term oral ambulatory treatment** with TMP-SMZ appeared to be an effective alternative to the conventional medicosurgical treatment of chronic **MDR *Staphylococcus* sp.-infected orthopedic implants** (Stein et al., 1998).

- A report has shown high rates of susceptibility to TMP-SMZ **(94%) in community-acquired MRSA (CA-MRSA)** isolates (Chen et al., 2006).

- In another study, **97% of 320 isolates of MRSA (**USA300 strain) from outpatients with **SSTIs(skin & soft tissue infection) were** susceptible to TMP/SMZ (Moran et al., 2006).

TETRACYCLINES

- Tetracycline was derived from Chlortetracycline in **1953.**
- In the late 1960s, the second-generation long-acting compounds **doxycycline (in 1966) and minocycline (in 1967)** were semi-synthetically derived and commercialized.
- Tetracyclines are a class of broad-spectrum **bacteriostatic antibiotics active against Gram-positive and Gram-negative bacteria**, as well as against intracellular organisms. These characteristics, together with the **low cost and rarity of major side effects**, have made tetracyclines a widely used class of antibiotics (Nelson and Levy, 2011).
- However, these drugs are **contraindicated in pregnant woman, neonates, and young children** because of their particular effects on skeletal growth and dentition (Demers et al., 1968).

- Tetracyclines have been evaluated as an effective oral treatment option for patients with **SSTIs(skin & soft tissue infection) caused by MRSA** (Ruhe and Menon, 2007).
- **Doxycycline** has intrinsic activity against enterococci, including VRE, and has been stated as an **option for oral treatment of VRE(vancomycine ressistance eneterococci) cystitis** (Heintz et al., 2010) **AND Bacteremia caused by VRE** has been successfully treated with doxycycline (Moreno et al., 1994).

- **MDR strain of MRSA (genotype USA300)** has emerged that confer **resistance to tetracycline, macrolides, and clindamycin** (Diep et al., 2008
- In June 2005, **tigecycline,** the NEW member of tetracyclines group was introduced to treat infections that are resistant to other antimicrobics including conventional tetracyclines.

TIGECYCLINE

- **Tigecycline** for the treatment of multidrug-resistant Enterobacteriaceae: a systematic review of the evidence from microbiological and clinical studies

  ---*Journal of Antimicrobial Chemotherapy*, Volume 62, Issue 5, 1 November 2008, Pages 895–904, https://doi.org/10.1093/jac/dkn311

- **Conclusions -** Tigecycline is microbiologically active against almost all of **the ESBL (Extended-spectrum beta-lactamases) or MDR *E. coli* isolates and the great majority of ESBL or MDR *Klebsiella*** spp. isolates.

CHLORAMPHENICOL

- Chloramphenicol inhibits protein synthesis by binding reversibly to the **50S subunit of the bacterial ribosome**
- Chloramphenicol has good oral bioavailability and excellent tissue penetration.
- Its has **Broad spectrum of activity** including **Gram-positive and Gram-negative bacteria, anaerobes, spirochetes, rickettsiae, chlamydiae, and mycoplasma.**
- But, soon after chloramphenicol was released in the United States in **1949,** reports linked this drug to rare but potentially **lethal hematological side effects** that restricted its use as last-resort therapy. However, as it is readily available and inexpensive, it is still used in many resource-limited settings (Falagas and Kopterides, 2007).

- Chloramphenicol was found to be effective against **vancomycin-resistant *Enterococcus faecium* (VRE*f*), with bacteriostatic activity** (Norris et al., 1995).
- Of 697 VRE samples from 28 US medical centers, only **2.4% were resistant to chloramphenicol** (Zhanel et al., 2003).
- A significant low resistance-rate to chloramphenicol among isolates of enterococci was reported from **2006 to 2009** in a Brazilian monocentric survey (Conceição et al., 2011).

PRISTINAMYCIN

- Pristinamycin is an oral streptogramin antibiotic made up of two synergistic but structurally unrelated components, **pristinamycin IA and pristinamycin IIA**. It was discovered **over 50 years ago** (Cooper et al., 2014).**(QUINUPRISTIN & DALFOPRISTIN)**
- Although the data are limited, pristinamycin is a well-tolerated and effective alternative for the **treatment of BJI(bone & joint infection) due to Gram-positive bacteria including MRSA and VRE** (Dancer et al., 2003; Ng and Gosbell, 2005; Ruparelia et al., 2008; Reid et al., 2010).
- The extended use of pristinamycin for BJI and other infections requires **further evaluation**.

- **Many VRE (Vancomycin-resistant enterococcal** species) are susceptible to pristinamycin (Collins et al., 1993).
- In France, **resistance** to pristinamycin has remained **low** over the **last 40 years**, and typical susceptibility rates amongst **staphylococci are**

  98% in the community (Quentin et al., 2001) and **93% in hospitals** (Leclercq et al., 2003).

RIFAMICIN

- Rifampicin was introduced **in 1967** as major part of the anti-tuberculous treatment.
- Rifampicin has an excellent tissue penetration and a **unique activity on bacteria in biofilms,** growing on the surface of prosthetic devices.
- Despite the excellent bactericidal activity and oral bioavailability, the rapid emergence of resistance in bacteria constitutes a major limitation and therefore rifampicin should be **used in combination** with other antimicrobial agents. (Forrest and Tamura, 2010).

Steps of Biofilm formation

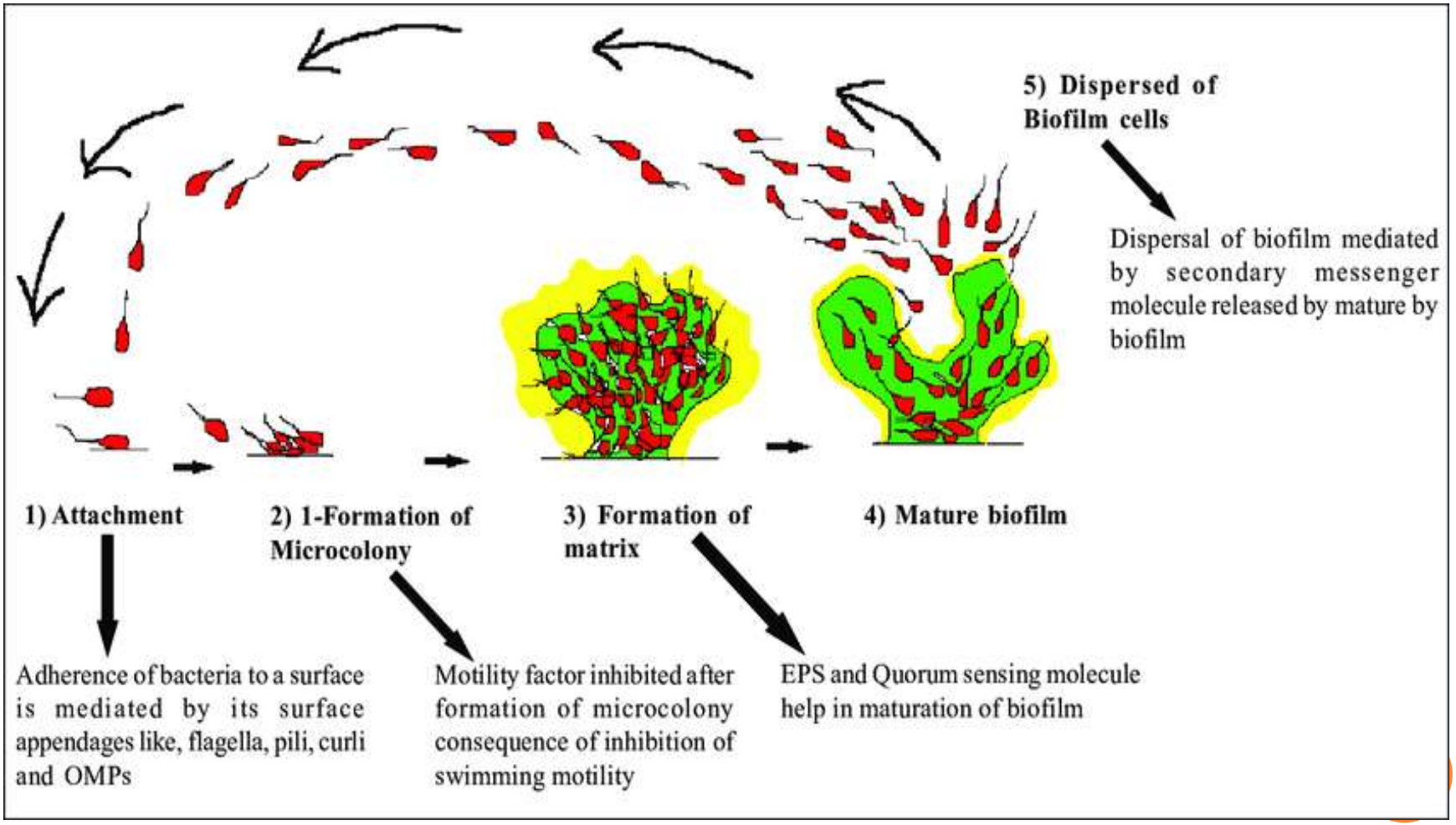


Table 2. A list of common biofilm forming bacterial species [17].

S.No	Common biofilm forming bacterial species
1	*E. coli*
2	*P. aeruginosa,*
3	*S. epidermidis,*
4	*S. aureus,*
5	*Staphylococcus epidermidis*
6	*E. cloacae*
7	*K. pneumoniae*
8	*Actenomyces israelii*
9	*Haemophilus influenza*
10	*Burkholderia cepacia*

- **Colistin and rifampicin** appeared to be an effective and safe combination therapy for severe infections caused by **MDR *Acinetobacter baumanii*** (Motaouakkil et al., 2006; Bassetti et al., 2008) or **MDR *Pseudomonas aeruginosa*** (Tascini et al., 2006).
- Rifampicin with fluoroquinolones treatment has been shown to be effective, in combination with **surgical debridement, on early prosthesis joint infections (PJI) caused by MRSA** (Aboltins et al., 2007).

Fusidic Acid (FA)

- Fusidic acid was introduced into clinical practice in 1962 (Godtfredsen et al., 1962). It inhibits polypeptide-chain elongation by binding to the ribosome elongation factor G (EF-G)–GDP complex.
- FA has excellent **oral bioavailability** and is metabolized and excreted by the liver.
- The action of FA is mainly **bacteriostatic against Gram-positive bacteria,** but this drug has bactericidal activity at higher concentrations. Notably, FA has only limited activity against **streptococci and enterococci**. It is highly protein-bound and has been shown to have good concentrations in **soft tissue, bone and synovial fluid** (Turnidge, 1999).

- Although there have been no randomized controlled trials of FA as a treatment for **BJIs(Bone & Joint Infecions) due to MRSA, several case series have reported its effectiveness, mostly in combination with another oral antibiotic** (Drancourt et al., 1997; Aboltins et al., 2007; Ferry et al., 2010).
- In INDIA, mostly available as ointment form for dermatological infection.

CONCLUSION

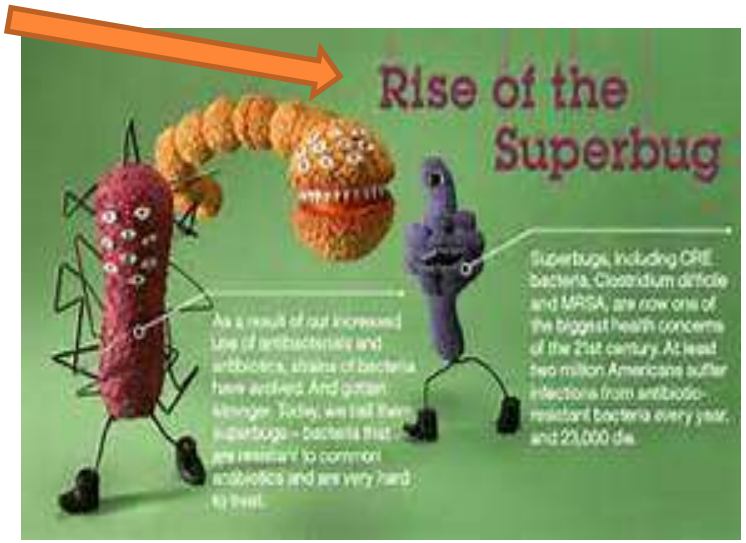
- In an **era of increasing emergence of drug resistance and a scarcity of new antibiotics**, there is a growing need to optimize the use of old and new antibiotics to treat infections.
- Despite the increasing evidence of their effectiveness and safety, the United States Food and Drug Administration **(FDA) has still not approved** the use of some old antibiotics (i.e. **IV fusidic acid, pivmecillinam, temocillin, pristinamycin)** http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.

- **Sub-therapeutic concentrations** may favor the development of resistance in both the infecting pathogen and the commensal flora (Mohamed et al., 2012).
- Moreover**, dosage adjustments, avoidance of co-administration of other toxic agents, and prompt discontinuation after early signs of toxicity** are critical for the clinical revaluation of old antibiotics. For instance, recent studies revealed that adverse events with **colistin** were not as frequent as previously reported, in part due to more accurate prescription (Falagas and Kasiakou, 2006).
- Updates of old antibiotics **toxicity assessment with optimized dosing and monitoring** and adapted pharmacological studies are urgently warranted.

- As **old antibiotics are rarely included in surveillance programs, data regarding resistance rates and minimal inhibitory concentration (MIC)** are **lacking** (Mouton et al., 2011).
- Thus, susceptibility testing for **old but effective and safe antibiotics may be integrated into routine practice** in the way to ensure antimicrobial resistance local surveillance.
- As some of these old antibiotics (i.e., fosfomycin, TMP/SMX, Tetracyclines,cloramphenicol, and fusidic acid) could also **favor horizontal spread of resistance**, their reuse should be considered **as combination therapy**

TAKE HOME MASSAGES

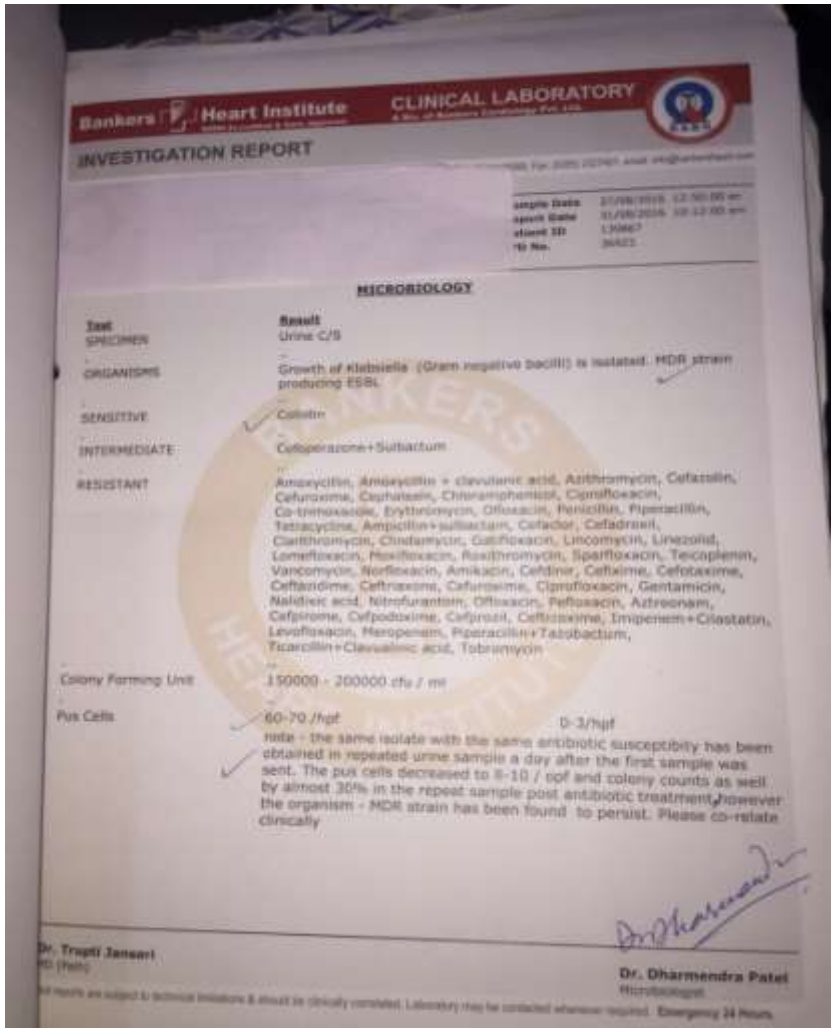
OLD ANTIBIOTICS included in this review have been associated with **successful treatment of MDR bacterial Infections.**



Their reuse represents a **promising strategy to fight antimicrobial resistance.**

ANTIBIOGRAM : URINE – KLEBSIELA

ONLY SENSITIVE TO COLISTIN (DATED: 8/2016)



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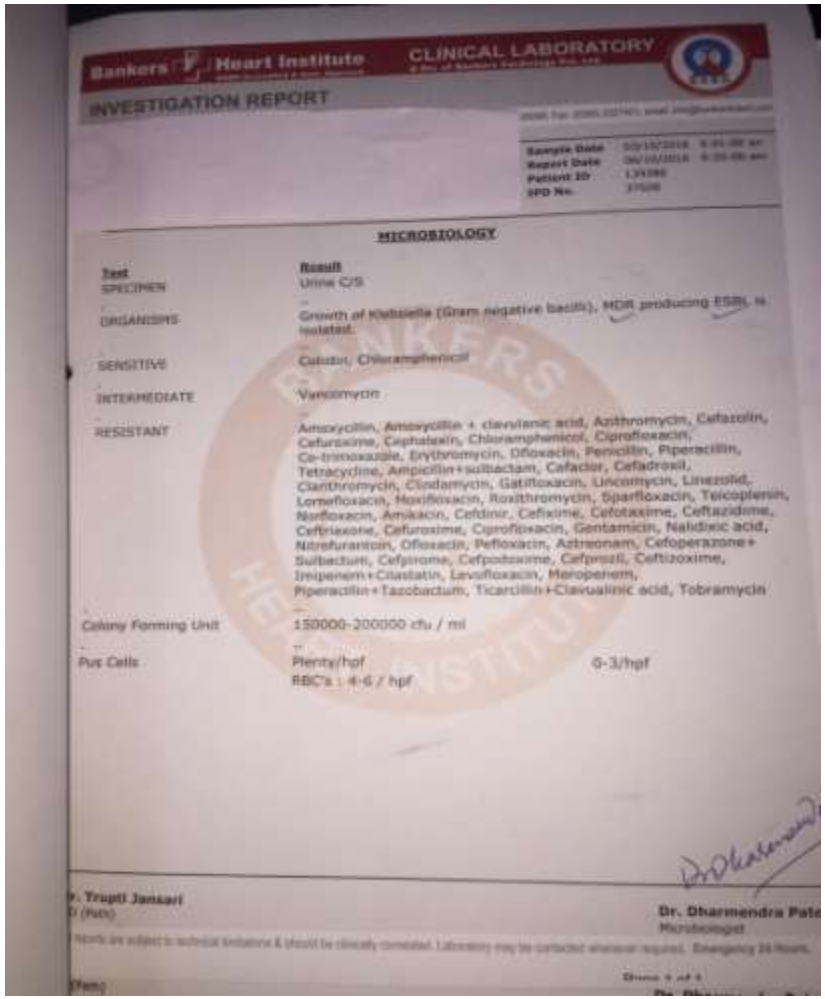
Dr. Dharmendra Patel

URINE – KLEBSIELA ONLY SENSITIVE TO COLISTIN & CHLORAMPHENICOL (DATED:10/2016)



Bankers Heart Institute CLINICAL LABORATORY

INVESTIGATION REPORT

MICROBIOLOGY

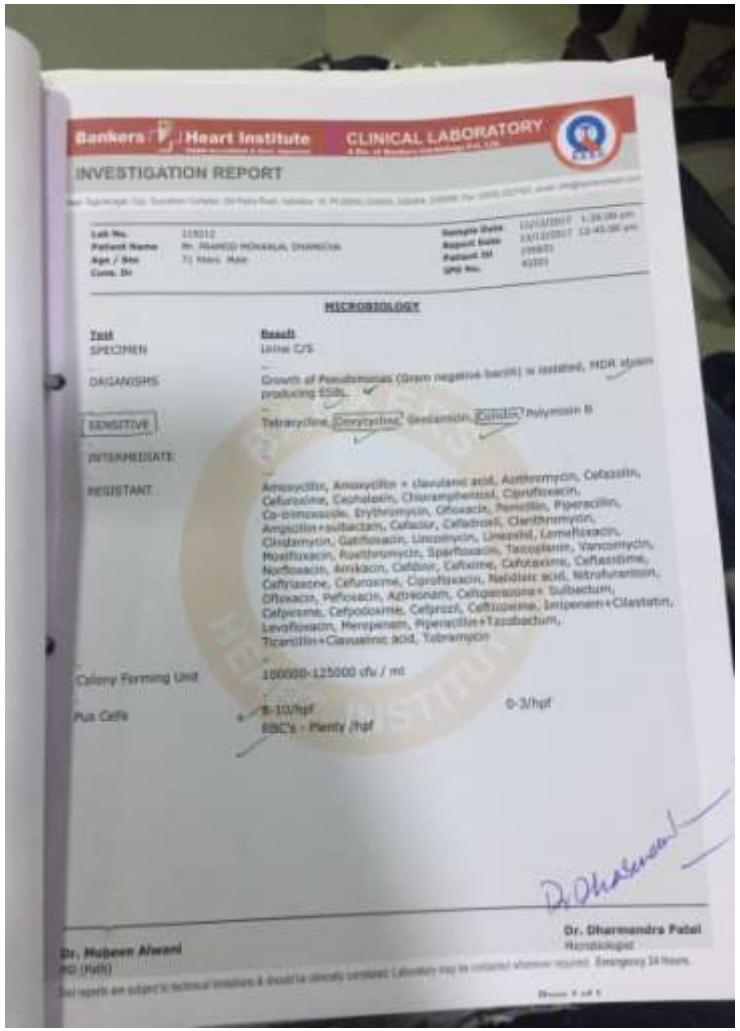
Test	Result
SPECIMEN	Urine C/S
ORGANISMS	Growth of Klebsiella (Gram negative bacilli). MDR producing ESBL is isolated.
SENSITIVE	Colistin, Chloramphenicol
INTERMEDIATE	Vancomycin
RESISTANT	Amoxycillin, Amoxycillin + clavulanic acid, Azithromycin, Cefazolin, Cefuroxime, Cephalexin, Chloramphenicol, Ciprofloxacin, Co-trimoxazole, Erythromycin, Ofloxacin, Penicillin, Piperacillin, Tetracycline, Ampicillin+sulbactam, Cefaclor, Cefadroxil, Clarithromycin, Clindamycin, Gatifloxacin, Lincomycin, Linezolid, Lomefloxacin, Moxifloxacin, Roxithromycin, Sparfloxacin, Teicoplenin, Norfloxacin, Amikacin, Cefdinir, Cefixime, Cefotaxime, Ceftazidime, Ceftriaxone, Cefuroxime, Ciprofloxacin, Gentamicin, Nalidixic acid, Nitrofurantoin, Ofloxacin, Pefloxacin, Aztreonam, Cefoperazone+ Sulbactum, Cefpirome, Cefpodoxime, Cefprozil, Ceftizoxime, Imipenem+Cilastatin, Levofloxacin, Meropenem, Piperacillin+Tazobactum, Ticarcillin+Clavualinic acid, Tobramycin
Colony Forming Unit	150000-200000 cfu / ml
Pus Cells	Plenty/hpf 0-3/hpf RBC's : 4-6 / hpf

Dr. Trupti Jansari

Dr. Dharmendra Pate
Microbiologist

URINE : PSEUDOMONAS :

TETRACYCLIN,COLISITN,POLYMYXIN-B (DATED:12/2017)



Bankers Heart Institute CLINICAL LABORATORY

INVESTIGATION REPORT

MICROBIOLOGY

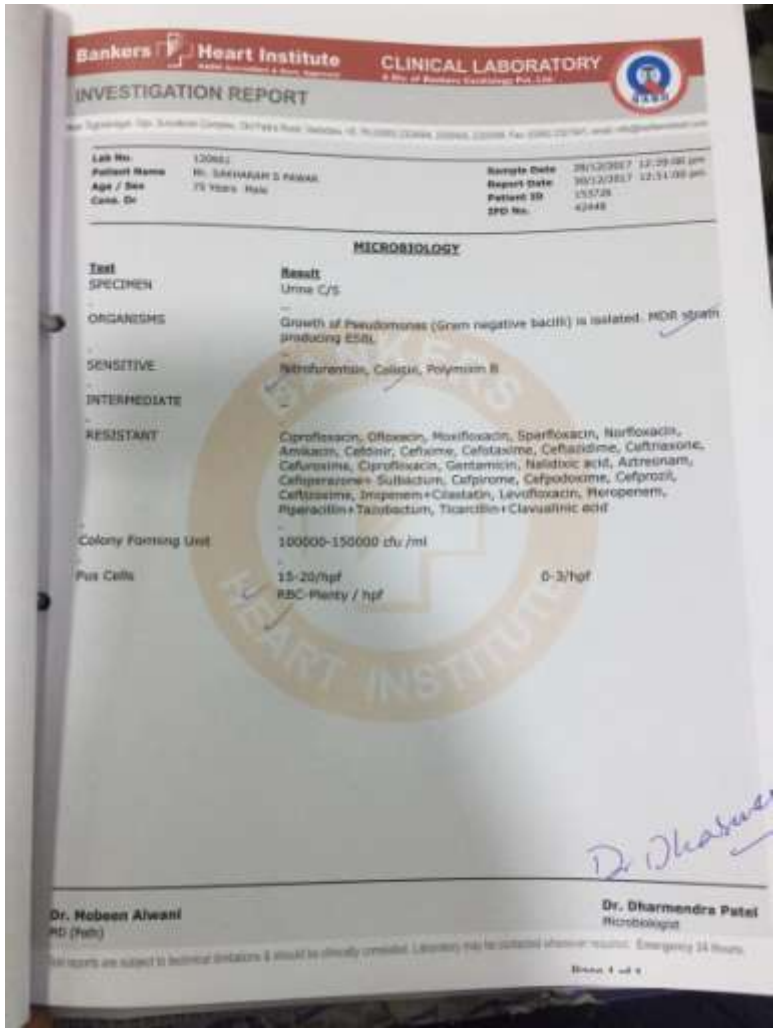
Test	Result
SPECIMEN	Urine C/S
ORGANISMS	Growth of Pseudomonas (Gram negative bacilli) is isolated, MDR strain producing ESBL.
SENSITIVE	Tetracycline, Doxycycline, Gentamicin, Colistin, Polymixin B
INTERMEDIATE	
RESISTANT	Amoxycillin, Amoxycillin + clavulanic acid, Azithromycin, Cefazolin, Cefuroxime, Cephalexin, Chloramphenicol, Ciprofloxacin, Co-trimoxazole, Erythromycin, Ofloxacin, Penicillin, Piperacillin, Ampicillin+sulbactam, Cefaclor, Cefadroxil, Clarithromycin, Clindamycin, Gatifloxacin, Linezolyn, Linezolid, Lomefloxacin, Moxifloxacin, Roxithromycin, Sparfloxacin, Teicoplanin, Vancomycin, Norfloxacin, Amikacin, Cefdinir, Ceftazime, Cefotaxime, Ceftazidime, Ceftriaxone, Cefuroxime, Ciprofloxacin, Nalidixic acid, Nitrofurantoin, Ofloxacin, Pefloxacin, Aztreonam, Cefoperazone+ Sulbactum, Cefpirome, Cefpodoxime, Cefprozil, Ceftizoxime, Imipenem+Cilastatin, Levofloxacin, Meropenem, Piperacillin+Tazobactum, Ticarcillin+Clavuanic acid, Tobramycin
Colony Forming Unit	100000-125000 cfu / ml
Pus Cells	8-10/hpf 0-3/hpf RBC's - Plenty /hpf

Dr. Mubeen Alwani MD (Path)

Dr. Dharmendra Patel Microbiologist

URINE : PSEUDOMONAS :

NITROFURANTOIN,COLISITN,POLYMYXIN-B



Bankers Heart Institute CLINICAL LABORATORY

INVESTIGATION REPORT

MICROBIOLOGY

Test	Result
SPECIMEN	Urine C/S
ORGANISMS	Growth of Pseudomonas (Gram negative bacilli) is isolated. MDR strain producing ESBL
SENSITIVE	Nitrofurantoin, Colistin, Polymixin B
INTERMEDIATE	-
RESISTANT	Ciprofloxacin, Ofloxacin, Moxifloxacin, Sparfloxacin, Norfloxacin, Amikacin, Cefdinir, Cefixime, Cefotaxime, Ceftazidime, Ceftriaxone, Cefuroxime, Ciprofloxacin, Gentamicin, Nalidixic acid, Aztreonam, Cefoperazone+ Sulbactum, Cefpirome, Cefpodoxime, Cefprozil, Ceftizoxime, Imipenem+Cilastatin, Levofloxacin, Meropenem, Piperacillin+Tazobactum, Ticarcillin+Clavualinic acid
Colony Forming Unit	100000-150000 cfu /ml
Pus Cells	15-20/hpf 0-3/hpf RBC- Plenty / hpf

Dr. Mobeen Alwani MD (Path)

Dr. Dharmendra Patel Microbiologist

STOOL C&S :ENTEROCOCCI

CHLORAMPHEMICOL,COTRIMOXAZOLE, TETRACYCLINE (DATED 11/2017)

Bankers Heart Institute CLINICAL LABORATORY

INVESTIGATION REPORT

Lab No. 117276
Patient Name Mrs. BHUMIKA SANDEEPBHAI CHAUHAN
Age / Sex 37 Years Female
Cons. Dr
Sample Date 10/11/2017 6:48:59 pm
Report Date 13/11/2017 11:46:00 pm
Patient ID 156108
IPD No. 41876

MICROBIOLOGY

Test	Result
SPECIMEN	Stool C/S
ORGANISMS	Growth of Enterococci (Gram positive cocci) is isolated.
SENSITIVE	Chloramphenicol, Co-trimoxazole, Tetracycline, Nitrofurantoin
INTERMEDIATE	-
RESISTANT	Amoxycillin, Azithromycin, Cefazolin, Cefuroxime, Cephalexin, Ciprofloxacin, Erythromycin, Ofloxacin, Penicillin, Piperacillin, Norfloxacin, Amikacin, Cefdinir, Cefixime, Cefotaxime, Ceftazidime, Ceftriaxone, Cefuroxime, Ciprofloxacin, Gentamicin, Nalidixic acid, Ofloxacin, Pefloxacin, Aztreonam, Cefoperazone+ Sulbactum, Cefpirome, Cefpodoxime, Cefprozil, Cefuroxime, Levofloxacin, Meropenem, Piperacillin+Tazobactum, Ticarcillin+Clavulanic acid, Tobramycin
Colony Forming Unit	60000-70000 cfu/ml
Pus Cells	15-20/hpf 0-3/hpf

Note- Plenty of growth of Normal gut flora E.coli has also been isolated. Enteric Salmonella not isolated

Dr. Hobeen Alwani MD (Path)

Dr. Dharmendra Patel Microbiologist

- But some points remain critical for their revival in a sustainable manner and need further evaluations.

1. **Clinical trials** comparing the clinical, safety, and cost effectiveness with current antibiotics **are lacking**.
2. Prescription of old antibiotics needs **also to be regulated by antibiotic stewardships and guided by resistance rates monitoring.**
3. Optimization of the usage of old antibiotics remains a priority that may be considered **of similar importance to that of the assessment of new drugs.**


Thank You