A Study of Antibiotic De-Escalation Practices In Medical Wards In A Teaching Hospital

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF M.D. GENERAL MEDICINE BRANCH I EXAMINATION OF THE TAMIL NADU DR. M.G.R. UNIVERSITY, CHENNAI TO BE HELD IN APRIL, 2020

Registration Number 201711453

CERTIFICATION

This is to certify that the dissertation entitled “ A study of antibiotic de-escalation practices in medical wards in a teaching hospital” is a bona fide original work done by Dr Caroline Nandita E during her academic term April 2017 to March 2020, at Christian Medical College, Vellore in partial fulfilment of rules and regulations for the MD General Medicine examination of the Tamil Nadu Dr. M.G.R Medical University, Chennai to be held in May, 2020. This work was carried out under my guidance in the department

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Dr Thambu David Sudarsanam
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Dr. Anna Pulimood
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Christian Medical College, Vellore-632004

DECLARATION

This is to certify that the dissertation entitled “ A study of antibiotic de-escalation practices in medical wards in a teaching hospital” which is submitted by me in partial fulfillment towards M.D. Branch I (General Medicine) Examination of the Tamil Nadu Dr. M.G.R. University, Chennai to be held in May, 2019 comprises my original research work and information taken from secondary sources has been given due acknowledgement and citation.

Caroline Nandita
PG Registrar, Department of General Medicine
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Plagiarism certificate

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Finally, my genuine thankfulness to all my patients, for teaching me medicine and so much more.

Abbreviations

ADE - Antibiotic De-escalation

AMR – Antimicrobial Resistance

ASP – Antimicrobial stewardship Program

BAL- Bronchioalveolar Lavage

CDI – Clostridium Difficile infection

CIMS - Current Index of Medical Specialties

DDD – Defined Daily Dose

DNA – Deoxy ribonucleic acid

DOT – Days of therapy

ESBL – Extended spectrum beta lactamases

FDC - Fixed Dose Combinations

GNB – Gram negative Bacteria

ICU – Intensive Care Unit

PAF – Prospective audit and feedback

RCT - Randomized control Trial

SOFA - Sequential organ failure assessment

UTI – Urinary tract Infection

VAP –Ventilator associated Pneumonia

WHO – World Health Organization

Table of contents

Introduction

Antimicrobial resistance has been identified as a global health hazard with serious implications. It is usually associated with significant higher morbidity, mortality, prolongation of illness and reduced labor efficiency. Resistance is thought to be a reaction of the organism for survival, developing mutations that enable it to exist in hostile environments which include antibiotic exposure. Organisms develop mutations which are then transmitted by horizontal gene transfer and this results in the formation of a resistant population. De-escalation of antibiotics is a mechanism that has been described to prevent unnecessary use of antibiotics and thus reduce the development of resistance. It has been shown to reduce mortality and reduction in overall antibiotic related side effects.

India is one of the largest consumers of antibiotic with large multi-drug resistant population as well. There are many reasons that have led to the development of AMR such as poor regulation of sale of antibiotics, preferred use of broad-spectrum antibiotics, indiscriminate use of antibiotic in poultry, widespread use of fixed drug combinations and the lack of awareness in the community. Over the last 10 years, India has launched initiatives to improve antimicrobial stewardship but there are few studies which have looked at the same.

This study was formulated to assess the percentage of de-escalation in a tertiary hospital setting and the reasons associated with the decision not to de-escalate. A qualitative study to

understand the challenges and issues concerning de-escalation of antibiotics was also planned among the post graduate students.

Aim and Objectives

Aim

The aim of the study is to describe incidence and determinants of antibiotics de-escalation among patients started on empiric antibiotic therapy

Objectives

1. To determine the proportion of patients in whom antibiotic de-escalation is implemented
2. To study factors associated with de-escalation of initial empiric antibiotics
3. To understand perceptions of PG medical doctors on issues concerning de-escalation of antibiotics, its importance and the challenges associated with it

Materials and methods

Setting

The Christian Medical College is a 2400 bed teaching hospital in Vellore, South India. The hospital serves the population of Tamil Nadu and the neighboring state of Andhra Pradesh, besides being a referral center for patients from other parts of the country and the Indian subcontinent.

This study has been conducted among patients who were admitted and started on empirical antibiotic therapy in all Medical wards- C, I, E, MTS4 excluding Medical ICU and HDU.

Patients were recruited for this study from September 2018 till May 2019.

Study design

This is a prospective study aimed at looking at the incidence and determinants of antibiotics de-escalation among patients started on empiric antibiotic therapy.

Inclusion Criteria

1. Adults >18 years of age
2. Admitted to medical wards
3. Started on empiric antibiotic therapy for a syndrome/clinical diagnosis
4. Culture positivity or Serological test positivity leading to a definite diagnosis

Exclusion Criteria

1. Patients refusing consent
2. Patients started on antibiotics for targeted treatment
3. Re-admissions (e.g., for recurrent UTI)
4. Patients admitted to the intensive care unit

Intervention

Empiric antibiotic therapy was prescribed by the physician in charge of the patient on the basis of patient medical history, characteristics, severity, suspected site of infection, and hospital ecology. Patients who fulfilled inclusion criteria were re-assessed at 72 to 96 hours to see if a definitive (microbiologically confirmed) diagnosis has been reached. If a definitive diagnosis

was reached, these patients were assessed to determine whether de-escalation of the initial antibiotic could be carried out.

Clinical improvement was assessed by the treating team as the absence of fever, and no sign of clinical instability such as systolic blood pressure below 90 mm Hg or heart rate more than 100/minute.

De-escalation therapy was defined as change from a

1. Broad-spectrum to a narrower spectrum agent (e.g., meropenem to amikacin)
2. Combination of antibiotics to a single agent
3. Stopping antimicrobial treatment if the etiology is non-infectious or non-bacterial infection. (1)

De-escalation was not protocolized and was performed by the physician in charge of the patient in accordance with the evolution of the patients' clinical condition, and bacterial identification and antibiotic susceptibility data.

Data sources and collection

The selected patients were screened for evidence of sepsis using the qSOFA score. The diagnosis as well as the vital signs at initiation of empiric therapy was recorded.

We recorded the following: demographic characteristics (age and gender), underlying diseases such diabetes, chronic obstructive airway disease), chronic renal failure, chronic heart failure, hypertension and vital signs at admission.

Data regarding the baseline investigations such as a complete blood profile, liver function and renal function was also collected. The patients in whom an opportunity presented to de-escalate were further followed up and data regarding the microbiological evidence, type of de-escalation carried out and if there was no change in therapy, the reason for the decision as well was recorded.

Outcomes

1. To determine the proportion of patients in whom antibiotic de-escalation is implemented.
2. To study factors associated with de-escalation of initial empiric antibiotics

Statistical analysis

The data entry was performed using Epidata software and analysis by using Stata software. The frequency tables and descriptive statistics were used to describe the variables of interest. The prevalence of de-escalation and its 95% CI were presented. The association analysis will be performed using Chi-square test.

Sample size calculations

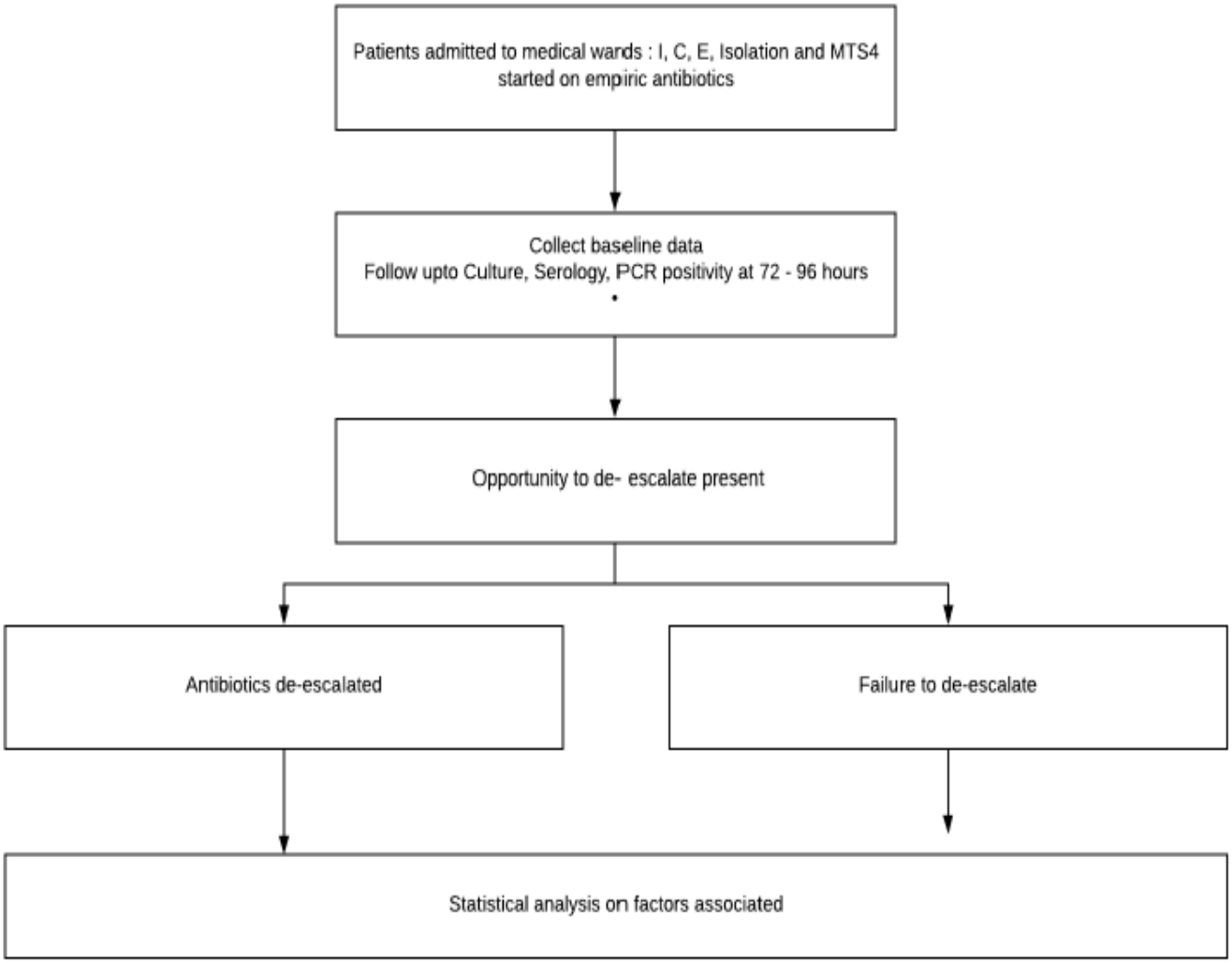
In the general medical population, assuming in the patients with an opportunity to de- escalate, 50% undergo the same, the sample size was calculated to be 100.

Single Proportion - Absolute Precision				
Expected Proportion	0.5	0.5	0.5	0.5
Precision (%)	3	5	7	10
Desired confidence level (1- alpha) %	95	95	95	95
Required sample size	1067	384	196	96

Software used for sample size calculation: nMaster 2.0

Reference article: Tabah et al. (2015): A Systematic Review of the Definitions, Determinants and Clinical Outcomes of Antimicrobial De-escalation in the Intensive Care Unit. CID: 62{41009-17}.

Study protocol



Qualitative study

Perceptions of PG medical doctors on issues concerning de-escalation of antibiotics

The second part of the study was a qualitative semi-structured interview

Sample Selection

We used purposive sampling technique in the selection of our sample of post-graduates for the SSIs. The individuals constituted a subset of the registrars who were pursuing General Medicine at Christian Medical College during 2018-2019. 10 was selected as the number which would give us sufficient data to conduct the study

Methods

Informed consent was taken. The interview guide was formulated based on other studies performed in a similar vein with supplementary questions which were relevant to the process. The interviews took place in the participants' workplace, in participants' own time. All interviews were audio recorded and transcribed verbatim. Interviews lasted on average 26 minutes each (range, 17 minutes to 35 minutes). All qualitative interviews were transcribed verbatim and then translated into English. Analysis began by gaining familiarity with each of the transcripts. Initially, each transcript was read through (data immersion) and coded by the author. After coding two interviews, a code book was developed to assure consistency and uniformity in the coding process for all the remaining interviews.

Each transcript was then coded. New issues emerging in subsequent interviews were given a new code and inserted into the code book. Once all the transcripts had been coded we used matrices to organize the data, structured around our primary research questions. From the matrices, we pieced together segments of text related to a common topic to identify emergent themes.

Definitions

Diabetes Mellitus (2)

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.

The diagnosis is established by

i. Symptoms of diabetes plus casual plasma glucose concentration ≥ 200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss OR

ii. FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8h OR

iii. HbA1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay* OR

iv. 2-h post load glucose ≥200 mg/dl (11.1mmol/l) during an OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water(2).

Chronic obstructive airway disease

COPD is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases(3).

The diagnosis of COPD is confirmed by the following:

- Spirometry demonstrating airflow limitation (i.e. a forced expiratory volume in one second/forced vital capacity [FEV_1/FVC] ratio less than 0.7 or less than the lower limit of normal [LLN]) that is incompletely reversible after the administration of an inhaled bronchodilator.
- Absence of an alternative explanation for the symptoms and airflow limitation

Bronchial Asthma

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation(4).

Chronic Kidney Disease

CKD is defined by the presence of kidney damage **or** decreased kidney function **for three or more months**, irrespective of the cause(5).

Acute Kidney Injury(6)

- Increase in serum creatinine by ≥0.3 mg/dL (≥26.5 micromol/L) within 48 hours OR
- Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior seven days OR
- Urine volume <0.5 mL/kg/hour for six hours

Systemic Hypertension

Hypertension is defined as elevated blood pressure and categorized as stage 1 hypertension (130-139/80-89 mm Hg), or stage 2 hypertension (≥140/90 mm Hg)

Chronic liver disease

Progressive destruction of the liver parenchyma over a period greater than 6 months leading to fibrosis and cirrhosis

Community acquired pneumonia

Community-acquired pneumonia (CAP) refers to an acute infection of the pulmonary parenchyma acquired outside of a health care setting.

The diagnosis of CAP is based on the presence of select clinical features (e.g., cough, fever, sputum production, and pleuritic chest pain) and is supported by imaging of the lung, usually by chest radiography.

Pyelonephritis

Cystitis is an acute urinary tract infection (UTI) that is presumed to be confined to the bladder. Pyelonephritis refers to an acute UTI with any of the following features, which suggest that the infection extends beyond the bladder (7).

- Fever (>99.9°F/37.7°C) – This temperature threshold is not well defined and should be individualized, taking into account baseline temperature, other potential contributors to an elevated temperature, and the risk of poor outcomes should empiric antimicrobial therapy be inappropriate.
- Other signs or symptoms of systemic illness (including chills or rigors, significant fatigue or malaise beyond baseline).
- Flank pain
- Costovertebral angle tenderness

Meningitis

Meningitis is an inflammatory disease of the leptomeninges, the tissues surrounding the brain and spinal cord, and is defined by an abnormal number of white blood cells in the cerebrospinal fluid (CSF).

Encephalitis

Encephalitis is defined as inflammation of the brain parenchyma associated with neurologic dysfunction

Acute gastroenteritis

Acute gastroenteritis is defined as diarrheal disease (three or more times per day or at least 200 g of stool per day) of rapid onset that lasts less than two weeks and may be accompanied by nausea, vomiting, fever, or abdominal pain

Acute undifferentiated febrile illness

Acute undifferentiated febrile illness (AUFI) connotes fever of <14 days duration without any evidence of organ or system specific etiology (8).

INSTITUTIONAL REVIEW BOARD

The institutional review board and ethics committee approved this study. The research funding was obtained from the fluid research grant of the institution. IRB Minute Number: 11285 (OBSERVE) (04/04/2018)

Review of Literature

Introduction

Effective antimicrobial therapy ranks among the most significant tools in modern clinical medicine. The usage of antibacterial agents in clinical practice began during the decade 1930 – 1940, when sulfonamides, penicillin, and streptomycin became available. It was recognized early that bacteria exposed to antimicrobial agents evolved strategies to survive them, raising the concern that these agents should be used carefully in order to preserve their effectiveness. Sir Alexander Fleming, the British physician who discovered penicillin made the following admonitory statements in a New York Times article (June 26, 1945) "... The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out....In such cases the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted".(9)

What is Antimicrobial Resistance??

Antimicrobial resistance (AMR) occurs when microbes (i.e., bacteria, viruses, fungi, and parasites) develop mechanisms to evade antimicrobials rendering them ineffective.(10)

Burden of Antimicrobial Resistance

AMR has been identified as a global health threat with serious health, political, and economic implications. It is usually associated with significant higher morbidity, mortality, prolongation of illness and reduced labor efficiency (11).

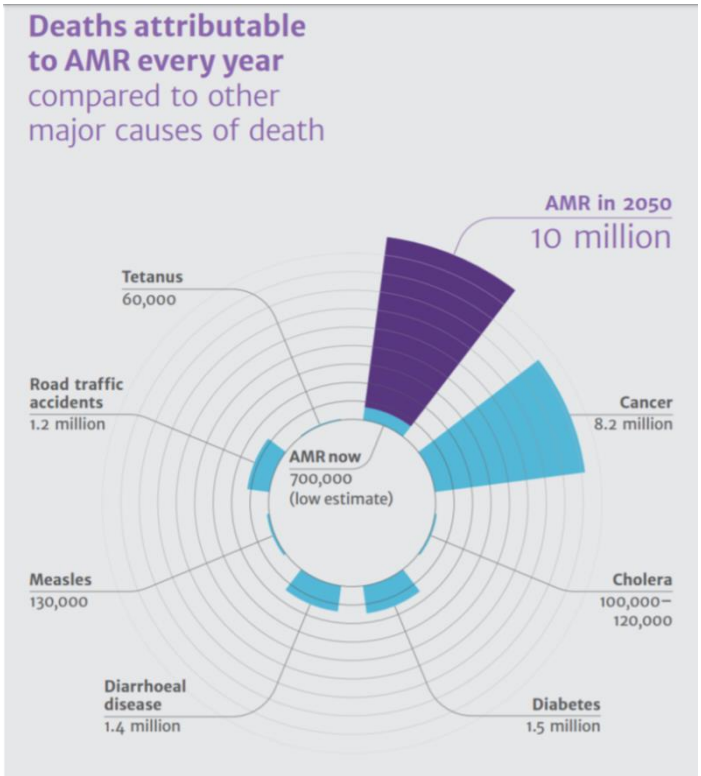


Fig 1: Deaths attributable to AMR every year (12)

Currently according to 2014 data, an estimated 700000 die every year from anti-microbial resistance related diseases. This number in another 25 years is projected to hit 10 million. In India, two million deaths are projected to occur due to AMR by the year 2050.(13)

Why does Antimicrobial Resistance occur?

Microorganisms have developed strong mechanisms for self-preservation from many toxic substances. Most of the antimicrobial substances are naturally produced by microorganisms including fungi and saprophytic bacteria. Most drugs are in fact synthetic modifications of these substances with only a few that are completely synthetic such as sulphonamides and fluoroquinolones.

These mechanisms include producing enzymes that destroy the drug, changing the antimicrobial target on the organism and preventing the drug from entering the system. Therefore, in one sense resistance can just be the Darwinian competition from natural microorganism towards the antimicrobial molecule. In fact metagenomic analysis of microorganisms in the soil have shown a wide variety of genetic determinants which cause antibiotic resistance (14). Only a few of these have been currently described in human pathogens. For example, one of the common forms of resistance that we encounter that is in beta-lactam antibiotics in the form of enzymes that de activate these molecules, has actually existed for millions of years (15).

However there is little evidence to suggest that naturally produced antimicrobial substances contribute to the selection of organisms. First, the concentration of antibiotic molecules in the soil is too low to inhibit the growth of other bacteria and second there is evidence to suggest that even sub lethal concentrations of antibiotics have large effects on bacterial physiology(16). That's why the most important drivers for resistance are human use of antibiotics.

Causes of Antimicrobial Resistance

1. Selection pressure

In individuals, antibiotic resistance has emerged due to selection pressure exerted by any condition (e.g. antimicrobial exposure) that allows microorganisms with inherent resistance or newly acquired mutations or resistance genes to survive and proliferate. (15).

In an environment free from external antimicrobial selection pressure antimicrobial-resistant and non-resistant species co-occur in a stable balance. At an individual level, every human since birth is colonized by a microbiome which is polymicrobial(17)

Antimicrobial use applies such selective pressure on commensal human microflora, and pathogens, increasing the risk of isolating of resistant organisms from patients. (18)

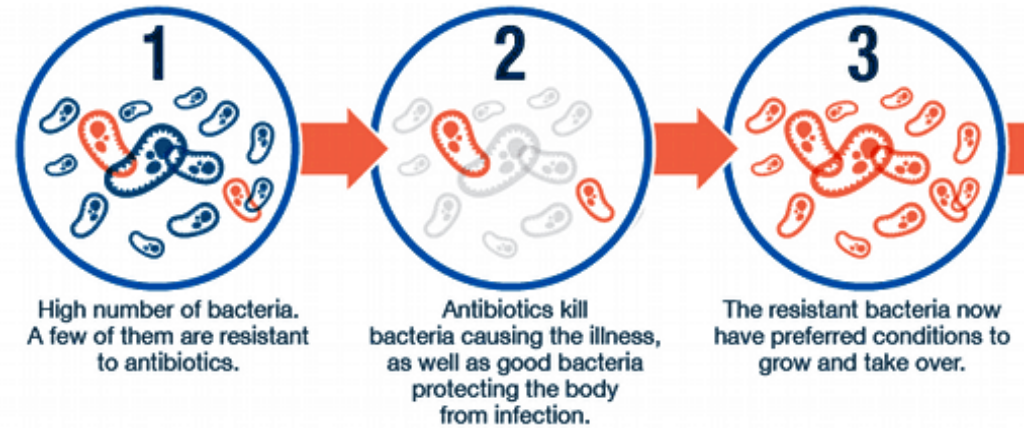


Fig 2: Selection Pressure (19)

2. Discovery Void

This refers to a gap in antibiotic discovery for the last 30 years. Looking at the time line below no major contribution has been made to the field since 1987. Therefore, it is essential to preserve the efficacy of existing drugs through measures to minimize the development and spread of resistance to them, while efforts to develop new treatment options proceed.

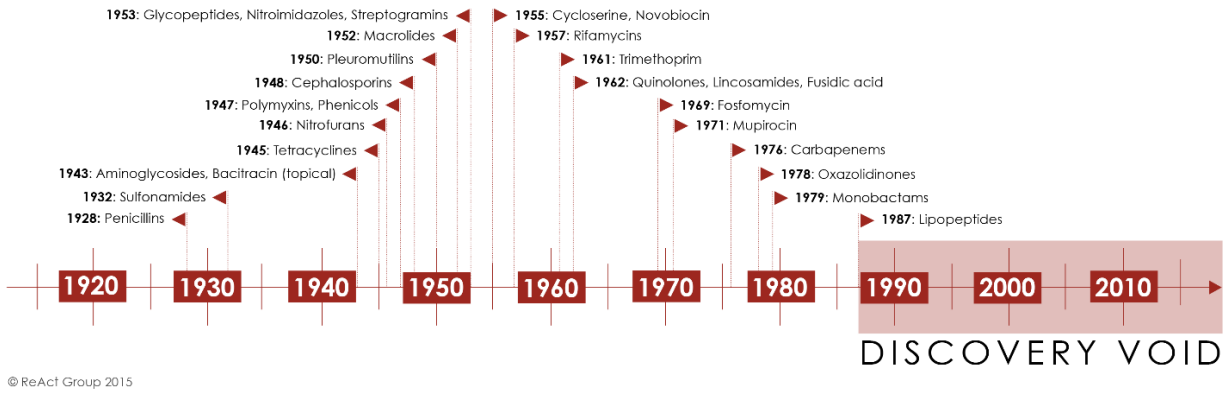


Fig. 3: Time-line of the discovery of different antibiotic classes in clinical use(20)

3. Antibiotic prescribing practices

One of the most commonly prescribed drugs used in human medicine used are antibiotics. The use, misuse and overuse of antimicrobial drugs is a major driving force towards antimicrobial resistance.

Increased consumption of broad-spectrum antibiotics

Ideally, they should be prescribed when the patient is in serious sepsis and requires empirical therapy. Based on antibiotic sales data, in 2014, India was the highest consumer of antibiotics,

followed by China and the United States. However, the per capita consumption of antibiotics in India is much lower than in several other high income countries.(21)

From 2000 to 2015, cephalosporin and broad-spectrum penicillin consumption increased rapidly, whereas narrow spectrum penicillin consumption was low and decreasing.

Third generation cephalosporins are also replacing penicillin's in the treatment of upper respiratory tract infections in outpatient settings and lower respiratory tract infections in inpatient setting(22). There is also increased use of carbapenem, especially since the advent of oral faropenem. It has increased 150% between 2010 and 2014. In India, faropenem is currently approved for treatment of a variety of common infections, including respiratory tract, urinary tract, skin and soft tissue, and gynecological infections. The sharp increase in use of faropenem is of concern because of the potential for cross-resistance to carbapenems.

Lack of widespread availability of narrow-spectrum agents

The production of first-generation penicillin's, (penicillin G, benzathine penicillin) in contrast to third-generation cephalosporins in the pharmacies is very low. According to a review of the April–July 2017 edition of the Current Index of Medical Specialties (CIMS) INDIA, only one formulation company is making penicillin G or benzathine penicillin, whereas 135 companies are manufacturing cefixime.

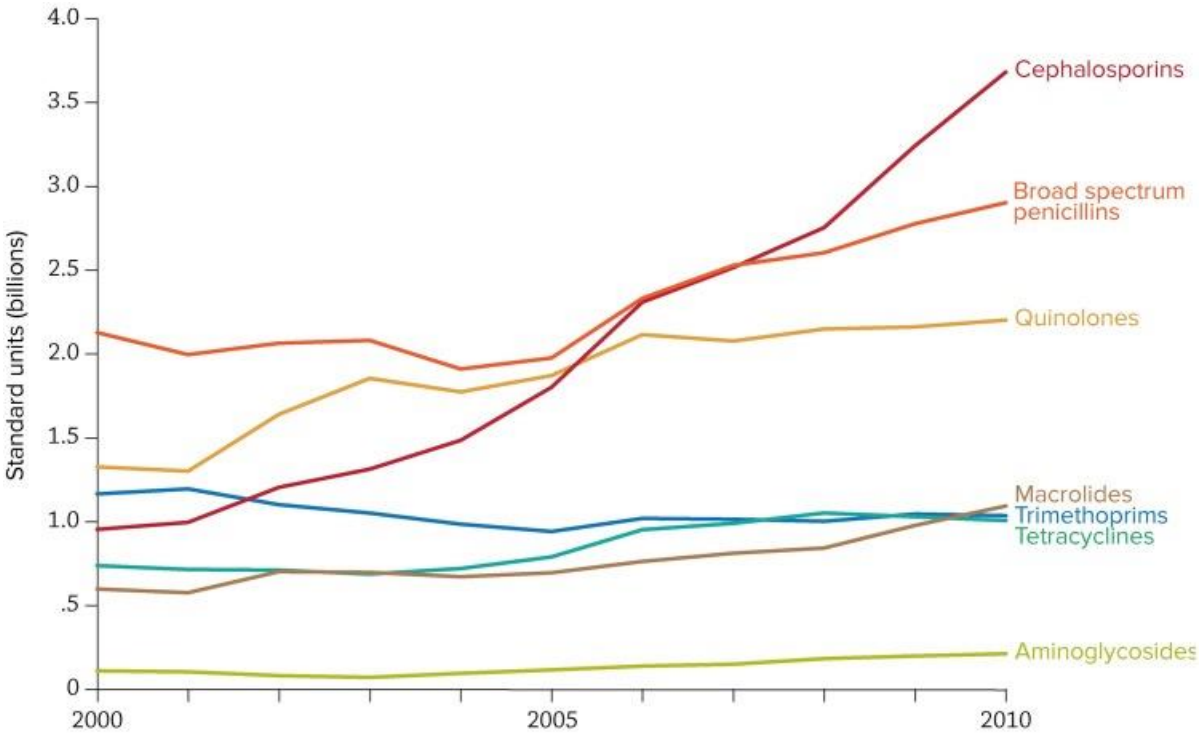


Fig 4: Trends in antibiotic consumption in India, 2000–2010 (23)

Antibiotic fixed-dose combinations

Antibiotic fixed-dose combinations (FDC's) are combinations of two or more active antibiotics in a single dosage form. Antibiotic FDC's should be prescribed when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety, or compliance. However, in India, antibiotic FDC's are heavily prescribed even without the knowledge of a proven advantage over single compounds. In 2018, a study published in the British Journal of Pharmacology showed that, of 118 systemic antibiotic FDC formulations sold in India, 43 (36%) were permitted but 75 (64%) had no record of regulatory approval. Almost half of formulations (58/118; 49%) comprised dual antimicrobials, most unapproved in India (43/58; 74%), and many were pharmacologically wrong(15).

Lack of clinical confidence and non-availability of competent diagnostic laboratory services has led to increased use of antibiotic FDC's in India. Injudicious use of antibiotic FDC's could lead to emergence of bacterial strains resistant to multiple antibiotics.

>>*Antibiotic use in the food animal industry*

Although direct antibiotic sales data in food animals are not available for India, it is estimated that India was the fifth-largest consumer of antibiotics in food animals (poultry, pigs, and cattle) in 2010, after China, the United States, Brazil, and Germany, based on livestock density (24).

Changing patterns of affluence and dietary preferences mean that there is increasing demand for animal protein, which is driving antibiotic use in food animals. Accordingly, antibiotic consumption in food animal production in India is projected to grow by 312%, making India the fourth-largest consumer of antibiotics in animals in 2030(25).

Use of antibiotics as growth promoters in poultry is a common practice; however, the true extent of this practice is unknown. Antibiotics such as colistin, tetracycline, doxycycline, and ciprofloxacin, which are critical to human health, are commonly used for growth promotion in poultry. A recent study done by Sahu and Saxena in 2014 examining antimicrobial residues in chicken meat sold for human consumption, they found that of the 70 chicken meat samples tested, 40% contained antimicrobial residues(26).

The major antibiotics that were found were ciprofloxacin (14.3%), doxycycline (14.3%), oxytetracycline (11.4%), and chlortetracycline (1.4%).

The most worrying aspect of this undiscriminating antibiotic use is the use of polymyxins (colistin) for growth promotion, prophylaxis, and therapeutic purposes in poultry, as this class of drugs is used as a last recourse in many infections.

Emergence of resistance in animals which could then be transferred to humans indicates an urgent need to ban the use of antibiotics that are critically important to humans.

Ironically whereas only one antibiotic formulation company manufactures benzathine penicillin for human use, at least six companies manufacture benzathine penicillin for animal use. This mismatch gives owners a ready access to antibiotics whereas the common man experiences the effects of resistance.

Sanitation

Poor sanitation plays a major role in the spread of antibiotic-resistant bacteria. According to the World Bank, more than 50% of the Indian population does not have access to sanitation facilities for safe disposal of human waste.

In addition, a large proportion of sewage is disposed untreated into receiving water bodies, leading to gross contamination of rivers with antibiotic residues, antibiotic-resistant organisms. As a result, recreational travel to India is recognized as an important risk factor for acquisition of antibiotic resistant organisms such as Extended spectrum beta lactamase (ESBL) organisms. In fact, in a study conducted on how international travel contributes to the spread of multidrug resistant gram negative bacteria, the risk of asymptomatic intestinal colonization with ESBL producing E. Coli among Swiss travelers visiting India was 87%.(27)

Travel

The human microbiota has assimilated antimicrobial resistant Enterobacteriaceae on an unprecedented scale. In some parts of the world the carrier rate of ESβL-positive Enterobacteriaceae in the gut is more than 50%(28).The increased risk of gut colonization is clearly linked to travel with these organisms. A prospective study from the Netherlands showed that 8·6% of travelers were colonized with ESβL-producing Enterobacteriaceae before travel, but 30·5% acquired gut colonization during travel, with independent risk factors being travel to south and east Asia(29).

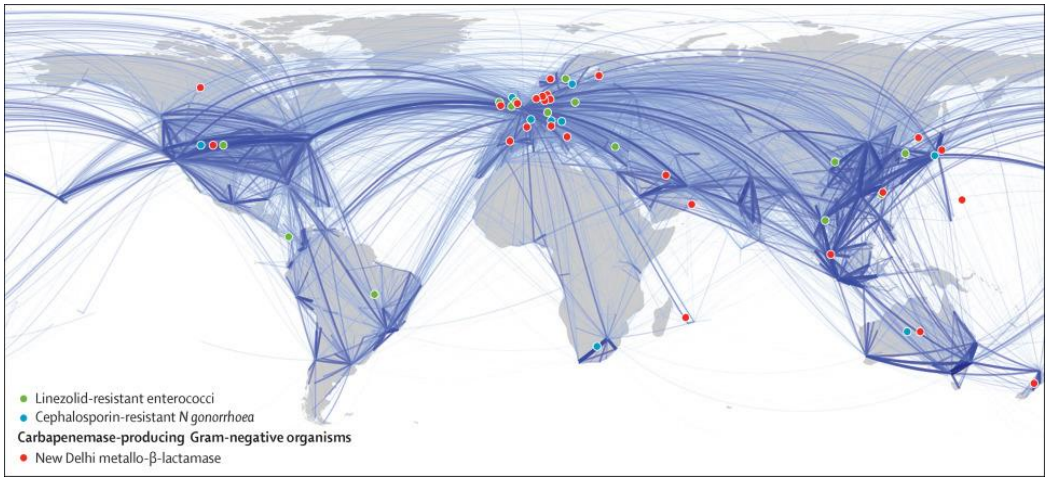


Fig 5 : Worldwide travel routes and emergence of antimicrobial resistance(9)

Biocides

Biocide is an umbrella term encompassing agents directed to kill the offending pathogen or microbe. It includes pesticides, fertilizers, insecticides and disinfectants(30). Sub-lethal concentrations of biocides have been shown to increase the number of resistant organisms in the environment(31). Nitrogen-based fertilizers have shown to alter the soil content selecting out *van*A gene and contributing to clinical vancomycin resistance(14).

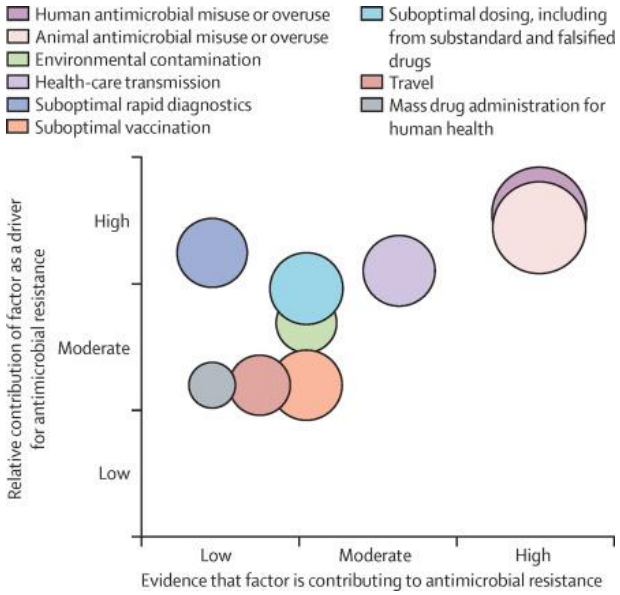


Fig 6: Role of modifiable drivers for antimicrobial resistance: a conceptual framework(9)

Social Factors

The general public has free access to antibiotic therapy, as it is not strictly regulated strictly and are is given over the counter. Most people resort to self-medication, mainly to avoid the financial burden of expensive allopathic medical visits and is compounded by ready availability. They might even use previous doctors' prescriptions and leftover medicines from previous illnesses(32).

In rural areas, where there is a lack of healthcare services in a village, people may want to avoid the travel and extra expenditure. In urban areas, doctor's fees and diagnostic investigation charges may prevent people from visiting formal healthcare providers.

Healthcare providers have to take the bulk of the blame for inappropriate antibiotic usage. Doctors are under pressure to prescribe antibiotics as patients have fixed ideas and

demand swift relief. As health care is treated as a consumer service, doctors may fear that if they do not give antibiotics and instead request diagnostic investigations, the patients will never return to them and thus they will lose their practice. The non-availability of good quality, reliable, microbiological and other laboratory services leaves the doctors in a state of diagnostic uncertainty which leads them to prescribe broad-spectrum antibiotics out of fear of clinical failure. When doctors have to see large numbers of patients on OPD, they may not find the time to counsel patients against the use of antibiotics and instead prescribe them out of sheer impatience.

Pharmaceutical companies put pressure on doctors and pharmacists and have incentivized the process to push them to prescribe new antibiotics. The medicine supply in the public sector is often erratic and patchy. Doctors may not have access to the appropriate antibiotic and hence resort to broad spectrum cover even when it is not needed.

Transmission of antibiotic resistance

Genetic basis of antimicrobial resistance

Bacteria use two fundamental strategies to adapt to anti–microbials: -

- Mutations in gene(s) often associated with the mechanism of action of the compound
- Acquisition of foreign DNA coding for resistance determinants through horizontal gene transfer (HGT)(33)

Mutational resistance

A population of cells in the at-risk population develop mutations in genes that affect the activity of the drug resulting in preserved survival. Once a resistant mutant is formed, the antibiotic eliminates the susceptible population and the resistant bacteria remain.

These mutations can be either

i) Antibiotic Modification or Degradation

A common strategy used by bacteria is antibiotic modification. It makes the antibiotic ineffective especially in the case of aminoglycoside antibiotics (for example, kanamycin, gentamycin, and streptomycin), chloramphenicol, and β-lactams.

A large number of aminoglycoside modification enzymes (AMES), including N-acetyl transferases (AAC), O-phosphotransferases (APH), and O-adenyl transferases (ANT) that acetylate, phosphorylate, or adenylate the aminoglycoside antibiotic, respectively, are known to exist in producer bacteria. (34)

In contrast to the modification of antibiotics described above, resistance to β-lactam antibiotics is normally conferred by antibiotic-hydrolyzing enzymes known as β-lactamases. These enzymes are widespread among Streptomyces, and, together with similar enzymes found in pathogenic and non-pathogenic bacteria, they constitute the ‘β-lactamase superfamily’ of proteins. (35)

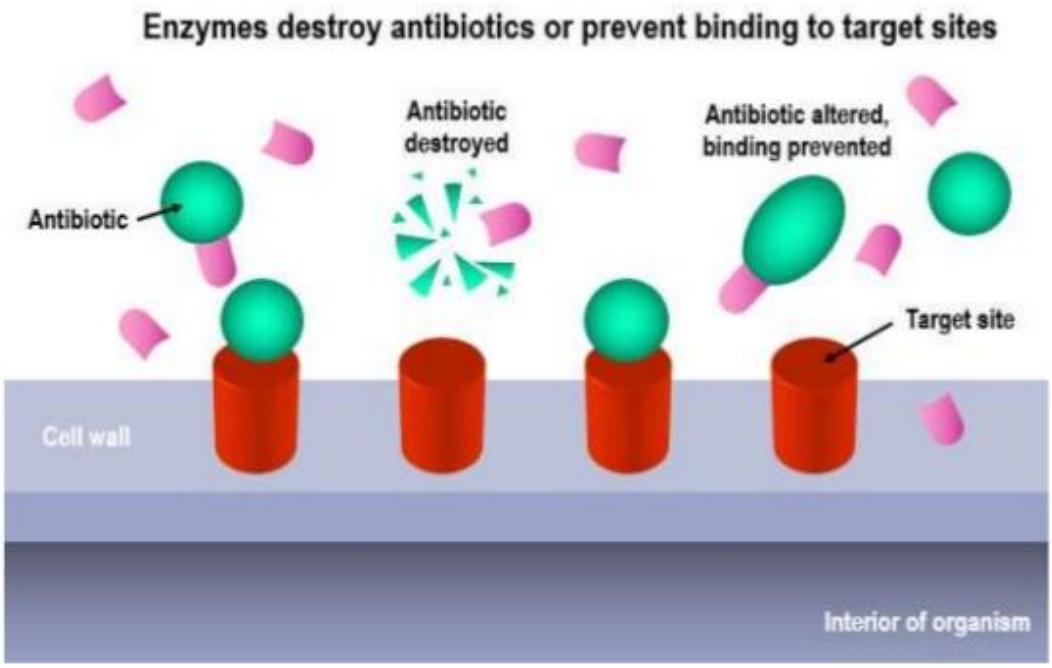


Fig 8: Antibiotic resistance mechanisms

ii) Antibiotic Efflux

Efflux of antibiotics is another commonly used mechanism for self-resistance, although it usually occurs in conjunction with other mechanisms, such as modification of the antibiotic or the target.

Research has elucidated many efflux pumps in Gram-positive bacteria (GPB) including methicillin-resistant Staphylococcus aureus (MRSA), *Streptococcus pneumoniae*, *Clostridium difficile*, *Enterococcus* spp. *and Listeria monocytogenes* and Gram-negative bacteria (GNB*) such as Acinetobacter baumanii , Escherichia coli, Klebsiella pneumoniae,* (36,37)

These efflux pumps are energy dependent as they work against a concentration gradient. Based on the mechanism by which these derive this energy, the efflux pumps are broadly classified into two categories. The primary efflux pumps draw energy from active hydrolysis of ATP,

whereas the secondary efflux pumps draw energy from chemical gradients formed by either protons or ions such as sodium(38).

iii) Target Modification/Bypass/Protection Mechanisms

Target modification acts as a self-resistance mechanism against several classes of antibiotics, including β-lactams, glycopeptides, macrolides, lincosamides, and streptogramins (MLS), and aminoglycosides.

The β-lactam antibiotic has a similar structure to PBP substrates (peptidoglycan precursors), thus allowing the antibiotic to associate and cause acylation of the active site serine resulting in its inhibition (39).

Glycopeptides, such as vancomycin and teicoplanin, inhibit cell wall transpeptidation and transglycosylation by associating with peptidoglycan precursors (D-Ala-D-Ala)(40).Antibiotic resistance results from a change in the peptidoglycan precursor from D-Ala-D-Ala to D-Ala-D-Lac or D-Ala-D-Ser, which has a 1000- and 6-fold reduction in affinity for the glycopeptides, respectively. Genes conferring vancomycin resistance were originally identified in clinical strains, with the VanA cluster on the transposon Tn1546 being the most frequently seen (40).

Horizontal gene transfer

Acquisition of foreign DNA material through HGT is one of the most important drivers of bacterial evolution and it is frequently responsible for the development of antimicrobial resistance. Characteristically, bacteria acquire external genetic material through three main approaches.

i) Transformation

Natural transformation — the stable uptake, integration and functional expression of extracellular DNA that can occur under natural bacterial growth conditions. Many human pathogenic bacteria, including representatives of the genera Campylobacter, Hemophilus, Helicobacter, Neisseria, Pseudomonas, Staphylococcus and Streptococcus, are naturally transformable.

The steps involved in this process include the release of extracellular DNA into the environment and the uptake of DNA into the cytoplasm of the recipient bacterial cell that has developed a regulated physiological state of competence. Following uptake, for the transferred DNA to persist it must integrate into the bacterial genome through homologous recombination or by sequence-independent, illegitimate recombination.

ii) Transduction

Transduction is the process of moving host DNA from one bacterium to another using a bacteriophage (a virus of bacteria, often referred to as phage) as the vector. The process was first described by Zinder and Lederberg [18] after they observed that genetic traits could be transferred between strains of Salmonella enterica serovar Typhimurium using a vector that could be passed through a filter which excluded bacteria.

iii) Conjugation

This involves cell-to-cell contact and is likely to occur at high rates in the gastrointestinal tract of humans under antibiotic treatment. As a general rule, conjugation uses mobile genetic elements (MGEs) as vehicles to share valuable genetic information, although direct transfer

from chromosome to chromosome has also been well characterized (9). The most important MGEs are plasmids and transposons, both of which play a crucial role in the development and dissemination of antimicrobial resistance among clinically relevant organisms.

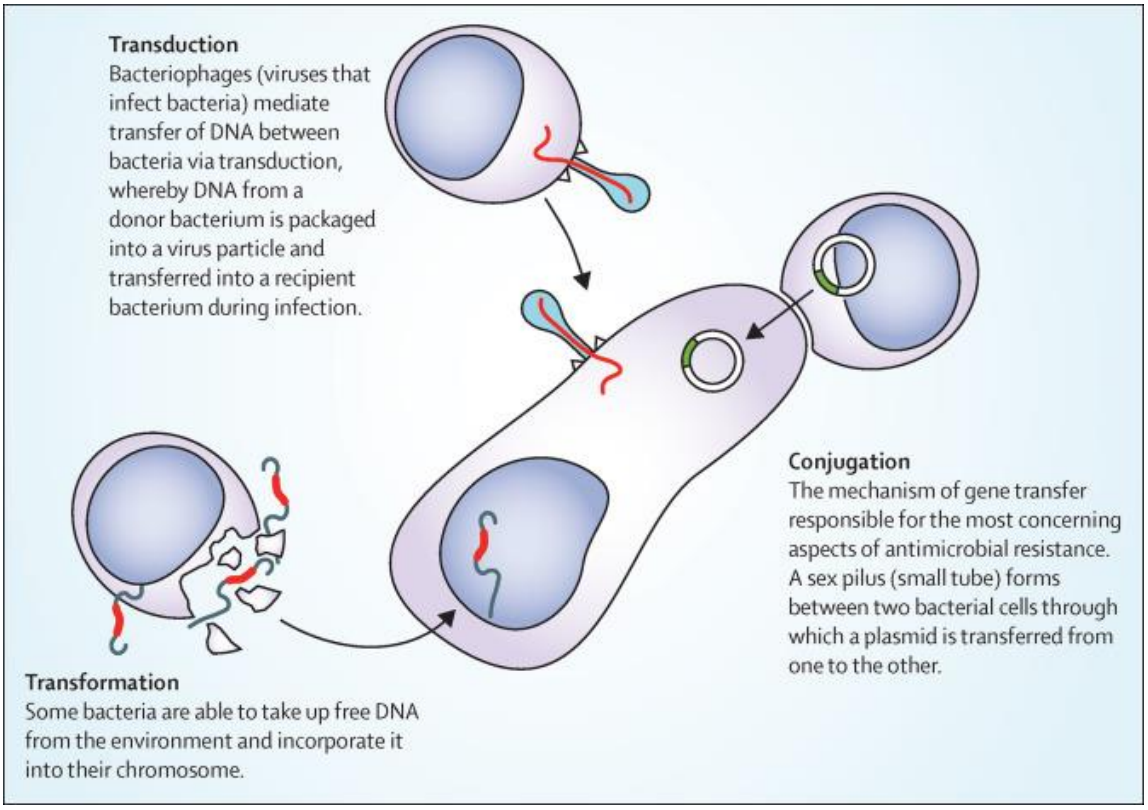


Fig 7: Mechanisms of Horizontal gene transfer

How to tackle antimicrobial resistance

The approach is based on the principle of prolonging useful therapeutic life of antimicrobials available at present and preventing the emergence of further resistance.

1. Maintain heterogeneity of antimicrobial agents

Excessively homogeneous antimicrobial use might contribute to selective pressure. Maintaining prescribing diversity can be achieved through several methods such as

- Drug cycling (replacing an antimicrobial belonging to one class with one or more belonging to different classes, sequentially, at the level of the unit or hospital).
- Drug mixing (diversification of antimicrobial prescription at the individual level allowing for patient variation), which maintains personalization of infection treatment. (41)

2. Assure and ensure adequate serum drug concentrations

Subtherapeutic concentrations contribute to poor treatment responses and exert non-lethal selective pressures.

3. Repurposing of withdrawn and underused antimicrobial drugs

Repurposing previously discovered (often FDA-approved) pharmacotherapies might provide a potentially less economically risky pursuit than de-novo drug discovery(42). This approach has already been evident with the return of Colistin and Fosfomycin use for multidrug-resistant Gram-negative infections, repurposing of older drugs for bacteria such as *Acinetobacter baumannii*, and more widespread consideration of fusidic acid in clinical practice in some countries since the 1960s.

4. Combination therapy

Combination therapy is use of several antimicrobials to which the targeted organisms do not show cross-resistance. This relies on microbial populations containing singly resistant mutants, but none that are resistant simultaneously to several drug.

5. Government initiatives

Development and implementation of infection prevention and control initiatives at national and local levels should be established to curtail onwards transmission of antimicrobial-resistant microbes.

6. Animal industry

- Antimicrobials used as animal growth promoters and for inappropriate routine infection prevention in herds should be banned
- Access to non-medicated animal feed for farmers should be provided
- Use of specific classes of antimicrobials like colistin should be restricted to human beings.

Antimicrobial stewardship

Definition:

Antimicrobial stewardship is the umbrella term used to define comprehensive quality improvement activities that together represent a cohesive program aiming to optimize the use of antimicrobials, improve patient outcomes, reduce the spread and development of

antimicrobial resistance and reduce the incidence of healthcare acquired infections(43). It has also been described as an inter-professional effort, across the continuum of care which involves timely and optimal selection, dose and duration of an antimicrobial for the best clinical outcome for the treatment or prevention of infection with minimal toxicity to the patient and minimal impact on resistance and other ecological adverse events such as *C. difficile.*(44)

Framework of an Antimicrobial Stewardship Program

The CDC has brought out guidelines regarding the development and functioning of an ASP. They looked at 7 broad domains necessary to create a cohesive program.

1. Leadership Commitment: Dedicating necessary human, financial and information technology resources
2. Accountability: Appointing a single leader responsible for program outcomes. Experience with successful programs show that a physician leader is effective.33
3. Drug Expertise: Appointing a single pharmacist leader responsible for working to improve antibiotic use.
4. Action: Implementing at least one recommended action, such as systemic evaluation of ongoing treatment needs after a set period of initial treatment (i.e. “antibiotic time out” after 48 hours)
5. Tracking: Monitoring antibiotic prescribing and resistance patterns
6. Reporting: Regular reporting information on antibiotic use and resistance to doctors, nurses and relevant staff
7. Education: Educating clinicians about resistance and optimal prescribing

Interventions and policies that improve antibiotic use

The AMS interventions can also be classified as restrictive measures and persuasive measures. Restrictive interventions were implemented through restriction of the freedom of prescribers to select some antibiotics. Persuasive interventions used one or more of the following methods for changing professional behavior: dissemination of educational resources, reminders, audit and feedback, or educational outreach. Restrictive interventions could contain persuasive elements.

Although equivalent to persuasive measures at 12 or 24 months, restrictive interventions had statistically greater effect size on prescribing outcomes at 1 month (+32%; 95% CI, 2%–61%; P = .03) and on colonization or infection with *C. difficile* or antibiotic-resistant bacteria at 6 months (+53%; 95% CI, 31%–75%; P = .001)(11)

The common goal is to optimize and make antibiotic use effective. There are certain policies that can be universally implemented:

- Document dose, duration, and indication. Specify the dose, duration and indication for all courses of antibiotics so they are readily accessible
- Develop and implement facility specific treatment recommendations.
- Treatment recommendations, based on national guidelines and local susceptibilities can improve antibiotic selection and duration, particularly for common infections such as community-acquired pneumonia, urinary tract infection, intra-abdominal infections, skin and soft tissue infections etc.

There are certain interventions which can be implemented as a broad indication

Antibiotic "Time outs".

In many infective conditions such as community acquired pneumonia, urinary tract infection, meningitis there is benefit of empiric therapy that is initiated as soon as the patient is clinically diagnosed. However, providers often do not revisit the selection of the antibiotic after more clinical and laboratory data (including culture results) become available.

The concept of antibiotic "time out" prompts a reassessment of need and choice of antibiotics when the clinical picture is more defined and the diagnostic test results are available. All clinicians should perform a review of antibiotics 48 hours after antibiotics are initiated to answer these key questions:

- Does this patient have an infection that will respond to antibiotics?
- If so, is the patient on the correct antibiotic(s), dose, and route of administration?
- Can a more targeted antibiotic be used to treat the infection (de-escalate)?
- What duration should the patient receive the antibiotic(s)?

Prior authorization

Some facilities restrict the use of certain antibiotics based on the spectrum of activity, cost, or associated toxicities to ensure that use is reviewed with an antibiotic expert before therapy is initiated.

There are many advantages to this strategy such as: - Reduction of initiation of unnecessary/ inappropriate antibiotics, optimizing empiric choices and influencing downstream use, prompt review of clinical data/prior cultures at the time of initiation of therapy, decreasing antibiotic costs and giving direct control over antibiotic use.

White et al (45) reported that initiation of a preauthorization requirement for selected antibiotics at a county teaching hospital was associated with a 32% decrease in total parenteral antibiotic expenditures ($P < .01$) and increased percentages of susceptible gram-negative isolates—all without changes in hospital length of stay and survival.

However, the success of this intervention depends heavily on the skills of the person providing approval and the real time availability of the facility. Antibiotic approval by an antibiotic stewardship team consisting of a clinical pharmacist and an infectious diseases attending physician was more effective than off-hour approval by infectious diseases fellows in recommendation appropriateness (87% vs 47%; $P < .001$), cure rate (64% vs 42%; $P = .007$), and treatment failures (15% vs 28%; $P = .03$) (46). Errors in communication of the clinical scenario by the treating physician to the antibiotic stewardship team increased the likelihood of inappropriate recommendations (47). There is also the possibility that the clinicians may simply shift to other antibiotic agents and select for different antibiotic-resistance patterns. For example, Rahal et al(48) implemented a preauthorization requirement for cephalosporins. This was associated with a reduction in the incidence of ceftazidime-resistant Klebsiella, but imipenem use increased and a 69% increase in the incidence of imipenem-resistant P. Aeruginosa was seen.

Prospective audit and feedback

External reviews of antibiotic therapy by an expert in antibiotic use have been highly effective in optimizing antibiotics in critically ill patients and in cases where broad spectrum or multiple antibiotics are being used.

PAF interventions also have been shown to improve antibiotic use, reduce antibiotic resistance, and reduce CDI rates, without a negative impact on patient outcomes. For instance, PAF conducted by a clinical pharmacist and infectious diseases physician at a community hospital led to a 22% reduction in the use of parenteral broad-spectrum antibiotics as well as a reduction in rates of CDI and nosocomial infections due to antibiotic-resistant Enterobacteriaceae over a 7-year period of time(49). PAF has also been effective in the ICU (50,51). For example, a PAF intervention in multiple ICU's at a large academic institution demonstrated decreased meropenem resistance and decreased CDI's ($P = .04$) without adversely affecting mortality (51).

The effectiveness of PAF may depend on the infrastructure in place at an institution. It can also require multiple personnel and be a challenge to implement. However even a limited PAF can make a difference.

At St. Joseph Medical Center in Bellingham, WA, a thrice-weekly ASP was initiated in 2010 with the goals of decreasing carbapenem, fluoroquinolone and vancomycin use and tailoring duration of therapy. The pharmacy department teamed up with the local infectious disease physicians to implement an ASP with four major initial objectives: to decrease the use of (i) carbapenems, (ii) fluoroquinolones and (iii) vancomycin, and to (iv) tailor the duration of

antimicrobial therapy. Other interventions made by the ASP are therapeutic modifications based on culture sensitivities (drug–bug mismatches), conversion from IV to oral antimicrobials, weight-based dosing adjustments and renal dosing adjustments. The ASP also reviews all positive blood cultures to ensure that possible infections are not overlooked. The program consists of thrice weekly pharmacist review of patients on antimicrobials targeting the aforementioned medications. Antimicrobial days of therapy per 1000 patient-days declined by 64% after implementation of the ASP. There was also a 37% reduction in total antimicrobial expenditures. (10).

Pharmacy-driven Interventions

These are the interventions that can be implemented which can be pharmacy centered.

- Automatic changes from intravenous to oral antibiotic therapy in appropriate situations and for antibiotics with good absorption. This improves patient safety by reducing the need for intravenous access
- Dose adjustments in cases of organ dysfunction such as renal dysfunction
- Dose adjustments based on therapeutic drug monitoring, optimizing therapy for highly drug-resistant bacteria, achieving central nervous system penetration, extended-infusion administration of beta-lactams, etc.
- Automatic alerts in situations where therapy might be unnecessarily duplicative including simultaneous use of multiple agents with overlapping spectra

Infection and syndrome specific interventions

The interventions below are intended to improve prescribing for specific syndromes; however, these should not interfere with prompt and effective treatment for severe infection or sepsis.

Community-acquired pneumonia. Interventions for community-acquired pneumonia have focused on correcting recognized problems in therapy, including: improving diagnostic accuracy, tailoring of therapy to culture results and optimizing the duration of treatment to ensure compliance with guidelines(52).

Urinary tract infections (UTI) Many patients who get antibiotics for UTI's actually have 3asymptomatic bacteriuria .(53) Interventions for UTI's should focus on avoiding unnecessary urine cultures and treatment of patients who are asymptomatic and ensuring that patients receive appropriate therapy based on local susceptibilities and for the recommended duration.(54)

Skin and soft tissue infections: To focus on ensuring that patients do not get antibiotics with overly broad spectra and ensuring the correct duration of treatment.

Clostridium difficile infections : Reviewing antibiotics in patients with new diagnoses of CDI can identify opportunities to stop unnecessary antibiotics which improve the clinical response of CDI to treatment and reduces the risk of recurrence(55)

Treatment of culture proven invasive infections: Blood stream infections present good opportunities for interventions to improve antibiotic use because they are easily identified from microbiology results. The culture reports give adequate information to de-escalate antibiotics to the most appropriate drug with the narrowest spectrum

Tracking and Reporting Antibiotic Use and Outcomes

One of the cornerstones of all antimicrobial stewardship programs is the monitoring component. It is important to assess the impact and efficiency of interventions and to look for opportunities for improvement. This consists of

1. Monitoring antibiotic prescribing

   Perform periodic assessments of the use of antibiotics or the treatment of infections to determine the quality of antibiotic use. These reviews can be done retrospectively on charts which could be identified based on pharmacy records or discharge diagnoses.

2. Antibiotic Use Process measures

One can measure antibiotic use as either days of therapy (DOT) or defined daily dose (DDD). DOT is an aggregate sum of days for which any amount of a specific antimicrobial agent is administered or dispensed to a particular patient (numerator) divided by a standardized denominator (e.g., patient days, days present, or admissions).(56) DDD estimates antibiotic use in hospitals by aggregating the total number of grams of each antibiotic purchased, dispensed, or administered during a period of interest divided by the World Health Organization-assigned DDD.(57)

Outcome measures

>>Track clinical outcomes that measure the impact of interventions to improve antibiotic use.

>>Monitoring antibiotic resistance

Education

Antibiotic stewardship programs should provide regular updates on antibiotic prescribing, antibiotic resistance, and infectious disease management that address both national and local issues.

Difficulties in implementing AMSP

Wide disparities exist in the availability of resources to implement antimicrobial stewardship initiatives in hospitals in both developed and developing healthcare systems. In a study conducted by ESCMID Study Group for Antimicrobial Policies (ESGAP) and ISC Group on Antimicrobial Stewardship through an internet-based survey, the main barriers to implementing AMS programs were perceived to be a lack of funding or personnel, a lack of information technology and prescriber opposition

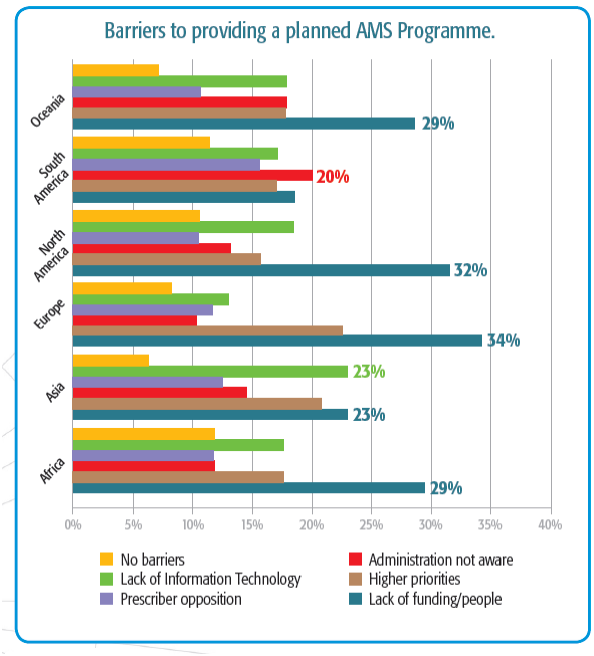


Fig 8: Barriers to providing a planned AMS program

It is unlikely that there will ever be enough infectious disease specialists in any healthcare system to drive all the antimicrobial stewardship programs. Faced with the problem of insufficient on-site resources to implement stewardship program as typically seen in large teaching hospitals, other options may be used such as: partnering with a larger hospital with an established stewardship program and developing targeted quality improvement intervention for a common and recurring problem related to the overuse of antimicrobials. The other way to go ahead is to embed it within existing local patient safety programs.

Another misconception is perhaps that stewardship activities have to be driven by core medical microbiology and infectious diseases specialties. Other healthcare professionals and specialties can initiate activities and develop programs with contribution from specialists that

effectively bring about a positive change in antimicrobial prescribing and infection management programs.

Antibiotic de-escalation

The delivery of effective antimicrobial therapy in a timely manner and of a suitable spectrum is one of the backbones of the treatment of infectious diseases. De-escalation of therapy is an approach aimed at matching the effective treatment of patients with infections and the prevention of an increase in antimicrobial resistance.

Definition

Antimicrobial de-escalation is a mechanism whereby the provision of effective initial antibiotic treatment, particularly in cases of severe sepsis, is achieved while avoiding unnecessary antibiotic use that would promote the development of resistance. This definition therefore encompasses 2 key features. First, there is the intent to narrow the spectrum of antimicrobial coverage depending on clinical response, culture results, and susceptibilities of the pathogens identified, and second, there is the commitment to stop antimicrobial treatment if no infection is established(58).

The surviving sepsis guidelines has a Grade 2B recommendation stating that empiric combination therapy should not be administered for more than 3 to 5 days and that de-

escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known.(59)

Benefits of de-escalation therapy

The following benefits can be associated with antibiotic de-escalation:

--Treatment outcomes are unchanged from the conventional therapy approach of continuing patients on their originally selected antimicrobials

--There is an advantageous impact observed through surveillance on the antimicrobial resistance profile for the institution at both micro and macro level

--There is a decrease in antibiotic related adverse events such as *Clostridium difficile* infection and/or of superinfection with resistant bacteria

--There is a cut in overall antimicrobial costs(58)

Evidence for antimicrobial de-escalation

The first systematic review on de-escalation of antibiotics was published in 2013 in the Cochrane Database(60). They had planned to include randomized controlled trials (RCTs) comparing de-escalation (based on culture results) versus standard therapy for adults with sepsis, severe sepsis or septic shock. Mortality at 28 days, hospital discharge or at the end of the follow-up period was the primary outcome. However, they found only one ongoing RCT

that adhered to the criteria. They then concluded the study expressing the need for further research via RCT's and that they would be awaiting the results of the ongoing study.

Following this review in 2015 Tabah et al published a systematic review of the Definitions, Determinants, and Clinical Outcomes of ADE in the Intensive Care Unit. They however included uncontrolled before-and-after, case-control, and cohort studies. The investigators found that ADE was associated with reduced mortality. However, the clinical and statistical heterogeneity in the meta-analysis questioned the validity of this result. There was heterogeneity in many variables such as study design and populations, in the definition of ADE, and in the adjustment for confounding variables.

Since patients with improving severity scores are more likely to undergo antibiotic de-escalation, in the cohort with the largest weight, the authors attempted to lessen bias by performing a propensity score adjusted multivariable analysis. Although it is a state-of-the-art statistical adjustment, it is not possible to exclude an interaction with clinical improvement, because it is a determinant for both mortality rate and performance of ADE(61). As a result, in a non-randomized setting ADE could be considered a marker of clinical improvement, whereas the hesitancy to narrow the antimicrobial spectrum may indicate deterioration.

They also describe a high risk of bias in the cohort studies. Most importantly, because this effect was not confirmed in the only available RCT, these data should not be read as a causal association between ADE and outcomes.

ADE was also variably defined across the studies, making comparability problematic. There are inherent difficulties in defining ADE.

In patients with improving severity scores, it is not known how many were already microbiologically and/or clinically cured. For those patients, ADE may not have influenced outcome.

Thus, the reviewers concluded that there was a need for a larger cluster randomized control trial to assess the effect of the ADE strategy on the bacterial ecology, on MDR carriage, and on patient outcomes.

Evidence in individual infections

>>Community acquired pneumonia

There was a secondary analysis performed of Community-Acquired Pneumonia Organization database, which contained data on 660 bacteremic patients hospitalized because of CAP in 35 countries (2001-2013)(62). De-escalation of therapy was defined as changing an appropriate empirical broad-spectrum regimen to a narrower-spectrum regimen according to culture results within 7 days from hospital admission the primary study outcome was 30-day mortality. ADE was performed in 165 patients (63.2%). The non-de-escalation therapy group was characterized by a more severe presentation at admission. After adjustment for confounders, ADE was not associated with an increased risk of 30-day mortality(62).

>>Hospital acquired pneumonia

In study conducted by the Washington University School of Medicine they looked prospectively at ADE in patients admitted to the ICU with a ventilator associated pneumonia (VAP)(63). The most frequent ICU admission diagnoses in patients with VAP were

postoperative care (15.6%), neurologic conditions (13.3%), sepsis (13.1%), and cardiac complications (10.8%). The mean (+/- SD) duration of mechanical ventilation prior to VAP diagnosis was 7.3 +/- 6.9 days. Major pathogens were identified in 197 patients (49.5%) through either tracheal aspirate or BAL fluid and included primarily methicillin-resistant Staphylococcus aureus (14.8%), Pseudomonas aeruginosa (14.3%), and other Staphylococcus species (8.8%). In the majority of cases (61.6%), therapy was neither escalated nor deescalated. Escalation of therapy occurred in 15.3% of cases, and de-escalation occurred in 22.1%. The overall mortality rate was 25.1%, with a mean time to death of 16.2 days (range, 0 to 49 days). The mortality rate was significantly lower among patients in whom therapy was deescalated (17.0%), compared with those experiencing therapy escalation (42.6%) and those in whom therapy was neither escalated nor deescalated (23.7%; chi2= 13.25; p = 0.001)

>>Severe Sepsis

Garnacho-Montero et al. performed a prospective observational study enrolling patients admitted to the ICU of a university hospital in Spain with severe sepsis and septic shock. A total of 712 patients with severe sepsis or septic shock at ICU admission were treated empirically with broad-spectrum antibiotics. De-escalation was applied in 219 patients (34.9%). By multivariate analysis, factors independently associated with in-hospital mortality were septic shock, SOFA score the day of culture results, and inadequate empirical antimicrobial therapy, whereas de-escalation therapy was a protective factor [Odds-Ratio (OR) 0.58; 95% confidence interval (CI) 0.36-0.93). (61)

>>Bacteremia

Shime et al. published two retrospective observational studies on this subject, based on positive blood cultures, at, Kyoto Prefectural University of Medicine in Japan. The first concerned bacteremia diagnosed between 2004 and 2009, and there was a trend toward a lower death rate (1 vs. 5%) and treatment failure (4 vs. 10%)(64),

The second study concerned bacteremia caused by Gram-negative diagnosed between 2006 and 2011 at the same institution. Again, there was no difference in in-hospital mortality between the de-escalation group (0/28 patients) and the non-de-escalation group (2/11 patients) (p = 0.20).(65)

Challenges of de-escalation

1. Evidence

As is evident from the studies reviewed above, most of the studies mentioned above have concluded that de-escalation is safe and therapy is non-inferior to the standard line of care. There are cohort studies which show that there is a trend towards better mortality rates in patients who undergo de-escalation but there is a dearth of high-quality evidence.

It is difficult to hypothesize why the impact of de-escalation should be to improve clinical outcome, and therefore it remains to be determined whether this effect is genuine or merely reflects the characteristics of the patients in whom de-escalation is both feasible and chosen.

Patients who have already responded to potent, broad-spectrum antimicrobial therapy are similarly at a low risk of death and therefore may derive more harm than benefit from continued broad-spectrum therapy where de-escalation is not implemented, perhaps as a consequence of the modest but measurable toxicity/side effects of such regimens.

2. Implementation

The rates of de-escalation range from about 10% - 70% in trials which suggests that getting clinicians to actually use de-escalation is the major barrier(58). There is a natural tendency, particularly in severe sepsis when the patient who has been very seriously ill is starting to get better, to stick with a treatment regimen that is working rather than change to an alternative agent. One of the solutions to this is to gain clinical confidence in de-escalation. The second would be to use high quality specimens as evidence for de-escalation.

In a prospective observational study involving 143 patients with VAP in a multidisciplinary ICU, diagnosis was made by positive quantitative cultures of either tracheal aspirate or BAL and assessment by appropriateness of treatment for all significant isolates. In tracheal aspirate patients there was 21% de-escalation as compared to the BAL patients where there was 66.1% de-escalation(66).

In the many of the studies presented, the exact time to de-escalation was not set, which tended to reflect the time taken for the results to become available. In most studies, microbiology results became available at around 48 to 72 hours, and this seems to be an ideal time for ADE. However, in a study conducted by a university hospital ICU, they showed that although de-escalation was successfully implemented in 69% of patients supported by microbiological data,

there was a mean period of around 48 hours from the microbiological data being available to action being taken.

Providing adequate support to the physician to enable them to make the decision regarding de-escalation has been proven to be useful. In a before-and-after study, prescriptions of 13 selected intravenous antibiotics from surgical or medical wards were screened from a computer-generated listing and prospectively included. They compared 3 strategies were compared over three consecutive 8-week periods: conventional management by the attending physician (control group); distribution of a questionnaire to the physician (questionnaire group); or distribution of the questionnaire followed by IDP advice (Q-IDP group). The primary outcome was the percentage of modifications of antibiotic therapy at day 4, including withdrawal of therapy, de-escalation, oral switch or reducing the planned duration of therapy. They found the greatest changes in the Q-IDP group than the control group. More prescriptions were modified in the Q-IDP group as compared with the control group (P 5 .004). Stopping therapy in the absence of apparent infection also occurred significantly more often in the Q-IDP group than in the control ($P < .002$)(67).

Antibiotic resistance and India

India carries one of the largest burdens of drug-resistant pathogens worldwide, including the highest burden of multidrug-resistant tuberculosis, alarmingly high resistance among Gram-negative and Gram-positive bacteria (68) even to newer antimicrobials such as carbapenems and faropenem since its introduction in 2010

AMSP capacities in most Indian healthcare institutions (HCIs) are simple or non-existent. This has been well documented in one of the surveys carried out by ICMR in 2013 among 20 tertiary HCIs about AMSP components, implementation and outcome(69). The survey also reported the absence of IDs physicians and clinical pharmacists in institutions.

Over the past 8 years, national commitment to address AMR has steadily increased. National and international attention was brought to the issue with the emergence of NDM-1; global examples of successful strategies were available to address the problem.

The first major step toward undertaking this problem was taken in the form of a National Task Force on AMR Containment in 2010 followed by the adoption of National Policy for Containment of AMR, the Jaipur Declaration and the addition of antimicrobial containment in the 12th 5-year plan in 2011. However, this policy made little progress due to difficulties in execution.

Further progress was made with the Indian Council of Medical Research (ICMR), and the adoption of the “Chennai Declaration” at the second annual conference of the Clinical Infectious Disease Society at Chennai on August 24, 2012.

The meeting was called "A Roadmap to Tackle the Challenge of Antimicrobial Resistance - A joint meeting of Medical Societies in India" and was organized as a pre-conference symposium of the 2nd annual conference of the Clinical Infectious Disease Society (CIDSCON 2012) at Chennai on 24th August. This was the first ever meeting of medical societies in India on issue of tackling resistance, with a plan to formulate a road map to tackle the global challenge of

antimicrobial resistance from the Indian perspective. The meeting consisted of plenary and interactive discussion sessions designed to seek experience and views from a large range of health care professionals(70).

The Government also recently adopted a National Action Plan (NAP) on AMR in 2017. Six strategic priorities have been identified under the NAP-AMR: (i) improving awareness and understanding of AMR through effective communication, education, and training; (ii) strengthening knowledge and evidence through surveillance; (iii) reducing the incidence of infection through effective infection prevention and control; (iv) optimizing the use of antimicrobial agents in health, animals, and food; (v) promoting investments for AMR activities, research, and innovations; and (vi) strengthening India's leadership on AMR.

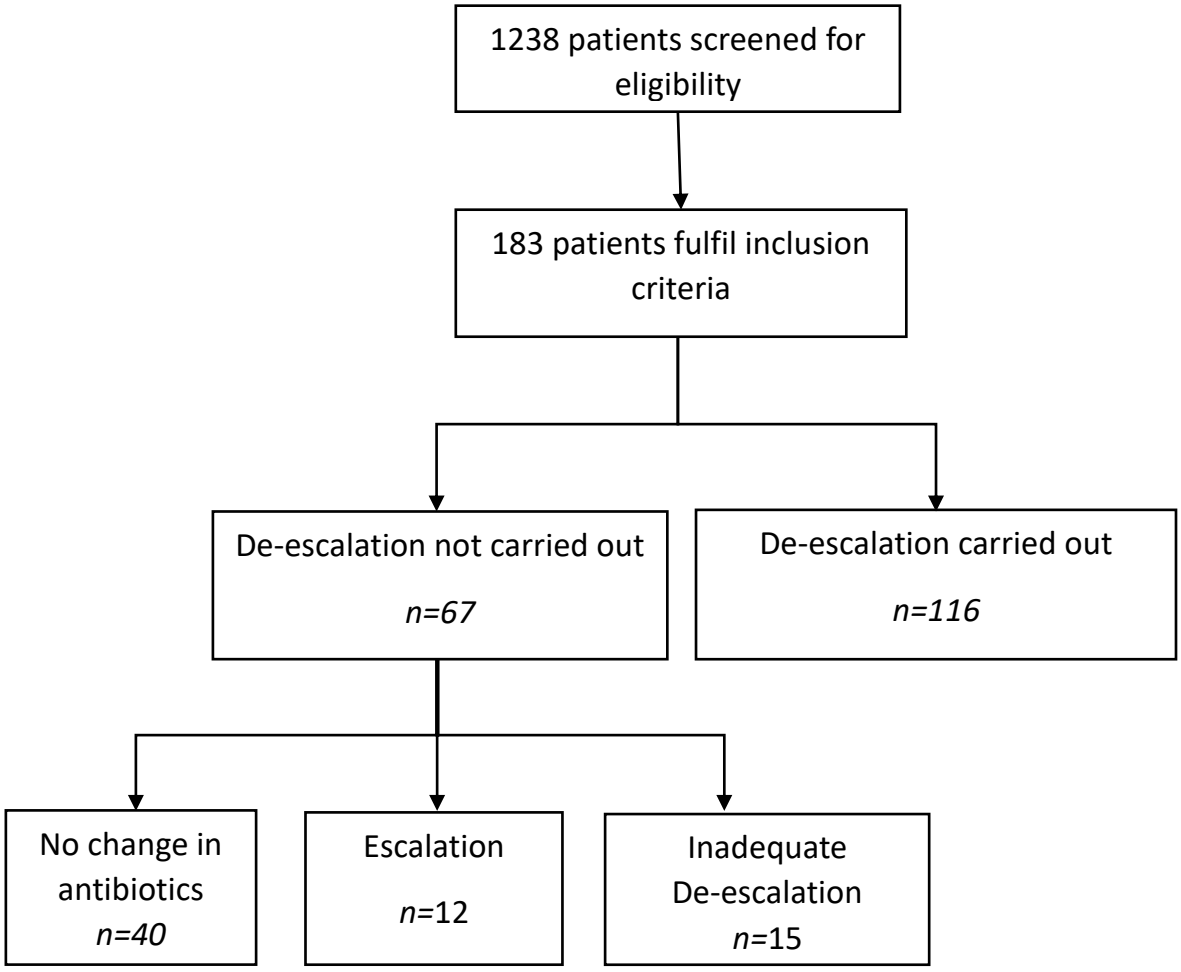
In the Indian setting, research on antibiotic de-escalation is limited. One of the few studies done took place in a tertiary care center in Kerala where they assessed the impact of implementing an antimicrobial stewardship. The study primarily looked at cost and defined daily dose in ADE. They had recruited 1575 patients admitted to the ICU with suspected or known infection (65 percent had a respiratory tract infection. Procalcitonin levels were checked daily, and clinicians were advised to stop antibiotics when levels were ≤0.5 ng/mL or if the level decreased by ≥80 percent from peak. Compared with controls, the procalcitonin group had significantly lower median antibiotic exposure (7.5 versus 9.3 defined daily doses) and lower 28-day mortality (19.6 versus 25 percent).(71)

There are no studies assessing the percentage of de-escalation or qualitatively assessing the knowledge and practices in an Indian setting. This study aims to fill that gap in literature.

RESULTS

This prospective observational study was conducted from September 2018 through May 2019. During this period 1238 patients were screened. A total of 183 patients fulfilled all the inclusion criteria.

The STROBE diagram for the present study is presented below.



DEMOGRAPHIC CHARACTERISTICS

The cohort consisted of 183 patients who were admitted during the above-mentioned period to the general medical wards of CMC and started on empirical antibiotic therapy.

The final analysis showed 94 males (51.4%) and 89 females (48.6%) with no clear gender preponderance. The median age of the patients recruited was 55 years (IQR 39-46), and mean 51.45 years (SD 17.135) as shown below.

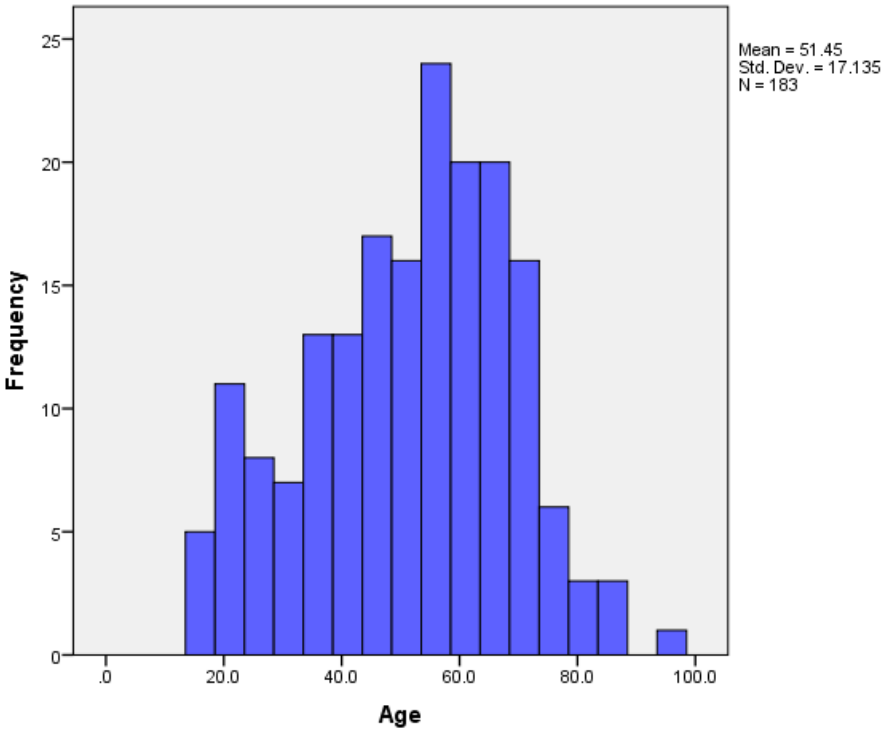


Figure 1: Histogram showing age distribution

Majority of the patients had comorbid illnesses. One hundred and twenty-five (68.3%) patients had one or more co-morbidities, the most common being diabetes mellitus (53%), systemic hypertension (38.8%) and ischemic heart disease (12%). Only 18 out of the 183 patients had history of substance abuse. This is illustrated below.

The mean Charlson comorbidity index was 1.

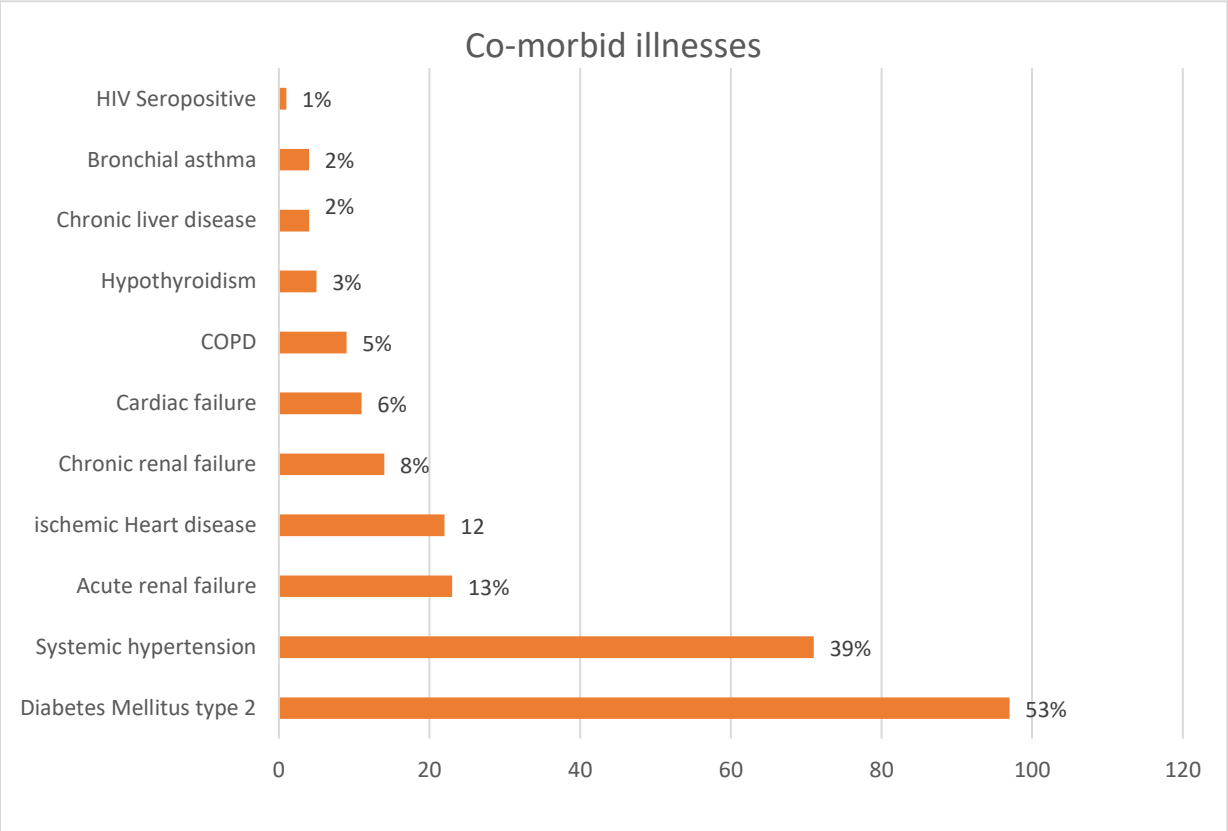


Figure 2: Distribution of comorbid illnesses

Demographics	**N (%)**
Age (years) (mean +/- SD)	51 (17)
Gender	
Male	94 (51.4)
Female	89 (48.6)
Co-morbidities	
Type 2 diabetes mellitus	97 (53)
Systemic hypertension	71 (39)
Acute renal failure	23 (13)
Ischemic heart disease	22 (12)
Chronic renal failure	14 (8)
Cardiac failure	11 (6)
Chronic obstructive airway disease	9 (5)
Hypothyroidism	5 (3)
Chronic liver disease	4(2)
Bronchial asthma	4(2)
HIV infection	1(1)
Charlson comorbidity index (median, IQR)	1(0.0-2)
Pregnancy	3(1.6)
Substance abuse	18(9.8)

Table 1: Demographic characteristics of patient population

Mean heart rate was 106/min, mean arterial pressure 85 mm Hg and mean respiratory rate 26/min (table).

Vital signs at admission	Mean (SD)
Pulse rate (bpm)	106 (22)
Respiratory rate (per minute)	26 (10)
GCS	15 (6)
Systolic Blood pressure (mm Hg)	114 (28)
Diastolic blood pressure (mm Hg)	70 (28)
Mean arterial pressure (mm Hg)	85 (19)
Median SOFA score at admission (IQR)	1 (1-1)
Median qSOFA score at admission (IQR)	1(0-1)

Table 2: Vital signs at admission

Baseline investigations

The following were the baseline laboratory parameters to assess complete blood counts, liver function and renal function.

Baseline lab investigations	Median (IQR)
WBC Count ($x10^4$per cmm)	1.1 (0.8-1.5)
Platelet counts ($x10^5$ per cmm)	2.05 (1.16- 2.92)
Creatinine (mg/dl)	1.1 (0.8-1.88)
Total bilirubin (mg/dl)	0.59 (0.18-0.71)
Direct bilirubin (mg/dl)	0.32 (0.18-0.71)
Total protein (g/dl)	6.9 (6.2-7.3)
Serum albumin (g/dl)	3.2 (2.7-3.6)
SGOT (U/L)	33 (18-68)
SGPT (U/L)	22 (15-53.5)
Sodium (mmol/l)	130.5 (6.5)
Potassium (mmol/l)	3.8 (1.02)

Table 3: Baseline investigations

Diagnosis at initiation of treatment

The most common clinical diagnosis made was pyelonephritis followed by community acquired pneumonia.

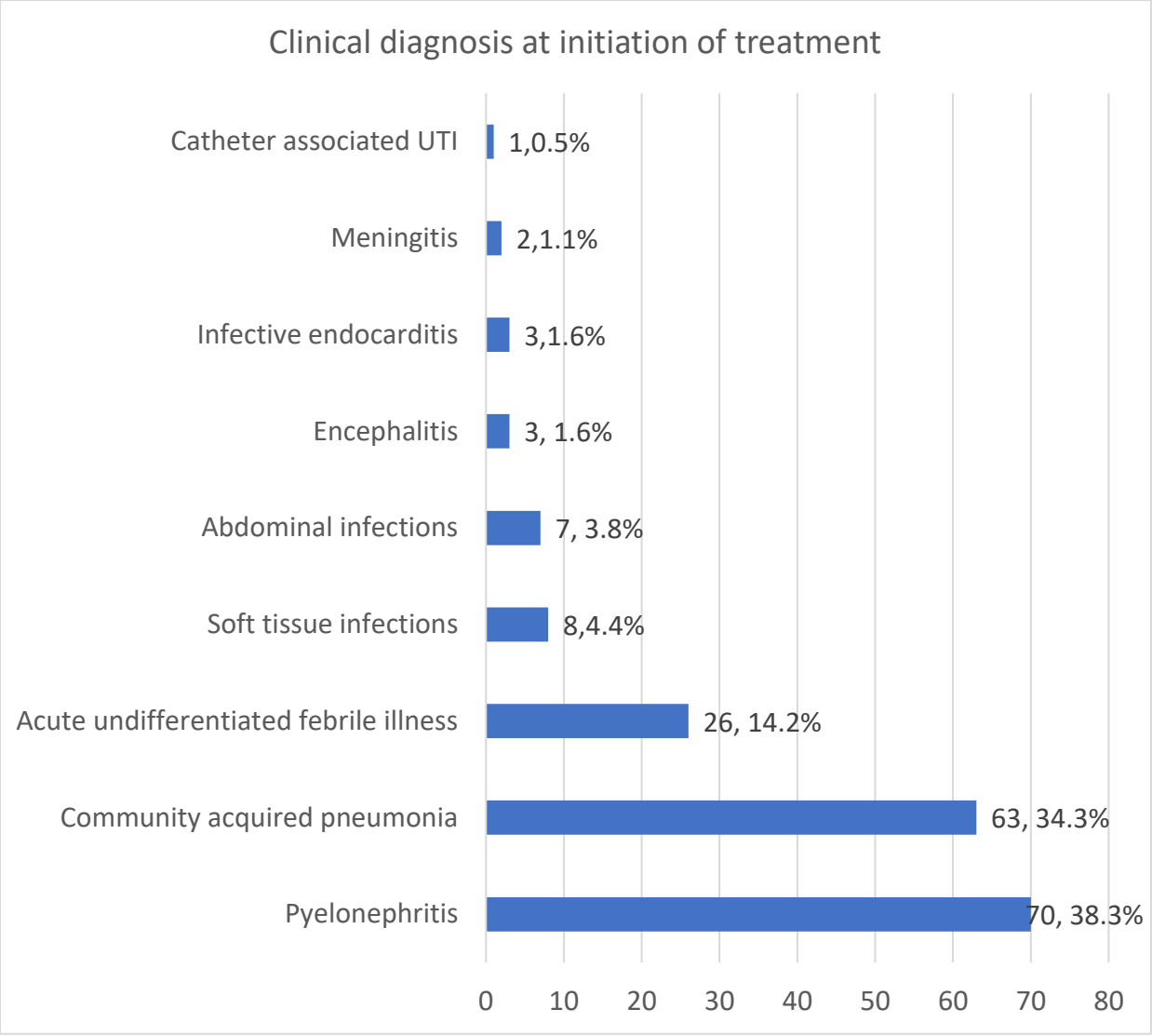


Figure 3: Clinical Diagnosis at treatment initiation

Diagnosis at initiation of treatment	n (%)
Pyelonephritis	70 (38.3)
Community acquired pneumonia	63 (34.4)
Acute undifferentiated febrile illness	26 (14.2)
Skin and soft tissue infections	8 (4.4)
Abdominal infections	7 (3.8)
Encephalitis	3 (1.6)
Infective endocarditis	3 (1.6)
Meningitis	2 (1.1)
Catheter associated UTI	1 (0.5)

Table 4: Clinical diagnosis at initiation of treatment

The most common antibiotics prescribed as initial empirical treatment were piperacillin-tazobactam (44.8%), azithromycin (41.1%) and meropenem (38.3%).

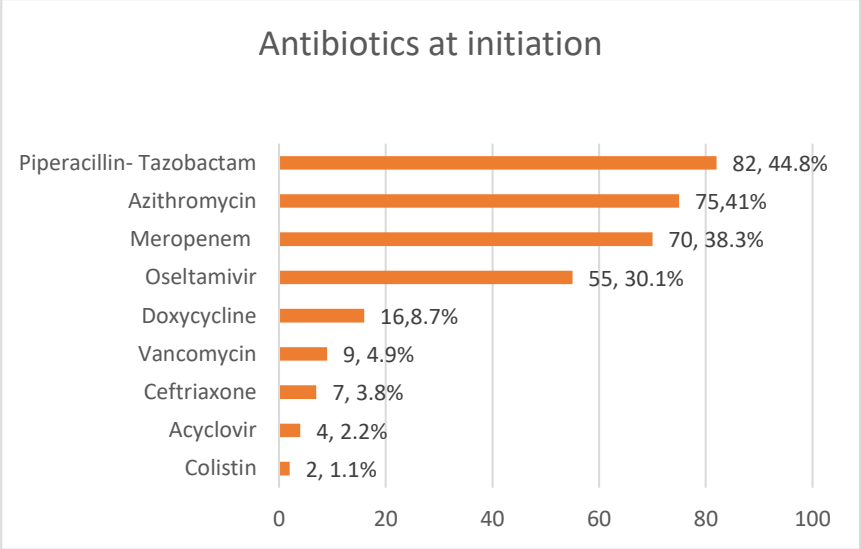


Figure 4: Distribution of antibiotics used

Antibiotics at initiation	N (%)
Colistin	2 (1.1)
Acyclovir	4 (2.2)
Ceftriaxone	7 (3.8)
Vancomycin	9 (4.9)
Doxycycline	16 (8.7)
Oseltamivir	55 (30.1)
Meropenem	70 (38.3)
Azithromycin	75 (41)
Piperacillin-Tazobactam	82 (44.8)

Table 5: Distribution of antibiotics used

Confirmation of the microbial etiology of the infection

The most common methods of confirming the microbial etiology of infection were blood culture isolates and urine culture isolates, followed by PCR for influenza and *Entamoeba histolytica*.

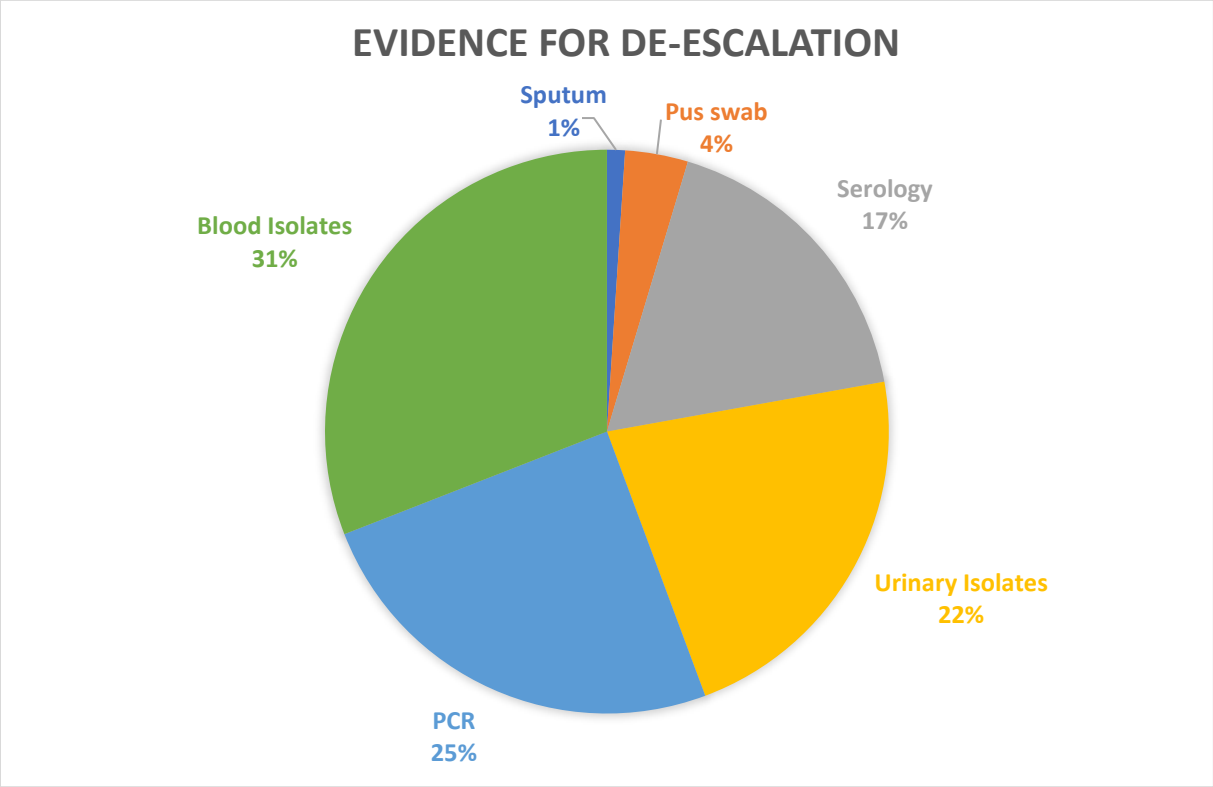


Figure 5: Confirmation of microbial etiology

Diagnostic Evidence	N %
Blood culture	60 (32.8)
Urinary culture	42 (23.0)
PCR	48 (26.2)
Serology	34 (18.6)
Sputum culture	2 (1.1)
Pus culture	7 (3.8)
CSF culture	2 (1.1)

Table 6: Confirmation of microbial etiology

Among all the blood cultures that showed microbiological growth, *Escherichia coli* was the most common organism isolated.

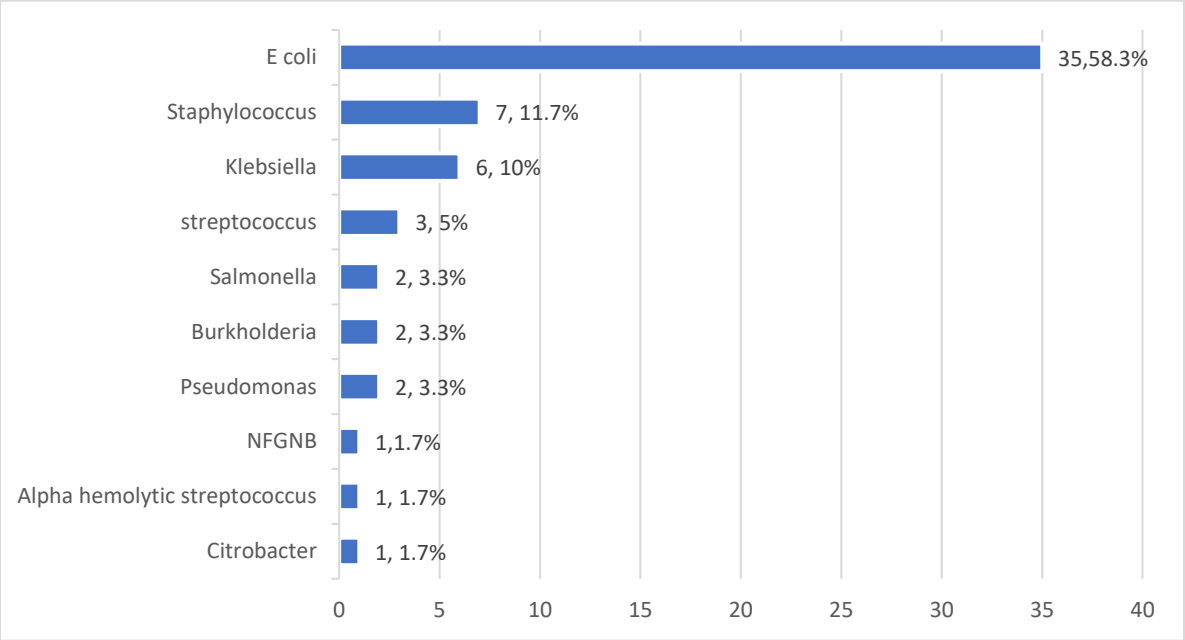


Figure 6: Distributions of blood culture isolates

Blood culture isolates (n=60).	N (%)
Citrobacter spp.	1 (1.7)
Alpha-hemolytic streptococcus	1 (1.7)
Non-fermenting Gram-negative bacteria	1 (1.7)
Pseudomonas spp.	2 (3.3)
Burkholderia pseudomallei	2 (3.3)
Salmonella typhi	2 (3.3)
Streptococcus pneumoniae	3 (5.0)
Klebsiella pneumoniae	6 (10.0)
Staphylococcus aureus	7 (11.7)
Escherichia coli	35 (58.3)

Table 7: Organisms isolated from blood

The most common urinary isolate was also *Escherichia coli* followed by *Klebsiella* spp.

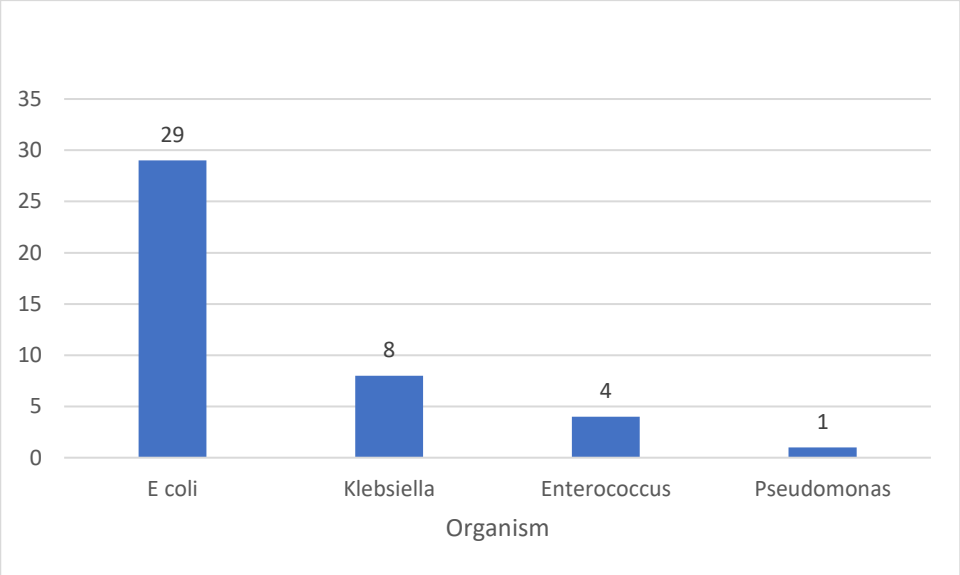


Figure 7: Distributions of urinary isolates

Organisms isolated from urine	N (%)
Escherichia coli	29 (69)
Klebsiella spp.	8 (19)
Pseudomonas spp.	1 (2.3)
Enterococcus spp.	4 (9.5)

Table 8: Urine Isolates

PCR	
Influenza	44 (91.7)
Entamoeba histolytica	4 (8.3)
Serology	
Leptospira	3 (7.0)
Widal	3 (7.0)
Scrub	19 (44.9)
Dengue	9 (20.9)

Table 9: PCR and serological positivity distribution

Action taken by the physician

Out of the 183 patients who were a part of this study 116 (63.4%) underwent de-escalation. The de-escalation was mainly in the form of narrowing the spectrum (35.2%).

The other forms also seen were converting intravenous to oral, stopping therapy if there was no evidence of an infection and converting combination therapy to single agent therapy.

Action taken (n=116)	N (%)
Narrower spectrum	74 (35.2)
IV to oral	12 (5.7)
Stopping therapy	9 (4.3)
Multiple to single agents	21 (10.0)

Table 10: Actions taken by the physician after availability of reports

The 67 patients (31.9%) who did not undergo de- escalation included patients who continued on the same therapy (19%), experienced antibiotic escalation (5.1%) and other forms such as inadequate de-escalation (7.1%). Inadequate De-escalation meant that the therapy was not changed to its most targeted form.

The reasons for not de-escalating were numerous. The most common encountered was the fact that the treating team felt that there was an underlying secondary bacterial infection which was missed by the tests done. Reason expressed by the registrars is tabulated below.6'/

Reasons for non-de-escalation	n (%)
"Patient is improving, why change	4(1.9)
Patient is in severe sepsis, fear of worsening	6(2.9)
Seniors doctors' orders	8(3.8)
Lab report cannot be relied	7(3.3)
Report not available on time	1(0.5)
Cost of changing antibiotic is high	12(5.7)
Secondary bacterial Infection	18(8.6)
Concurrent infections	2(1.0)
New organism Identified	11(5.2)

Table 11: Reasons for non- de- escalation

Factors associated with de-escalation

Statistical analysis was performed to detect an association between the action taken by the physician and characteristics of the patient such as severity of illness, age and comorbidities (Carlson comorbidity index) using the chi- square test.

	Non-De-escalated	De-escalated	p value	Odds ratio
Age			0.38	1.341
≤40	22(41.5)	31(58.5)		
>40	45(34.6)	85(65.4)		
Charlson Comorbidity Index			0.427	1.277
<2	37(39.4)	57(60.6)		
≥2	30(33.7)	59(66.3)		
SOFA			0.034	3.663
<2	64(39.3)	99(60.7)		
≥2	3(15.0)	17(85.0)		

Table 12 Factors associated with de-escalation

While assessing factors associated with de-escalation we found that 60.7% of patients with a SOFA score less than 2 underwent de-escalation as compared to 85% of patients with SOFA score more than 2(p=0.034; OR 95% CI, 1.032-13.005)

Results of Qualitative analysis

The people interviewed was representative of post graduates undergoing training in all three years (n=10). The analysis revealed the following key themes:

1. Awareness regarding antimicrobial resistance
2. Causes of antimicrobial resistance
3. Antimicrobial prescribing practices and Challenges faced by Registrars during antibiotic use
4. Improving antibiotic stewardship

Awareness regarding antimicrobial resistance

The interviewees were all aware of AMR and the burden in the world today. The increase of multi drug resistance organisms in the hospital setting and community was expressed.

"…. what we see from the HICC guideline and what we see in CMC the resistance pattern is quite high and alarming." - (Second year registrar)

"Community acquired resistance bugs are on the rise. Even prior to hospital admission, patients are coming with highly resistant organisms wherever the infection is. They come with especially Gram-negative organisms which was not the scenario 5 or 10 years back". - (Second year registrar)

Many of them were also aware of the primary mechanism of selection pressure. They described it as follows:

"...a lot of bugs in the patients eventually which remain (after exposure to antibiotics) would be the ones resistant to it and which would end up causing the infections that develop in the same patient later so we are selecting a group of bacteria in the patient which are resistant to drugs letting them proliferate." - (Third year registrar)

"..because when we are using a broader spectrum antibiotic that may be suppressing a lot of normal flora and give opportunity for the so called not needed to be supressed flora and there will be selective proliferation of the flora and we may recruit mutation which in future may cause drug resistance to some other antibiotic which we are trying to use." - (Second year)

"For example, if the same organism is in a particular environment for a long time, it's sort of an adaptation that the Organism does for survival. So, it will induce some changes in the genetic make-up via some mutations which will make it resistant to the particular chemical molecule."- (First year)

Causes of AMR

The following reasons for the development of AMR were found to recur in the conversations with the registrars.

1. Poor Community awareness

They felt that there was a mix of poor patient awareness regarding the need for antibiotics, the necessity of targeted therapy and compliance to a regimen.

"Patients themselves don't know that is an antibiotic...they end up taking it and people who own medical shops freely prescribe it without knowing whether it is needed or not." - (Second year registrar)

"There is no check to how long they take the drugs. They may not finish the course of antibiotic. Or they .... So... There is a knowledge deficit among the public also." - (First year registrar)

"That can be a thought process also for patients who are affordable and knowledgeable and read up about what the patient is getting. They tend to think; yeah meropenem is the best for UTI; why are they downgrading it. Patient side also there can be some pressure." - (Third year registrar)

I do agree there are patients who come to our center hoping to get an antibiotic…if we don't give them antibiotic, they are not comfortable. They feel they are not treated well and taken care of. And they need to get an antibiotic! - (Second year registrar)

2. Lack of regulation on manufacturing and sale of antibiotics

There was concern expressed regarding the role pharmaceutical companies and local pharmacies play in indiscriminate access and use of antibiotics. The need for tighter regulation by the government was also brought up.

"…there should be tighter regulation of the drugs and antimicrobials... Indiscriminate use happens because anybody having diarrhea goes and buys a set of antibiotics just to treat diarrhea which is indiscriminate use. So we should put tighter regulation zone for circulation of drugs. That onus is on the government to release those drugs not to release those drugs without proper description." - (First year registrar)

"The fault is with a lot of people in the community; even the medical shops. When you go and ask "I have dysuria", they readily offer them ciprofloxacin. They don't have a restriction on the pharmacists prescribing antibiotics. There should be some regulation on how they receive and how they get the antibiotics." - (Second year registrar)

3. Discovery Void

A third year registrar also brought up the paucity of new antibiotic options in the armamentarium to treat multi drug resistant organisms.

"We are running out of antibiotics to treat these bugs. The best of what we had 5 years back is almost still the best what we have. We have some new drugs. So, we have superbugs and we are running out of drugs to treat." - (Third year registrar)

4. Lack of knowledge and confidence in clinical judgement among doctors

On an individual level, there was a knowledge deficit expressed which was a reason for improper prescribing practices. The deficit narrows through the course of post graduate training but need for improvement of base line knowledge was also brought up.

"Personally, the knowledge of two things; One the antibiotic used -what does it cover, so we have to keep updating … Second thing is what is happening in the community- the locality - where we have the isolates- their resistance pattern, not knowing that is a disaster to me because I'd be giving the wrong antibiotic. Those are the two things- that I think there is a lack of knowledge of those two things, then I'm going to make a wrong choice." (Second year registrar)

"…all those things are in the beginning of medical practice, so that with time we are learning and we are picking up things. So, at that time we were treating gastro-enteritis, URTI or Viral LRTI with antibiotics. We used to give it coverage. As you pick up more clinical acumen we tend to differentiate between Viral and Bacterial. How important it is to start an antibiotic soon and for the ones which we can wait. So early on you used to give more antibiotics but with more clinical acumen you try to narrow it down further…" - (First year registrar)

5. Inappropriate use of antibiotics leads to resistance

The registrars were also aware of the abuse of antibiotics by the non-medical industry such as poultry, farming to improve yield.

"I would say in lot of setups whether primary or tertiary set ups, in OPD basis or IP set ups even without clear Indication of bacterial Infection there is clear misuse of Antibiotics widespread in children and adults and this may have contributed to AMR" - (First year registrar)

"... we use Colistin and high-end drugs in poultry and animals these days, these bugs have come into humans and community acquired bugs are on the rise..." - (Third year registrar)

"Either way the use of antibiotics – indiscriminate use mostly in medicine and veterinary practice has led very high prevalence of resistance especially in hospital setting and now we are getting community acquired resistant bugs and it is quite scary." - (Second year registrar)

6. Poor hygiene/asepsis practices

The registrars also expressed the need for better asepsis in the practical day to day care of the patients.

"The hand hygiene practices may also at time may not be satisfactory and high chance of transmission of resistant bugs from one patient to another. On one side antimicrobial resistance is on the rise and on the other side these bugs are also being transmitted from patient to patient through devices" - (Third year registrar)

"There should be strict aseptic measures like hand washing which should be practiced in ICU and hospitals which might be lacking including in centers like ours so that can lead to spread of infection from patient to patient." - (Third year registrar)

7. Mistrust in simple/older antibiotics

One of the barriers that the registrars noticed during antibiotic de-escalation was that people preferred certain antibiotics over others especially the older, commonly used antibiotics with narrow spectrums.

"Sometimes the antibiotic recommended would be so simple so it's cheap and it might be an old antibiotic like penicillin, ciprofloxacin. That time I've seen people might de-escalate but they might not go down to that level. So if it's a pan sensitive GNB just to be satisfied that it's a good antibiotic people maybe de-escalate to piptaz (piperacillin- tazobactam)." - (Second year registrar)

8. De-escalation not a priority

Some of the registrars interviewed had also noticed that even after microbiological proof of disease with a sensitivity pattern providing an opportunity to de-escalate, there was a reluctance to change the antibiotic and often times was delayed.

"A lot of times de-escalation doesn't happen because primarily the culture doesn't come positive so the empirical one would go on and on .. and at times de-escalation is a call which is left to the head to decide. So it would be like ok this has grown this ok. Well wait and ask this person and well ask that person and finally well ask the head then we'll take a call on de-escalation so, it doesn't take priority and they'll end up sitting on it maybe 24-48 hours even after the sensitivity comes to take a call on de-escalation." - (Third year registrar)

9. Non-uniformity of thought across departments and Poor adherence to guidelines

Many of the registrars felt that despite having guidelines in place, compliance varied within and between departments due to lack of faith in them. They also felt that as a result there was no uniform practice of usage of antibiotics.

"Even across our department we know that we don't and departments practice differently and in Medicine units they practice differently. It will be nice to have a common platform but may not be feasible." - (Second year registrar)

"De-escalation happens much more in General Medicine setup than in Specialty. Sometimes de-escalation is thought of as an unwanted risk taking." - (Second year registrar

"It is not that people do not want to follow guidelines but they choose to follow some guidelines they believe in. It is a uniform guideline which we already have, but it is not used because of lack of trust." - (Third year registrar)

Challenges faced by registrars during antibiotic use

1. Source of knowledge on antibiotics and antimicrobial stewardship

Some of the registrars felt that most of the knowledge regarding AMS was handed down by seniors and shaped by consultants. For example,

'*For me if I think about antibiotics always OC sirs name….so the way he justifies the need for an antibiotic and justifies why not to give an antibiotic has shaped my concept of how to decide*

to give or not give antibiotic and the appropriate antimicrobial and stewardship.' - (Second year registrar)

"*Clinical correlation you have to learn by experience and (by) ask-(ing) your Seniors"* - (First year registrar)

2. Extent of education regarding prescribing practices: Varying schools of thought

When they were asked regarding their view on current prescribing practices and the extent of training received, 2 distinct lines of management emerged. As a final year registrar put it,

'I *would say we have two very starkly different exposures in training. 1. Where you are trained to hit hard irrespective of what the syndrome is. You end up with treating any patient with fever by you draw cultures, investigate thoroughly and you would give maximum of therapy. You would treat even a UTI with a sensitive bug you would give carbapenem for 14 days irrespective of what the existing guidelines are… we will investigate thoroughly and go through all the possibilities.*

The other side and the side I would like to do.. give a few choices where you identify a syndrome, you think of bugs you treat the bug empirically and wait for cultures.

If you have a culture positive you scale it down to the most appropriate in terms of money, duration of therapy, I would scale down to the best in that particular situation. So, these are the two types of training I have received.' -Third year registrar

'There are distinctly two school of thought running *– How much Patient centered and how much of it on future use of antibiotics'* (Second year registrar)

One final year registrar also brought up the importance of individual thought and clinical judgement stating,

"*you should be able to think independently and make a rational decision after identifying a clinical problem that is what MD training is about. It is not about following a particular school of thought"*

3. Adequate exposure and emphasis on proper antimicrobial use

When asked regarding whether they felt there was adequate exposure regarding AMS in our post graduate training, most registrars responded in the affirmative though they felt the scope for improvement.

". Definitely we deal with antibiotics and we deal with infections on a day to day basis… with all types of infectious syndromes in terms of the localization of the syndrome. We deal with it day in and day out. So definitely there is adequate exposure, there is adequate emphasis on antibiotic- discriminant use of antibiotics in our training." - (Third year registrar)

4. External pressures to choose antibiotics

The residents did feel pressure to prescribe antibiotic depending on the practice of individual seniors or units.

"Such decisions ultimately depend on what the general practice guidelines in that particular set up is by which I mean the unit of medicine. Our practice guidelines ultimately are decided by the senior person of that particular unit." - Third year registrar

However, the decision to stray from the hospital guidelines was justified by a second year as being a by-product of years of clinical experience.

"Mostly because of our clinical judgement of our Seniors, probably they are seeing more cases and they know better.. they may have burnt their fingers on a certain patient, so that this is something that you cannot wait on a smaller antibiotic. Can't blame them and they have experience which we do not have.." - (Second year registrar)

Antimicrobial prescribing practices

1. Guidelines

Registrars who were interviewed felt the guidelines were an integral part and enabled quick reference to aid in decision making.

"They are very useful. They are based on solid study and data and information that is researched and gathered. So, we must follow that." - (First year registrar)

"*the workstation (guidelines). Definitely, definitely... A lot of times in the OPD, it's like quick reference, I always go to it. It helps it really helps Rather than us searching in 101 places it's there so we open and see and we trust that it is getting updated."* - (Second year registrar)

"They are quite relevant to our setting because sometimes they take into consideration the local sensitivity pattern and give us a guideline but… guidelines are there to help us and but

the final decision should be from the physicians judgement. Correct clinicians' accurate judgement would be better than blindly following a guideline. Guideline is there to definitely to help us make the choice of antibiotic and would definitely benefit if we try following the guideline. We might not always have to stick to it considering it and going through our thought process would be an ideal scenario." - (Third year registrar)

2. Empiric therapy

Unanimously registrars expressed the need to base empiric therapy on how sick the patient presents and the clinical localization. If the patient had symptoms suggestive of organ dysfunction, broad spectrum antibiotic therapy would be warranted.

"First, I would like to see how sick the patient is. I would like to see what syndrome the patient has presented with in terms of where the focus of infection is. I would like to know if the patient is in sepsis or not." - (Third year registrar)

3. De-escalation

De-escalation was defined as targeted therapy. Registrars felt that there was a need to de-escalate once the organism is confirmed and there was clinical improvement. They felt that caution was advisable if there was no clinical improvement or if the reports did not correlate with clinical presentation.

"De-escalation is actually not a de-escalation. It's supposed to be a targeted antibiotic. It's just changing it to a narrower accurate antibiotic which would cover the bug that we have got in the culture." - (Third year registrar)

"It is to use the narrowest spectrum of antibiotic which is proven to be efficacious against the organism for its given site. It should be a rational antibiotic biologically available at the site. Once the culture is available, we can narrow it down. Most convenient form of dosage should also be taken into account." - (Second year registrar)

"Clinically improving patients with a sensitive organism de-escalation wouldn't be problem for anybody but at times since clinical improvement may not be there - de-escalation may be a tough decision to take…" - (Third year registrar)

"That is one situation where I didn't want to de-escalate because it's a fragile patient who we are dealing with and de-escalation may again, the 4 -5 days of improvement we have seen we may lose that patient because we are going to de-escalate. So, compared to the lot of abuse which is happening outside, the one patient who is very very sick and is critical it's better to continue broader spectrum for 2 or 3 days and finish it off rather than de-escalate." - (Second year registrar)

"There are situations where you are not sure about the culture whether it was an adequate culture or not or if a positive culture.. you feel that it does not explain that infection and the clinical presentation and again you would not deescalate." - (Third year registrar)

Improving antimicrobial stewardship

"Stewardship means we should be accountable. There should be proper use of it as well as prevent overuse of it. Use should be in appropriate situations and we should not use when it is inappropriate." - (Second year registrar)

1. Uniform antibiotic guideline

"So, when we have adequate microbiological support, I honestly believe you should have a uniform guideline which in fact should be there not only within the department but throughout the hospital." - *(*Third year registrar*)*

".. there should be a greater dissemination of the knowledge and of the current practices based on the guidelines that have been prescribed in our own institution. I think they should be more in circulation everywhere in all departments." - *(*First year registrar*)*

2. Audit

Registrars also brought up the need for a regular audit of prescription practices.

"Think there is auditing person or a third person who is seeing, following up the culture and patient -what antibiotic he is getting, they may be able to just send a reminder to the team." - (Third year registrar)

The problems of an external audit were expressed as they are isolated from the treating team.

"At times I feel a team which is totally disconnected with patient care coming and auditing the thing may not be that accurate, my experience from what I've seen the team who are auditing the antibiotic ...they may not look into the patient's profile at that phase. And times when audit goes in retrospect it's easy to say that decision was wrong but actually when the patient came in sick and the decision to start a broad spectrum antibacterial... actually that scenario if they analyze it, it may be correct" - (Third year registrar)

3. Regular updates in knowledge and sensitivity patterns

A multidisciplinary approach to stewardship and learning was expressed by registrars pointing out the importance of keeping one self-updated on the latest sensitivity patterns.

"Update classes in microbiology is useful and getting the microbiologists involved in patient care. A doctor from abroad presented one of the cases and they were presenting as a team. Medical people and microbiology people were always together." - (Second year registrar)

Incorporating it into the curriculum and making it an essential component was also brought up by a second-year registrar.

"Yeah definitely see like this CPR which we have monthly or yearly certification and yearly training same will be needed for antibiotics because it is in such a bad state that it requires reinforcement, not only for us but for all doctors, there should be structured training. The foundation has to be laid first." (Second year registrar)

"When we have a foundation course there should be a talk by the Senior Faculty telling us about the common antibiotics and the common mistakes we usually make and duration of the antibiotic profile we usually see in our population." - (First year registrar)

Discussion

Our study is one of the few studies looking at the proportion of antibiotic de-escalation in the Indian setting. The study was aimed at identifying the proportion of patients who underwent de-escalation among those receiving empirical therapy for a syndromic diagnosis and the factors associated with the same.

Out of 1238 patients who were screened from September 2018 to May 2019, we found 183 patients who fulfilled our inclusion criteria. Our initial sample size was 100 calculated with an estimated 50% rate of de-escalation which was achieved 4 months into the study. However, a decision to continue sample collection till May 2019 so as to achieve an adequate representation was made.

There was no gender preponderance but majority of the patients had concomitant co morbid illnesses (59.5%). The mean SOFA score was 1 indicating that fewer patients in our population were in severe sepsis. This can be explained by the exclusion of patients who were admitted or shifted after admission to the intensive care unit..

The microbiological evidence for de-escalation was predominantly through positive blood cultures. However through the course of screening patients for the study, it was noted that a

large number of patients who were treated for a clinical syndrome of bacterial sepsis did not have culture positivity and this may be due to lack of adequate properly time cultures.

Antibiotic use

A point prevalence survey conducted by Singh et al in October to December 2017 in 16 tertiary care hospitals across India found that penicillin's together with beta-lactamase inhibitors (47.6%) were the most frequently used antibacterial. This was in concordance with our study which showed the most common empirical therapy to be beta-lactams with a beta-lactamase inhibitor, piperacillin-tazobactam (43.6%)(72).

Diagnosis at initiation of antibiotics

The same study had also found that the most common diagnosis for which antibiotics were initiated was pneumonia or lower respiratory tract infection (19.9%). However in our study we found that urinary tract infections (38.3%) followed closely by respiratory tract infections (34.3%) were the predominant clinical diagnosis(72).

De-escalation

In our study, 116 (55.2%) patients underwent de-escalation. This is similar and actually higher to the findings in retrospective studies conducted by Gonzalez et al (51%) and by Morel et al (45%). Although the rate of de-escalation we observed appears acceptable in light of the literature, there is room for improvement. Among the non-de-escalated patients, an initial broad-spectrum antibiotic therapy could have been stepped down in an additional fifteen patients.

The reasons for non-escalation were initial presentation of severe sepsis, lack of improvement on appropriate antibiotic therapy, suspicion of concurrent bacterial infection which had not been detected in cultures and growth of an organism which was not covered by the initial therapy.

The systematic review by Tabah et al. found that lower severity of illness scores at baseline were positively associated with antibiotic de-escalation. This may explain why we had a higher rate of antibiotic de-escalation than expected(1).

We looked at the association of age, the baseline severity of illness and the presence of comorbidities. There was no statistical significance noted with the CCI or age more than 40 years. There was a significant p value of 0.034 favoring de-escalation when the SOFA score was more than 2. It can be due to sicker patients being more likely to be started on broad spectrum antibiotics and more likely to have adequate cultures being sent

Qualitative study

We conducted a qualitative study to look at the awareness and challenges faced by the registrars in antibiotic de-escalation. A semi-structured interview was used followed by a thematic analysis which showed the emergence of four major themes: awareness of increasing antimicrobial resistance causes for antimicrobial resistance, antimicrobial prescribing practices and ways to improve the antibiotic stewardship.

The study was important, considering that a large amount of contact between the treating team and the patient is through the post-graduates. Ideas regarding antibiotic prescribing practices are shaped through the course of his/her training, which will form the basis for future decisions.

Majority of post-graduates were aware of the burden and magnitude of the problem of antimicrobial resistance. The factors they had implicated included indiscriminate use of antibiotic by the public, the physicians and the food industry. Many of them felt a lacuna in their knowledge would have caused them to prescribe inappropriately. They also felt strongly that there was no uniformity of thought regarding antibiotic use within our department as well between specialty departments. This may be explained by the varying patient population seen by each department which shapes their practices.

Another study conducted in Norway investigating factors influencing doctors' antimicrobial prescribing practices showed that the doctors' attitudes towards the national guideline correspond with level of clinical experience(73). Whereas interns and inexperienced residents are dependent on the guideline, senior doctors are more skeptical to it. . This is also similar to our residents preferring to follow the guidelines while they see some senior faculty relying on their experience.

The registrars also felt there was pressure to prescribe according to the senior physician which may not be in line with the antibiotic guidelines. Some of them felt that it was justified considering the years of clinical experience the seniors had.

A similar study conducted in the 4 hospitals of the Imperial College Healthcare National Health Service Trust (ICHNT) to assess the prescribing etiquette also found that there was accepted noncompliance to policy in their hospitals. Deviations from policy recommendations were tolerated and put in the context of the prescriber's experience and expertise and the specific clinical scenario. They found that hierarchy and expertise, and not policy was a major determinants of prescribing practice behaviors(74).

Most of the interviewees expressed a common approach to choosing antibiotic therapy. Empiric therapy was to be chosen keeping in mind the localization, the severity of illness at presentation and our local susceptibility patterns.

In order to improve our stewardship practices, the need for a regular audit (internal being preferred over external) was stated. The need for a uniform structured training program on antibiotics and proper prescribing practices which would be a part of regular post graduate training was expressed.

During the course of the interviews, a difference in perception between the first years, second and third years was noted. The concepts of antimicrobial stewardship and proper prescribing practices were far clearer in the latter's mind. This is probably due to the knowledge and experience gained through the course of training.

This study highlighted the perceptions and practices regarding antibiotics and AMR among post graduates. There are no similar studies in the Indian setting.

Limitations

1. We included patients admitted to the general medical wards only. Patients admitted to the ICU and outpatients were excluded. This may limit the generalizability of our conclusions.
2. Data regarding whether de-escalation affected outcomes like mortality and length of hospital stay was not collected
3. A more diverse population for the qualitative study (including junior consultants, post-graduates from other departments) would have added more dimension to the themes that were elicited.

Conclusions

The aim of the study was to describe incidence and determinants of antibiotics de-escalation among inpatients started on empiric antibiotic therapy.

In our study, 116 (63.4%) patients underwent de-escalation out of the 183 recruited.

The major reasons for non-de-escalation that we found were initial presentation of severe sepsis, lack of improvement on appropriate antibiotic therapy, suspicion of concurrent bacterial infection which had not been detected in cultures and growth of an organism which was not covered by the initial therapy.

In our qualitative study we were able elicit the challenges and perceptions of our postgraduate in the process of antibiotic prescribing and towards antimicrobial stewardship. This study broadens the scope of research on prescribing behaviors and extends our understanding of how to optimize them.

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

November 10, 2018

Dr. Caroline Nandita,
PG Registrar,
Department of Medicine - 4,
Christian Medical College,
Vellore – 632 002.

Sub: **Fluid Research Grant: New Proposal:**
A study of antibiotic de-escalation practices in medical wards in a teaching hospital (ADEP Study)
Dr. Caroline Nandita, Employment Number: 29658, General Medicine Unit – 4, Dr. O C Abraham, Medicine Unit 4, Dr. Ronald Carey, Medicine Unit 4, Dr. Samuel George Hansdak, Medicine Unit 4, Dr. Alice Joan, Employment No 28529, Medicine 1, Dr. Aditya Binu, Employment No 29070, Medicine 3, Dr. Sohini Das, Employment No. 29139, Medicine 5, Dr. Tina George, Employment No. 29141, Medicine 2, Dr. Joy Michael, Microbiology.

Ref: IRB Min. No. 11285 [OBSERVE] dated 04.04.2018

Dear Dr. Caroline Nandita,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. O C Abraham, Professor, Dept. of Medicine - 4, CMC, Vellore

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

Dr. **B.J. Prashantham,** M.A., M.A., Dr. Min (Clinical)
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Ref: IRB Min. No. 11285 [OBSERVE] dated 04.04.2018

Dear Dr. Caroline Nandita,

The Institutional Review Board (**Blue**, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "A study of antibiotic de-escalation practices in medical wards in a teaching hospital (ADEP Study)" on April 04th 2018.

The Committee reviewed the following documents:

1. IRB application format
2. Waiver of Consent
3. Questionnaire
4. Cvs of Drs. Aditya, Hansdak, Alice, OC Abraham, Ronald Carey, Sohini and Joy Sarojini.
5. No. of documents 1- 4.

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on April 04th 2018 in the New IRB Room, Bagayam, Christian Medical College, Vellore 632 004.

Dr. **B.J. Prashantham,** M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Name	Qualification	Designation	Affiliation
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, Research), Additional Vice Principal , Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC, Vellore	Internal, Clinician
Rev. Joseph Devaraj	BSc, BD	Chaplaincy Department, CMC, Vellore	Internal, Social Scientist
Dr. B. J. Prashantham	MA(Counseling Psychology), MA(Theology), Dr. Min(Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist
Dr. Anuradha Rose	MBBS, MD, MHSC (Bioethics)	Associate Professor, Community Health, CMC, Vellore	Internal, Clinician
Dr. Thomas V Paul	MBBS, MD, DNB, PhD	Professor,Endocrinology, CMC, Vellore	Internal, Clinician
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Dr. Jayaprakash Muliyil	BSc, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, CMC, Vellore	External, Scientist &Epidemiologist
Ms. Grace Rebekha	M.Sc., (Biostatistics)	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M. Phil, BL.	Sr. Legal Officer, CMC, Vellore	Internal, Legal Expert
Dr. Ratna Prabha	MBBS, MD (Pharma)	Associate Professor, Clinical Pharmacology, CMC, Vellore	Internal, Pharmacologist
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Mrs. Sheela Durai	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
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Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Dr. Vivek Mathew	MD (Gen. Med.) DM (Neuro) Dip. NB (Neuro)	Professor, Neurology, CMC, Vellore	Internal, Clinician
Dr. Santhanam Sridhar	MBBS, DCH, DNB	Professor, Neonatology, CMC, Vellore	Internal, Clinician
Dr. Barney Isaac	M.B.,B.S. D.N.B (Respiratory Diseases)	Associate Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician
Dr. John Antony Jude Prakash	MBBS, MD	Professor, Clinical Microbiology, CMC, Vellore.	Internal, Clinician.
Dr. Ajith Sivadasan	MD, DM	Professor, Neurological Sciences, CMC, Vellore	Internal, Clinician
Mrs. Sophia Vijayananthan	MSc Nursing	Addl. Deputy Dean CMC, Vellore	Internal, Nurse
Dr. Asha Solomon	MSc Nursing	Associate Professor, Medical SurgicalNursing, CMC, Vellore	Internal, Nurse

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of Withdrawals for the study entitled: "A study of antibiotic de-escalation practices in medical wards in a teaching hospital (ADEP Study)" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

Fluid Grant Allocation:

A sum of 15,600/- INR (Rupees Fifteen Thousand Six Hundred Only) will be granted for 1 year.

Yours sincerely,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

IRB Min. No. 11285 [OBSERVE] dated 04.04.2018

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De-escalation of antibiotics after empiric initiation in the general medical population

Participant Information Sheet

PURPOSE OF THE STUDY

We are inviting you to participate in a research study that seeks to understand to understand perceptions of PG medical doctors on issues concerning de-escalation of antibiotics, its importance and the challenges associated with it
.

STUDY PROCEDURE

You have been selected to participate in this study because you are a postgraduate in the General medicine training Program in CMC Vellore. If you agree to be in this study you will be invited to participate in an interview. During the interview we will be interested to know your understanding of the prevalence of antimicrobial resistance, your understanding of anti biotic de-escalation and the barriers you face with the same. An interview may take about 40-45 minutes. Each interview will be audio recorded because it will be difficult to write down everything that you say during the interview. Your consent to audio record the interview will be sought and if you are uncomfortable with it we will not record the session. Your name will not be mentioned in any of our records or documents. We will transcribe the tapes so we can analyze the information. In each state a total of 10 such interviews with doctors/policy makers will be carried out.

RISKS, STRESS, OR DISCOMFORT

There are no physical risks to participating in this study. We will make every effort to make you feel comfortable during the interview. We will keep your identity confidential.

BENEFITS TO TAKING PART IN THE STUDY

There is no direct benefit to you on account of taking part in this study. However, you will have an opportunity to express your opinions about the nature and type of healthcare you provide .

ALTERNATIVES TO TAKING PART IN THIS STUDY

You do not have to be in this study if you do not want to. You may refuse to participate or may withdraw from the study at any time.

OTHER INFORMATION

All of the information you provide will be confidential. Only the study team will see your answers and your responses will be kept confidential. We will keep your audio files in a locked filing cabinet accessible only to study personnel for 5 years after the study ends. If you have any complaints you are free to contact any of the individuals listed on this consent form.

Printed name of study staff obtaining consent Signature
Date

Participant's statement

This study has been explained to me. I volunteer to take part in this research. I have had a chance to ask questions. If I have questions later about the research, I can ask one of the researchers listed above. I will receive a copy of this consent form.

Printed name of Participant Designation Signature of Participant
Date

Copies to: Researcher and Participant

De-escalation practices in medical wards after initiation of empirical antibiotic therapy

Serial No.

Date: Gender : Male/female

Hospital No. Age

Comorbid illnesses

1. Diabetes Mellitus
2. Hypertension
3. Ischemic Heart disease
4. Dialysis dependent
5. Chronic renal failure
6. Chronic liver disease
7. Acute renal failure
8. HIV Seropositive

Risk factors

1. Smoking Pack Years :
2. Alcohol
3. Pregnancy

Diagnosis at admission :

Treatment strategies:

Antibiotics initiated:

1. _____
2. _____
3. _____
4. _____

Inotropes used?

If yes, dosage _____

<u>Vital signs at admission</u>

Pulse Rate Respiratory Rate

Systolic Blood pressure Diastolic Blood pressure MAP:

GCS E V M = /15

Saturation Fio2

Temperature Urine output (ml /hr)

Arterial Blood Gas Analysis at admission

pH, median Pao2 (mm Hg), Paco2 (mm Hg),

Bicarbonate pA-a BE

Sodium Potassium Chloride Lactate

Base line Investigations

Haemoglobin Haematocrit Platelet count

Total count Differential count : N L M E Bandforms

Creatinine Urea Creatinine clearance

Blood Urea Nitrogen

SGOT SGPT ALP

Serum Albumin Total Protein

Total Bilirubin Direct Bilirubin

Opportunity to de- escalate : Yes/No?

Microbiological Confirmation

Culture isolate and Sensitivity

1. Blood

2. Urine

3. Sputum

4. CSF

5. Pus

Serology

- Leptospira
- Widal
- Scrub serology
- Dengue Serology

PCR

- Influenza
- Multiplex PCR : Blood/CSF

Imaging

- Ultrasound
- Computed tomography

Diagnosis after Microbiological results:

Action taken:

1. no change in antibiotics
2. De- escalation
    a. Narrower spectrum
    b. IV to oral
    c. Stopping antibiotics

    d. Multiple agents to single agent
3. Escalation
4. Mixed changes (where both escalation to a broader spectrum of coverage and discontinuation of antibiotics were carried out)

If no de- escalation;

Why not?

1. Patient is improving, why change antibiotic regimen
2. Patient is in severe sepsis, fear of worsening
3. Senior doctors orders
4. Cannot rely on lab report
5. Others:_____

Semi Structured Questionnaire Guide

1. What does anti-microbial resistance mean to you?
2. What do you know about the global disease burden?
3. What are the reasons you are aware to cause AMR?
4. Do you think antibiotic prescribing has potential to put patients at risk of
5. infection? If so, how?
6. Are you aware of the rates of resistance in our hospital?
7. What is your thought process regarding choosing antibiotics?
8. Have you ever prescribed an antibiotic which you think you shouldn't have and what were the factors that lead to it?
9. What do you know about antibiotic de-escalation?
10. Are there reasons when de-escalation doesn't work / should not be used?
11. What was the nature of training you received on antimicrobial prescribing? Please describe what all was taught to you
12. What emphasis is there on antimicrobials in our educational program?
13. What do you think of antimicrobial guidelines?
14. Do your colleagues comply with the policy?
15. Do you feel you are in a position to question the antibiotic prescribing/ management behavior of your colleagues and superiors?

16. Who, in your view, is responsible for making sure that the prescribing and management of antibiotics is optimal and why do you feel so?
17. How do you think we can improve our stewardship of antibiotics?
18. What barriers do you personally face when optimizing your prescribing and monitoring practices?

slno	gende	age	dm	htn	ihd	dialysis	crf	cld	arf	hiv	copd	ba	hypothy	ccf	smokin	ifsmc	alcoh	pregna	pneum	uti	utipy	meningitis	afi	age1	others	pipertazo	meropene	vancomyc	azithro	oselta	colistin	ceftri
1	1	58	2	2	2	2	2	2	2	2	2	2	2	2	1	10	2	2	2	2	2	2	1	2		1	2	2	2	2	2	2
2	2	40	1	2	2	2	2	2	2	2	2	2	2	2	2		2	2	2	2	1	2	2	2		2	1	2	2	2	2	2
3	1	49	1	1	1	2	2	2	1	2	2	2	2	2	2		2	2	2	2	1	2	2	2		1	2	2	2	2	2	2
4	1	65	2	2	2	2	2	2	2	2	2	2	2	2	1	24	1	2	1	2	2	2	2	2		1	2	2	1	2	2	2
5	1	69	1	1	2	2	2	2	2	2	2	1	2	2	2		2	2	1	2	2	2	2	2		1	2	2	1	1	2	2
6	1	65	2	1	2	2	2	2	2	2	2	2	2	2	2		2	2	1	2	2	2	2	2		2	2	2	1	1	2	2
7	2	48	1	1	2	2	2	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2	Cholangi	2	1	2	2	2	2	2
8	1	22	2	2	2	2	2	2	2	2	2	2	2	2	2		2	2	2	2	2	2	1	2		2	2	2	2	2	2	2
9	2	50	1	2	2	2	2	2	2	2	2	2	2	2	2		2	2	2	2	1	2	2	2		2	1	2	2	2	2	2
10	1	69	2	1	2	2	2	2	2	2	1	2	2	2	1		2	2	2	2	1	2	2	2		2	1	2	2	2	2	2
11	1	85	2	2	2	2	2	2	2	2	2	2	2	2	2		1	2	2	2	2	2	2	2	scrub ty	1	2	2	1	2	2	2
12	2	84	1	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	1	2	2	2		2	1	2	2	2	2	2
13	1	46	2	2	2	2	2	2	2	2	2	2	2	2	1	20	2	2	1	2	2	2	2	2		1	2		1	1		
14	1	48	1	1	2	2	2	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2	Facial ce	2	2	1	2	2	2	2
15	2	34	2	2	2	2	2	2	2	2	2	2	2	2	2		2	2	1	2	2	2	2	2		1	2	2	2	1	2	2
16	1	45	2	2	2	2	1	2	1	2	2	2	2	1	2		2	2	1	2	2	2	2	2		1	2	2	1	1	2	2
17	2	27	2	2	2	2	2	2	2	2	2	2	2	2	2		2	2	2	2	2	2	1	2		2	2	2	2	2	2	2
18	1	36	1	2	2	2	2	2	2	2	2	2	2	2	2		2	2	2	2	1	2	2	2		1	2	2	2	2	2	2
19	2	85	2	2	1	2	2	2	2	2	2	2	2	2	2		2	2	1	2	2	2	2	2		1	2	2	1	1	2	2
20	1	66	1	1	1	2	2	2	2	2	2	2	2	2	2		2	2	1	2	2	2	2	2		1	2	2	1	1	2	2
21	2	53	1	1	2	2	1	1	1	2	2	2	2	2	2		2	2	1	2	2	2	2	2		1	2	2	1	1	2	2
22	1	64	1	2	2	2	2	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2	Dissemi	2	1	1	2	2	2	2
23	2	38	2	2	2	2	2	2	2	2	2	2	2	2	2		2	2	1	2	2	2	2	2		1	2	2	1	1	2	2
24	2	38	2	2	2	2	2	2	2	2	2	2	2	2	2		2	2	2	2	1	2	2	2		1	2	2	2	2	2	2
25	2	39	2	2	2	2	2	2	2	2	2	2	2	2	2		2	2	1	2	2	2	2	2		1	2	2	1	1	2	2
26	2	40	1	2	2	2	1	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		1	2	2	2	2	2	2
27	2	56	1	2	2	2	2	2	2	2	2	2	2	2	2		2	2	2	2	1	2	2	2		1	2	2	2	2	2	2
28	2	38	1	2	2	2	1	2	1	2	2	2	2	2	2		2	2	2	2	1	2	2	2		2	1	2	2	2	2	2
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157	1	79	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2		2	1	2	2	2	2	2
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159	2	62	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2		1	2	2	1	1	2	2
160	2	70	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2		2	1	2	2	2	2	2
161	2	54	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2		2					
162	1	59	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2		2	1	2	2	2	2	2
163	2	25	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	1	2	2	2	2	2		2	2	2	1	1	2	2
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165	1	70	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2		1	2	2	1	1	2	2
166	1	62	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	Facial ce	2	2	1	2	2	2	2
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168	2	61	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2		2	1	1	2	2	2	2
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177	1	78	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2		2	1	2	2	2	2	2
178	2	51	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2		2	1	2	2	2	2	2
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180	2	55	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2		2	1	2	1	2	2	2
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185	1	64	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2		2	1	2	2	2	2	2
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187	2	37	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	1	2	2	2	2	2		2	1	2	1	2	2	2
188	2	35	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2		2	1	2	2	2	2	2
189	2	24	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2		1	2	2	2	2	2	2
190	2	49	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2		2	1	2	2	2	2	2
191	2	71	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2		2	1	2	2	2	2	2

doxy	acy	date	hospno	totalcount	pulserate	resprate	systolic	diastolic	gcstotal	saturation	temp	fio2	fio2	urineout	phmedian	pao2	paco2	bicarbon	paa	be	sodium	potassium	chloride	lactate
2	2	43602	270277G	5200	112	22	70	40	15	100	100	21	21		7.43	74	20	17.6		11	123	3.2	102	1.3
2	2	43354	309359C	9000	84	24	80	50	11	100	Normal	21	21		7.45	103	29	22.5			130	3.7	112	1.2
2	2	43719	354499H	13300	112	30	100	60	15	97	Normal	21	21		7.28	48	19	12.5			129	3.3	93	1.5
2	2	43725	357046H	19400	110	32	90	60	15	92	Normal	21	21		7.56	66	27	26.8			129	3.3	102	2
2	2	43348	016099H	6900	160	48	190	110	15	76	97	21	21		7.33	50	50	4					96	3.1
2	2	43369	070253D	10300	92	22	130	80	15	NA	Normal	NA	NA		NA	NA	NA	NA						
2	2	43369	163015H	9100	80	20	140	90	15	NA	Normal	21	21		NA	NA	NA	24			131	3.9		
1	2	43710	353649H	7000	70	22	100	70	15	NA	Normal	21	21		NA	NA	NA	NA						
2	2	43352	117759H	8000	90	18	100	60	15	NA	Normal	21	21		NA	NA	NA	NA						
2	2	43365	091371H	11100	90	30	60	40	15			21	21		7.45	92	97	21		5.2	127	3.3	99	1.2
2	2	43369	357770H	6200	114	24	140	80	15	NA	100	NA	NA		NA	NA	NA	20			128	3.4		
2	2	43369	908745H	18500	86	20	100	70	15	NA	101	21	21		NA	NA	NA				134	3.5	14	
		43356	174641F	13100	113	42	170	90	15	NA	Normal	21	21		7.44	134	41	27			133	2.8	102	1.1
2	2	43347	272310f	9500	94	18	150	90	15	100	NA	21	21		NA	NA	NA	22			140	4.2		
2	2	43373	330063c	8600	110	20	110	70	15	100	NA	NA	NA		NA	NA	NA	NA						
2	2	43363	555469f	9700	89	16	90	60	NA	NA	NA	NA			7.33	61	25	16			138	4.3	109	0.9
1	2	43353	354396h	2600	90	22	100	60	15	96	102	21	21		NA	NA	NA	20			130	4.2		
2	2	43733	514799f	7800	124	24	110	60	15	NA	NA	NA			NA	NA	NA	27			128	5.3		
2	2	43404	451592h	16800	102	30	100	60	15	98	NA	NA			NA	NA	NA	20			134	3.4		
2	2	43399	334713h	10300	106	44	90	60	15	94	101	21	21		7.49	69	30	24			137	3.2	110	2.1
2	2	43383	396730h	6500	114	34	160	100	15	72	NA	NA			7.34	113	34	19.7			136	5	12	0.9
2	2	43383	450049h	28400	164	44	80	60	15	90	99	NA			7.39	86	29	17.6			127	3.8	102	1.1
2	2	43382	189240h	11700	102	44	120	80	15	95	NA	21	21		7.49			22			133	3.9	104	2.4
2	2	43381	400124g	7200	136	22	90	50	15	98	103	21	21		NA	NA	NA	NA						
2	2	43382	189240h	11700	78	22	120	80	15	98	NA	NA			7.49	127	29	22			133	3.9	104	2.4
2	2	43383	413761g	18700	102	26	120	70	15	98	NA	21	21		7.35	85	27	14			131	2.9	102	1.7
2	2	43390	401797h	11200	80	16	160	100	15	21	NA	21	21		NA	NA	NA	29			138	3.3		
2	2	43383	358979h	6300	130	20	130	80	15	96	NA	21	21		NA	NA	NA	NA						
2	2	43382	734037b	8800	90	30	130	100	15	NA	NA	NA			7.27	95	22	13			129	4.2	99	14
2	2	43397	058154d	3400	106	30	90	60	15	98	NA	37	37		7.42	61	30	21			133	2.5	103	3.5
2	2	43396	983555f	23800	74	24	110	80	15	NA	NA	21	21		7.46	78	26	21			113	5	86	1.8
2	2	43374	030183M	9400	98	20	170	100	15	NA	NA	NA			7.28	43	34	16			120	4.6	92	2.6
2	2	43384	801736d	13300	68	20	118	84	15	NA	NA	NA			NA	NA	NA	NA						
2	2	43374	358181h	14900	144	36	100	70	15	100	101	21	21		NA	NA	NA	NA						
2	2	43377	358401h	2600	90	20	110	60	15	98	100	NA	NA		7.45	100	38	24		14	132	3.8	104	1.2
2	2	544603g	918598b	12800	90	24	210	80	15	98	NA	NA	NA		NA	NA	NA	NA						
2	2	43397	544603g	12400	86	30	130	80	15	NA	NA	24	24		7.49	53	31	24			134	3.7	11	6
1	2	43394	194279g	9200	110	40	110	60	15	87	NA	21	21		7.52	43	32	28		3.2	128	3.8	100	
2	2	43394	245424h	10900	140	30	90	60	15	98	102	NA	NA		NA	NA	NA	NA						
2	2	43393	947638F	17700	114	24	140	80	15	98	100	NA	NA		7.46	65	26	18			127	3.2	98	1.2
2	2	43391	210295f	8500	84	22	90	60	15	98	NA	NA	NA		NA	NA	NA	NA						
2	2	43384	450125h	9100	94	22	110	70	15	98	NA	NA	NA		NA	NA	NA	27			135	3.8	102	
2	2	43384	450113h	29900	98	22	100	70	15	98	98	NA	NA		7.39	57	31	18			135	3.8	104	0.8
2	2	43380	352809h	8700	160	40	130	90	15	98	102	NA	NA		7.49	107	25	22			130	3.5	103	2.6
1	2	43378	358593h	6500	76	22	100	60	15	99	98	NA	NA		7.5	90	31	26			135	3.5	111	1
2	2	43377	520622f	10100	120	22	110	70	15	NA	NA	NA	NA		7.49	103	20	15			133	3.6	104	3.7
2	2	43375	357526h	5500	90	22	110	80	15	98	98	NA	NA		NA	NA	NA	NA						
2	2	43400	451187h	17500	86	20	140	80	15	NA	NA	NA	NA		7.27	95	18	8.3			115	5.3	90	1.1
2	2	43399	451101h	14800	122	22	130	70	15	95	103	NA	NA		NA	NA	NA	NA						
1	2	43397	476019d	10400	118	20	100	60	15	93	102	NA	NA		NA	NA	NA	18			132	2.8		
2	2	43385	450174h	8000	104	24	100	60	15	95	104	NA	NA		NA	NA	NA	NA						
2	2	43385	450184h	14400	110	28	90	60	3	NA	NA	NA	NA		7.39	74	22	17			122	3.6	93	4.7
2	2	43384	702559g	13800	130	24	120	70	15	98	102	NA	NA		7.49	72	30	25			123	6.8	98	1.2
2	2	43384	450074h	13200	86	20	90	60	15	NA	NA	NA	NA		NA	NA	NA	19			134	4.5		
2	2	43379	285208d	13100	90	24	110	80	15	NA	NA	NA	NA		NA	NA	NA	21			132	3.6		
2	2	43377	354669h	16800	88	26	100	70	15	93	97	NA	NA		NA	NA	NA	25			137	3.3		
2	2	43400	070021c	4900	120	40	120	80	15	87	100	NA	NA		7.48	54	26	23			133	3.3	110	2.6
1	2	43116	450409h	8500	90	34	130	80	15	87	98	NA	NA		NA	NA	NA	NA						
2	2	43381	119162d	11800	114	40	100	60	15	89	Afeb	NA	NA		7.5	59	34	27			135	3.5	104	1.3
2	2	43379	162057c	4500	160	40	120	80	15	98	104	NA	NA		7.49	183	13	NA			123	4.6	98	
2	2	43377	544006g	27300	140	30	150	90	15	95	101	NA	NA		7.44	54	27	18			129	4	105	1.3
2	2	43376	796702d	7300	56	20	160	80	15	NA	NA	NA	NA		NA	NA	NA	26			135	4.6		
2	2	43374	629127f	10500	72	16	100	80	15	NA	NA	NA	NA		NA	NA	NA	21			138	3.8		
2	2	43416	452731h	2700	88	22	100	60	15	98	NA	NA	NA		7.53	56	20	16			132	3.7	98	2.5
2	2	43416	452713H	5300	91	16	120	90	15	93	NA	NA	NA		7.43	64	35	24			133	3.8	105	1.2
2	2	43415	540149G	11100	110	22	100	60	15	92	100	45	45		7.28	145	56	24			127	4.5	102	0.6
2	2	43416	835925G	20700	120	26	100	60	15	96	99	21	21		7.46	56	33	17			134	3.7	105	1.4
2	2	43450	518819a	4700	102	24	130	80	15	NA	NA	NA	NA		7.47	82	36	17			130	4.2	96	1.1
2	2	43426	912602c	7400	110	28	180	80	15	92	101	24	24		7.46	142	30	22			129	3.9	101	2.1
2	2	43407	951782b	15300	108	22	140	80	15	99	100	NA	NA		NA	NA	NA	21			139	3.4		
2	2	43405	291765a	6000	108	36	200	110	15	92	NA	37	37		7.31	179	31	22			121	3.6	92	4.2
2	2	43413	452423h	10000	146	40	130	80	15	90	NA	NA			7.5	154	29	25			127	3.3	100	1.6
2	2	43412	352935h	12400	142	38	100	60	15	85	101	NA	NA		NA	NA	NA	15			132	5.3		
2	2	43413	770344d	15500	124	48	100	60	15	85	NA	NA	NA		7.29	75	24	14			131	6.1	111	2.1
2	2	43414	567120g	10800	92	32	170	80	14	96	NA	28	28		7.33	65	58	27			128	3.9	96	
2	2	43420	452988h	1600	68	14	110	70	15	NA	NA	NA			NA	NA	NA	19			136	4.4		
2	2	43390	454068h	19800	140	28	150	60	15	NA	NA	NA			NA	NA	NA	17			133	3.7		
2	2	43405	023931b	900	102	20	100	60	15	98	100	NA			NA	NA	NA	19			134	3.9		
2	2	43412	570103a	7700	110	16	100	80	15	93	103	NA			NA	NA	NA	20			132	3.4		
2	2	40496	419357H	15100	104	14	140	70	15	98	100	NA			7.6	111	18	23			136	4	109	1.3
2	2	43419	686120C	2900	88	18	110	70	15	NA	NA	NA			NA	NA	NA	18			135	4.4		
2	2	43405	759569a	13700	116	24	100	60	15	NA	NA	NA			NA	NA	NA	18			134	4.3		
2	2	43405	451664h	6100	80	20	120	70	15	99	NA	NA			7.41	114	33	22			135	2.6	107	
2	2	43406	868354c	8800	136	36	140	100	15	96	NA	NA			7.45	73	38	25			135	3.9	101	1.6
2	2	43407	235579d	11700	84	18	110	60	15	NA	NA	NA			NA	NA	NA	NA						
1	2	43411	452220h	7500	140	28	140	80	15	96	104	NA			NA	NA	NA	NA			131	2.6	110	
2	2	43405	489096g	23900	126	42	120	90	15	93	101	NA			7.49	62	24	21			127	4.2	103	3.1
2	2	43408	667789g	10200	145	24	90	60	15	98	100	NA			NA	NA	NA	NA						
2	2	43378	4766006	16400	112	22	90	60	15	NA	NA	NA			NA	NA	NA	14			127	3.5		
1	1	43435	871983b	12000	90	24	110	80	13	NA	NA	NA			7.46	96	26	21.5		5.3	133	4.6	110	2.1
2	2	43435	060750a	15900	112	26	60	40	15	93	101	NA			7.42	94	18	16.2			121	3.7	91	7.7
2	2	43440	633953f	11500	90	16	120	90	15	NA	NA	NA			NA	NA	NA	14			127	3.8		
2	2	43439	062788g	6100	100	20	110	70	15	NA	NA	NA			NA	NA	NA	14			127	3.8		
1	2	43442	471380h	10400	148	24	120	80	15	99	103	NA			7.48	87	22	20.6			133	3.3	105	3.7
2	2	43452	454676h	17700	136	24	90	60	15	NA	NA	NA			7.52	42	28	NA			125	2.3	97	3.5
2	2	43444	944661a	9900	82	16	120	80	15	NA	NA	NA			NA	NA	NA	NA						
2	2	43441	842192c	7300	124	28	130	70	15	100	98	28	28		7.42	97	40	25			130	2.7	97	1.3
2	2	43442	455797h	4500	88	20	120	70	15	97	NA	NA			7.46	85	33	25		0.3	132	3.9	103	1.6
2	2	43443	423655d	8600	100	20	140	90	15	93	NA	NA			7.43	72	21	18			130	4.8	103	1.8
1	2	43449	265768c	6400	120	24	110	80	15	NA	NA	NA			NA	NA	NA	NA						
1	2	43458	561747f	12700	136	30	100	70	15	99	103	NA			7.53	69	19	21			113	3.4	86	5.4
2	2	43462	457394h	8400	110	22	80	40	15	95	100	NA			7.39	114	30	18			132	3.3	106	0.8
2	2	43478	354412h	37900	140	44	70	40	10	98	100	NA			7.53	67	27	26			132	1.3	99	3
2	2	43477	458591h	25600	84	36	100	60	15	98	NA	NA			7.2	114	13	8.6			139	2.3	120	1.1
2	2	43476	458565h	23800	92	24	100	60	15	97	98	NA			NA	NA	NA	NA						
2	2	43474	504754h	16200	98	30	100	70	15	95	NA	NA			7.42	77	29	21			132	4.2	101	3.1
2	2	43467	577423a	9000	78	20	100	70	15	98	101	NA			NA	NA	NA	NA						
2	2	43133	515543h	20400	125	30	80	60	15	NA	NA	NA			7.52	77	24	23			118	3.7	95	2.5
2	2	43505	478576f	6000	102	24	160	80	15	98	NA	NA			7.39	64	29	NA			130	3.5	105	4.1
2	2	43528	973520F	7700	92	12	90	60	15	NA	NA	NA			7.48	79	24	21			126	4.2	100	4.9
2	2	43534	322287f	11000	80	22	130	80	15	98	NA	NA			NA	NA	NA	17			136	4.4		
1	1	43540	566174h	9900	70	22	130	80	15	98	NA	NA			7.46	68	3	22			128	2.9		
2	2	43559	565062h	12300	88	20	130	70	15	98	NA	NA			NA	NA	NA	NA						
2	2	43563	5679211	8300	88	20	110	80	15	NA	NA	NA			NA	NA	NA	18			131		3.6	
2		43565	618787f	11800	130	28	90	60	15	97	101	NA			NA	NA	NA	19			130	4.9		
2	2	43567	568272h	12800	120	34	140	70	15	98	100	NA			NA	NA	NA	16			130	4.3		
2	2	43574	119599f	30700	120	24	120	80	15	98		21	21		7.31	130	23	12.4			135	2.8	107	9.1

2	2	43606	195977g	17900	90	24	120	70	15		98	NA		NA	NA			7.42		45		38	24				132	4.1		0.1
1	1	43453	456731h	8300	124	34	90	60	15		94		103	NA	NA			7.43		68		25	19.9				131	4.3	110	1.3
2	2	43450	229584h	15500	118	24	90	60	15		88	NA		NA	NA			7.41		54		34	22.8				128	3.1	104	2.7
1	2	43449	456419h	6300	86	22	100	80	15		88		98	NA	NA			7.46		72		38	27				133	3.2	101	1.5
2	2	43447	456200h	11100	110	22	130	80	15		98		98	NA	NA			7.38		95		25	14.8				111	11.4	88	1.9
2	2	43827	085633h	5300	100	20	100	70	15		97	NA		NA	NA			7.5		48		24	22				139	3.6	111	1
2	2	43436	460058h	15000	102	22	80	60	15		98	NA		NA	NA			7.54		79		28	24.3				129	2.5	102	2.6
2	2	43444	448195h	15000	86	20	100	60	15		98		99	NA	NA		NA		NA		NA		NA								
2	2	43452	584335b	6800	90	20	110	70	15		80		100	NA	NA			7.43		45		31	22				131	3.7	11	2.3
2	2	43446	456119h	27100	106	28	80	50	15		97	NA		NA	NA			7.32		104		22	15				121	3.9	9.2	5.9
2	2	43446	456129h	6600	140	30	90	60	15		97		103	NA	NA		NA		NA		NA		19				129	3.2		
2	2	43445	561116f	9600	122	22	130	90	15		89		100	NA	NA		NA		NA		NA		NA								
2	2	43444	279113b	9100	140	34	84	64	15		98	NA		NA	NA			7.48		76		25	18				125	3.3	98	3.2
2	2	43441	396559a	7800	52	32	120	80	15		88	NA		NA	NA			7.49		48		24	21				125	3.9	99	2.1
2	2	43439	195647h	8400	130	30	90	60	15		96		104	NA	NA			7.49		56		29	NA				135	3.6	105	1.5
1	1	43438	455509h	7600	104	20	90	60	13		95	NA		NA	NA			7.2		83		21	10.8				130	3.2	101	10.2
2	2	43561	858805B	8900	100	20	122	88	15	NA		NA		NA	NA		NA		NA		NA		17				138	4.4		
2	2	43560	567703h	10300	102	32	90	60	15		95		101	NA	NA		NA		NA		NA		NA				137	4.3		
2	2	43541	111231	12100	90	22	130	90	15		98	NA		NA	NA		NA		NA		NA		NA								
2	2	43538	565963h	20900	110	40	120	80	15		98	NA		NA	NA			7.2		73		20	7.8				154	3	130	3.6
2	2	43534	565787f	11000	88	28	140	80	15		99		99	NA	NA		NA		NA		NA		21				139	3.1		
2	2	43533	565189h	6400	110	20	100	70	15		98	NA		NA	NA		NA		NA		NA		23				138	4.4		
2	2	43527	119457f	11400	116	32	140	80	15		89	NA		NA	NA			7.52		100		29	26				129	3	99	
2	2	43503	562917h	8600	108	20	100	70	15		98		101	NA	NA		NA		NA		NA		NA								
2	2	43499	562619h	7300	140	22	110	70	11		98		99	NA	NA			7.45		74		20	12.6		5		126	4.7	112	
2	2	43497	562429h	23000	80	22	100	70	15		100	NA		NA	NA		NA		NA		NA		16								
2	2	43755	871983b	15100	106	44	84	50	15		78	NA		NA	NA			7.33		22		33	17.9				133	6	112	4.7
2	2	43476	458501h	17400	108	20	70	40	15		98	NA		NA	NA			7.47		87		28	18				133	4.7	105	3.5
2	2	43466	160396g	16100	102	22	120	60	15		99	NA		NA	NA			7.41		118		19	16.2				133	3.5	109	3
2	2	43755	138265g	11000	88	20	120	80	15		98		98	NA	NA		NA		NA		NA		NA								
2	2	43493	561704h	8800	92	26	100	70	15		98	NA		NA	NA		NA		NA		NA		13				138	5.7		
2	2	43595	620479h	16600	112	28	110	80	15		96		98	NA	NA		NA		NA		NA		16				131	4.2		
2	2	43597	047041f	9400	134	22	130	60	15		96		100	NA	NA			7.39		71		26	18				130	3.5	97	3.3
2	2	43600	620983h	10900	80	22	120	80	15		100		100	NA	NA		NA		NA		NA		22				124	4.2		
2	2	43558	567587h	13900	112	46	140	80	15		80	NA			40	40		7.49		64		48	34				138	2.8	105	2.2
2	2	43561	172514c	3300	110	36	220	110	15		100	NA		NA	NA		NA		NA		NA		13				133	4.3		
		43572	559364h	10300	128	22	100	60	15		99		104	NA	NA		NA		NA		NA		NA								
2	2	43573	568732h	10200	146	30	100	60	15		99		100	NA	NA			7.42		65		27	20				124	3.9	99	4.1
2	2	43529	723352d	16200	168	22	100	60	15		100	NA		NA	NA		NA		NA		NA		19				138	3.8		
2	2	43527	516145g	16900	100	20	100	60	15		74	NA		NA	NA			7.32		76		25	15				118	4.3	91	1.9
2	2	43535	361929c	28000	103	32	180	90	15		85	NA		NA	NA		NA		NA		NA		NA								
2	2	43538	565876h	16300	96	24	120	80	14		98	NA		NA	NA		NA		NA		NA		20				132	3.7		
2	2	43551	567083h	21700	86	20	120	70	15		94	NA		NA	NA			7.17		72		33	12				132	4.6	104	1.3
2	2	43497	562483h	46900	110	36	80	50	15		95	NA		NA	NA			7.42		46		38	24				127	3.3	97	2.9
2	2	43520	564413h	13700	110	24	140	60	15		99	NA		NA	NA		NA		NA		NA		16				112	3.6	91	1.9
2	2	43524	564741h	16700	112	22	110	70	15		98	NA		NA	NA		NA		NA		NA		17				130	3.1		
2	2	43488	561610h	15900	102	20	120	90	15		99	NA		NA	NA		NA		NA		NA		14				135	3.3		
2	2	43481	458439h	12700	110	30	140	90	15		86		100		24	24		7.46		59		30	23	131			131	3.1	101	2.3
2		43467	457851h	20700	80	30	60	0	15		90	NA		NA	NA			7.26		84		22	12				140	5	110	4.6
2	2	43468	071407d	13700	90	24	160	80	15		97		101	NA	NA			7.7		110		26	34				121	1.6	83	2.5
1	2	43468	457858h	13900	80	20	120	70	15		99	NA		NA	NA			7.28		94		21	13				133	4.8	109	6
2	2	43466	562265f	500	110	24	100	60	15		99	NA		NA	NA		NA		NA		NA		NA								
2	2	43479	611574f	11300	80	120	150	70	15		98	NA		NA	NA		NA		NA		NA		17				110	4.5		
2	2	43482	095545h	15200	132	20	90	60	15	NA		NA		NA	NA		NA		NA		NA		22				136	5		
2	2	43487	734840g	7200	148	24	100	60	15		96		103	NA	NA		NA		NA		NA		NA								
2	2	43488	561589h	18800	114	22	120	70	15		95		101	NA	NA		NA		NA		NA		16				137	4.8		
2	2	43522	565069f	15500	104	24	70	50	15		97		97	NA	NA		NA		NA		NA		10				139	3		
2	2	43516	541979g	26600	82	20	120	80	15		98	NA		NA	NA		NA		NA		NA		18				114	2.9		
2	2	43514	769098F	15100	120	40	0	0	15	NA		NA		NA	NA			7.41		121		14	14.8				119	5.4	95	7.2
2	2	43509	563381h	15400	92	22	130	70	15		98	NA		NA	NA		NA		NA		NA		19				138	4.4		
2	2	43502	684587c	25600	100	18	130	80	15	NA		NA		NA	NA		NA		NA		NA		NA								
2	2	43530	183928c	15500	88	22	110	70	15		99	NA		NA	NA		NA		NA		NA		16				139	4		
2	2	43527	308507h	11200	142	22	140	80	15		100	NA		NA	NA		NA		NA		NA		17				130	3		
2	2	43527	564991h	27700	116	22	90	60	15		98		101	NA	NA			7.37		104		21	16				127	2.3	100	1
2	2	43571	307124a	7300	120	24	130	80	15	NA		NA		NA	NA		NA		NA		NA		14				139	3.8		
2	2	43556	139057b	11100	98	20	110	60	98		98		98	NA	NA		NA		NA		NA										

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haemo	creatinin	haemato	n	l	m	e	b	bf	urea	platelet	banforms	creatclear	bloodurea	sgot	sgpt	serum	protein	totalbili	directbil	deescalat	bloodecol	bloodkleb	bloodpseu	bloodvibr
12.3	1.87	35	81	14	5	0	0	0	51	76000	0		23.83	68	32	2.8	5.7	1.29	0.94	1	2	2	2	2
9.6	0.63	30	73	17	8	2	0	0	18	572000	0		8.41	16	7	3	7.8	0.3	0.11	1	2	2	2	2
12.2	1.67	38	87	4	9	0	0	0	51	347000	0		23.83	56	16	2.3	6.8	0.49	0.2	1	2	2	2	2
10.5	0.75	31	89	4	3	0	0	4	27	206000	4		12.62	34	26	2.7	4.8	1.04	0.77	1	2	2	2	2
11.8	0.7	35	70	14	15	1	0	0	30	100000	0		14.02							1	2	2	2	2
13.9	1.27		81	11	8	0	0	0	31		0		14.49	34	16	4.3	7.1	0.81	0.17	1	2	2	2	2
11	0.58	36	72	23	5	0	0	0	17	227000	0		7.94	66	59	3.6	7.3	1.86	1.5	1	1	2	2	2
17.5	0.88	51	40	39	20	1	0	0		9000	0		0	201	106	4	7.3	0.75	0.39	1	2	2	2	2
9.5	0.72	29	87	11	2	0	0	0	13	303000	0		6.07							1	1	2	2	2
12.1	2.4	37	86	8	6	0	0	0	86	95000	0		40.19	23	15	2.4	5.4	0.71	0.22	1	1	2	2	2
13.8	1.12	41	58	24	17	0	0	0	34	91000	0		15.89	103	58	2.9	6.5	1.43	0.65	1	2	2	2	2
11.7	1.14	36	84	7	9	0	0	0	33	229000	0		15.42	16	13	3.7	8.1	0.5	0.2	1	1	2	2	2
14.2	0.64	44	70	20	9	1	0	0	35	314000			16.36							1	2	2	2	2
12.8	0.62	39	68	21	9	1	0	0	19	243000	0		8.88	14	17	4	6.3	0.52	0.24	1	2	2	2	2
14.3	0.88	42	80	13	7	0	0	0		142000	0		0	22	17	4.5	7.5	0.26	0.12	1	2	2	2	2
9.8	2.31	31	91	4	5	0	0	0	64	218000	0		29.91							1	2	2	2	2
12.5	0.87	36	54	50	4	0	0	0	24	46000			11.21	74	47	3.3	7.7	0.98	0.42	1	2	2	2	2
12.7	0.83	37	56	33	6	4	0	1		454000			0							1	2	2	2	2
8.1		26	93	5	2	0	0	0	15	469000	0		7.01	21	16	3.5	7.4	0.31	0.12	1	2	2	2	2
11.5	1.2	35	75	15	10	2	0	0	26	205000	0		12.15	16	14	3.9	7.4	0.55	0.33	1	2	2	2	2
8.2	3.09	25	84	8	7	1	0	0	60	130000	0		28.04	23	19	2.8	6.4	0.35	0.1	1	2	2	2	2
12.4	2.17	35	90	3	7	0	0	0	70	585000	0		32.71	45	112	2.6	7.5	0.67	0.39	2	2	2	2	2
9	0.95		94	4	2	0	0	0		250000			0	60	68	3.2	6.1	4.37	3.1	1	2	2	2	2
6.5	0.8		77	14	7	1	0	0					0	24	12	2	5.6	3.55	3	2	1	2	2	2
9	0.95		94	4	2	0	0	0					0	60	68	3.1	6.1	4.37	3.1	1	2	2	2	2
10.9	3.98	32	91	6	3	0	0	0	106	320000			49.53	98	32	2.4	8.4	0.6	0.35	1	2	2	1	2
11.3	0.62	34	72	17	11	0	0	0		265000	0		0	11	9	4.3	7	0.76	0.29	1	2	2	2	2
5.4	4.09	16								203000	0		0	16	13	2.7	8.8	0.21	0.1	1	2	2	2	2
13.4	1.1		81	10	8	9	0	0	36				16.82	105	279	3.8	7.2	1.54	1.06	2	2	2	2	2
11.6	0.81		73	22	5	0	0	0	31	127000	0		14.49	50	22	3.2	6.7	0.41	0.21	1	2	2	2	2
12.6	2.56	33	91	5	4	0	0	0	79	224000	0		36.92	10	22	3.7	6.7	0.8	0.2	1	1	2	2	2
10.3	2.4	30	90	6	4	1	0	0	63	170000	0		29.44	18	13	3.7	6.4	0.76	0.41	1	2	2	2	2
14.8	0.57	43	57	37	33	0	0	0	18	247000			8.41								2	2	2	2
11.8	0.64	34	86	3	10	0	0	0	24	109000	0		11.21	25	8	3	6	1.21	0.59	1	2	2	2	2
15.3	1.79	46	74	18	8	0	0	0	8	88000	0		3.74	33	19	4.7	7.5	0.3	0.18	1	2	2	2	2
12.9	0.73	38	78	10	12	0	0	0	19	263000	0		8.88	17	6	3.4	6.3	0.59	0.16	1	2	2	2	2
10.9	1.19	36	94	3	3	0	0	0	30	248000	0		14.02	17	10	4.5	7.2	0.52	0.18	1	2	2	2	2
10.1	0.54		80	17	3	0	0	0	13	48000			6.07	44	43	2.7	5.8	0.41	0.25	1	2	2	2	2
11.5	0.52	34	87	6	7	0	0	0	13	281000	0	0	6.07	38	24	3.6	6.2	0.36	0.13	1	2	2	2	2
12.5	5.04	38	83	8	8	0	0	0	97	265000	0		45.33	27	11	3.3	7.3	0.47	0.23	1	2	2	2	2
11.7	0.76	34	67	23	2	8	0	0	21	211000	0		9.81	17	11	3	6.5	0.6	0.17	1	2	2	2	2
19.4	0.89	53	32	54	11	1	0	2	12	10000			5.61	14	63	3.6	6.5	0.58	0.2	1	2	2	2	2
11	2.9	30	85	3	5	2	0	5	113	154000	0		52.8	1248	949	2.5	6.5	11.28	10.18	1	2	2	2	2
7.7	1.46	23	72	16	10	1	1	0	21	282000	0		9.81	12	9	2.3	6.8	0.39	0.2	1	2	2	2	2
10.6	0.42	30	54	31	14	1	0	0	9	17000			4.21	221	238	2.3	6.4	0.51	0.23	1	2	2	2	2
9.7	0.66	29	89	4	7	0	0	0		243000	0		0	30	16	3.1	5.6	0.2	0.14	1	2	2	2	2
10.1	0.73	31	63	22	14	1	0	0	33	228000			15.42								2	2	2	2
10.7	7.35	32	93	3	1	0	0	0	129	110000	0		60.28	67	31	3.4	6.7	1.67	1.04	2	1	2	2	2
12.8	0.74	35	82	9	9	0	0	0	20	292000	0		9.35	76	119	2.7	7.7	2.99	2.37	1	2	2	2	2
10.8	0.76	32	79	16	5	0	0	0	16	148000			7.48	121	87	2.8	6.6	0.79	0.16		2	2	2	2
13	1.94	37	79	15	6	0	0	0	63	11900	0		29.44	147	131	3	6.6	0.67	0.87	1	2	2	2	2
10.6	5.21	30	89	4	7	0	0	0	107	145000	0		50	84	30	2.3	4.8	0.55	0.34	1	2	2	2	2
13.7	0.89	40	80	8	12	0	0	0	12	166000	0		5.61							1	2	2	2	2
13	1.01	39	29	66	5	0	0	0	26	108000			12.15	372	311	2.9	7	1.18	0.83	1	2	2	2	2
13.7	1.35	40	82	9	8	0	1	0	26	204000			12.15	50	43	4.1	7.2	0.68	0.29	1	2	2	2	2
10.3	0.72	30	88	9	3	0	0	0		186000			0	37	36	3.5	6.1	0.31	0.15	1	2	2	2	2
10.1	0.6	30	85	12	3	0	0	0		50000			0	103	93	3.2	6.3	0.52	0.74	1	2	2	2	2
14.6													0								2	2	2	2
9.9	0.78									419000			0							1	2	2	2	2
7.7	4.44		60	38	2	0	0	0		217000	0		0								2	1	2	2
7.2	1.62	23	93	2	5	0	0	0	57	179000	0		26.64	29	16	3.4	7.2	0.54	0.35	2	2	2	2	2
9.1	0.95	28	70	15	6	9	0	0		430000	0		0	19	15	2.8	8	0.27	0.17	1	2	2	2	2
15.1			72	18	9	1	0	0	0		0		0	20	12	4.7	8.1	0.15	0.47	1	2	2	2	2
11.9	0.73	33	77	20	3	0	0	0	29	36000	0		13.55	187	78	1.9	6.6	1.89	1.09	1	2	2	2	2
13.2	0.6	40	86	12	2	0	0	0	22	185000	0		10.28	22	31	4.1	7.5	0.41	0.17	2	2	2	2	2
10.6	2.4	34	61	25	7	5	2	0	89	427000			41.59	55	64	3.1	7.3	0.2	0.1	2	2	2	2	2
	0.94		89	4	6	1	0	0	34				15.89	22	19	3.5	6.4	1.28	1.02	1	1	2	2	2
10.4	0.95	31	56	35	9	0	0	0	25	233000	0		11.68	31	20	3.8	6.9	0.2	0.1	1	2	2	2	2
10.3	0.97	31	75	14	10	1	0	0	33	195000	0		15.42	16	10	4.1	7.3	0.41	0.1	1	2	2	2	2
12.1	0.98		80	11	8	1	0	0	0	135000			0	17	9	3.2	7.5	0.98	0.51	1	2	2	2	2
8.6	2.3	24	73	12	15	0	0	0	55	236000			25.7	33	9	3	7.5	0.34	0.1	1	2	2	2	2
13.2	1.17		84	9	7	0	0	0	29	418000			13.55							1	2	2	2	2
11.3	3.32	34	88	7	5	0	0	0	153	264000	0		71.5	16	13	3.8	7	1.3	0.3	1	1	2	2	2
7.8	3.99	26	84	7	8	1	0	0	131				61.21	15	16	2.8	6	0.36	0.22	1	2	2	2	2
8.9	0.99	24	79	12	6	2	1	0	17	433000	0		7.94	68	70	3.5	7.5	0.69	0.36	1	2	2	2	2
12.9	0.9	36	70	23	6	0	1	0	11	115000	0		5.14	51	47	4.2	6.9	0.33	0.13	1	2	2	2	2
	0.69		88	6	6	0	0	0	34				15.89	14	19	3.6	8.4	0.57	0.21	1	2	1	2	2
5.7	0.6	19	50	40	10	0	0	0	15	109000			7.01	36	21	3.4	6.2	0.73	0.28	1	2	2	2	2
13.2	0.74	40	85	5	9	0	0	0	20	188000			9.35	16	12	4.6	7.8	0.7	0.1	1	2	2	2	2
10.7	0.59	35	88	8	4	0	0	0		144000			0	17	17	3.1	7.1	1.25	0.69	1	2	2	2	2
13.7	0.8	40	72	22	6	0	0	0	17	124000			7.94	465	279	3.9	7	0.78	0.4	1	2	2	2	2
9.7	3.12	29	91	6	2	1	0	0	84	216000			39.25	39	34	3.2	6.9	1.43	0.97	1	1	2	2	2
12.7	1.42	36	96	2	2	0	0	0	37	116000			17.29	116	54	3.4	6.8	0.5	0.22	1	2	2	2	2
15	0.91	44	80	4	16	0	0	0	22	86000			10.28	92	69	3.6	6.9	0.3	0.1	2	2	2	2	2
10	0.74	31	80	9	11	0	0	0	26	397000			12.15	52	14	3	6.4	0.51	0.16	1	2	2	2	2
9.3	0.82		51	16	3	0	0	0	26	158000			12.15	32	18	2.1	5.2	0.75	0.61	1	2	2	2	2
10.7	1.7	31	80	6	6	0	0	0	49	457000	0		22.9	44	23	2.8	7.3	0.37	0.28	2	2	2	2	2
14.6	0.6	41	84	9	7	0	0	0	13	209000			6.07	22	12	4.5	7.9	1.09	0.42	2	2	2	2	2
12.1	1.47	36	89	6	5	0	0	0	40	100000	0		18.69	29	17	2.7	7.3	1.68	1.05	1	1	2	2	2
9.2	1.03	29	80	8	7	5	0	0	35	406000			16.36	13	9	2.7	6.9	0.29	0.21	1	2	1	2	2
9.2	2.03		91	3	6	0	0	0	70	259000	0		32.71	30	14	3	6.4	0.72	0.45	1	1	2	2	2
11	1.57		74	16	10	0	0	0	34	350000	0		15.89	34	13	4.3	7.8	0.8	0.1	1	2	2	2	2
10.3	0.76		55	27	16	2	0	0		356000			0	45	48	4.3	8.2	0.23	0.11	1	2	2	2	2
12.4	0	36	50	45	5	0	0	0		80000			0	200	209	3.2	6.4	2.77	2.31	1	2	2	2	2
10.8	1.04	33	90	4	6	0	0	0	26	145000			12.15	29	22	2.4	6.3	0.52	0.27	1	1	2	2	2
15.1	0.77	45	82	7	10	1	0	0	20	200000	0		9.35	44	53	4.3	6.6	0.57	0.23	1	2	2	2	2
15.4	0.93	46	64	31	5	0	0	0	40	146000			18.69	37	22	3.4	6.8	0.46	0.16	1	2	2	2	2
14.3	0.75	42	78	14	8	0	0	0	29	5000			13.55	150	100	3	5.8	0.76	0.35		2	2	2	2
9.7	7.77	28	85	5	9	0	0	0	229	111000	0		107.01	18	22	4.1	7.4	0.55	0.27	1	2	2	2	2
11.5	0.82	33							13	109000			6.07	187	131	3	6	1.5	0.71	1	2	2	2	2
13	1.12	37	93	4	1	0	0	1	37	7000	1		17.29	103	58	2.8	6.9	8.84	7.73	1	2	2	2	2
11.4	1.56	33	64	34	1	0	0	0	44	122000			20.56	111	95	2.1	5.6	1.27	1.26	1	2	2	2	2
12.4	0.87		80	9	5	0	0	6	14	411000			6.54	31	18	2.6	6	0.56	0.32	1	1	2	2	2
7.9	4.62		92	4	4	0	0	0	116				54.21	21	37	2.1	6.2	0.26	0.18	1	2	2	2	2
													0								2	2	2	2
10.5	1.59	32	89	5	4	2	0	0	69	166000	0		32.24	17	20	3.1	7.1	0.77	0.49	1	1	2	2	2
	0.73												0								2	2	2	2
9.7	2.79	29	93	4	3	0	0	0	59				27.57								2	2	2	2
12.2	0.85	37	76	20	1	3	0	0		214000	0		0	18	13	3.9	7.1	0.51	0.16	1	1	2	2	2
	1.9		93	4	3	0	0	0	59				27.57							1	1	2	2	2
	1.33		75	15	11	0	0	0	36				16.82	13	19	4.3	7.7	2.54	0.75	1	1	2	2	2
	12.7		59	30	11	0	0	0	37				17.29	77	92	3.1	7.6	0.62	0.23	1	2	2	2	2
	2.04		75	17	8	0	0	0	37			2.04	17.29	35	21	3.6	6.9	0.38			1	2	2	2
9.5	0.41		69	16	15				8	192000	0		3.74	16	7	2.9	6.9	0.28	0.13	1	2	2	2	2
10.9	11.5	34	86	8	8				52	271000	16	5	24.3	14	13	3.4	7.2	0.56	0.26	1	2	2	2	2
8.8	2.13	26	79	8	7	2	1	0	40	261000	0		18.69	9	10	2.1	7.1	0.61	0.45	1	2	2	2	2
15.2			86	12	1	1	0	0		307000	0		0	69	61	4.1	7	0.32	0.17	1	2	2	2	2

11.7	1.29	38	89	8	3	0	0	0	153	459000	
10.5	2.4	30	51	29	17	1	0	0	171	86000	
9.3	0.62	28	81	13	5	1	0	0	24	306000	
12.3	1.29	37	77	16	6	1	0	0	39	39000	
11.8	2.95	34	91	6	3	0	0	0	150	106000	
10.2	0.64	31	76	22	2	0	0	0	16		
10.3	0.33	30	59	36	5	0	0	0		102000	0
11.2	0.62	34	74	22	4	0	0	0		225000	0
11.6	2.44	34	93	5	2	0	0	0	54	111000	0
	4.87		92	1	2	0	0	5	121		
10.2	0.68	30	60	37	3	0	0	0	17	58000	
9	0.67	28	72	21	7	0	0	0	24	65000	0
9.2	0.82	27	91	6	3	0	0	0		3000	
10	1.15	29	78	10	10	2	0	0	29	160000	
13.4	1.58	39	80	10	9	0	0	0	39	148000	
11.6	1.75	36	88	5	0	0	0	7	76	14000	7
			90	5	4	0	0	0	31	98000	0
9.7	1.34	28	82	9	9	0	0	0	54	262000	0
8.3	7.76		90	6	4	0	0	0	145	119000	0
12.9	1.47	40	82	9	9	0	0	0	104	235000	0
	1.18		84	8	7	1	0	0	43		
14.3	0.89	42	55	22	20	2	0	0	26	309000	
16.2	1.74	48	79	12	9	0	0	0	41		
12.9	1.11	39	75	7	4	1	2	11	24	370000	0
	4.54	34	34	32	9	0		23		374000	
11	2.22	35	93	4	3	0	0	0	86	98000	
8.2	2.02								43	157000	
8.6	1.84	28	89	6	5	0	0	0	41	342000	
12.2	0.65	37	79	10	10	1	0	0	15	265000	0
10.1	4.02	33	83	7	9	1	0	0	181	242000	
	0.7		84	9	5	2	0	0	17		
13.1	1.93	38	79	9	12	0	0	0	39	186000	
13.1	0.93	41	79	8	13	0	0	0		178000	
10.9	0.52	33	87	5	8	0	0	0	48		
11.5	1.4	35	87	12	1	0	0	0		143000	
10.8	3.94	32	92	4	2	0	0	2	98	70000	
14	0.97	41	74	16	8	2	0	0	26		
8.9	3.24	26	90	4	2	4	0	0	132	290000	
13	0.7	38	82	12	5	1	0	0	31		
11.8	4.33	34	90	5	5	0	0	0	149	268000	
14.2	1.87	43	88	9	3	0	0	0	40	315000	0
8.9	0.97	26	86	4	10	0	0	0			
11.9	1.68	36	92	4	4	0	0	0			
8.1	1.15	25								179000	
14.3	1	41	66	29	3	2	0	0	37	187000	0
13.2	3.15	40	96	2	2	0	0		54	169000	
9.8	1.75	26	73	15	11	1	0	0	29	294000	
20			64	12	18	0	6	6		9000	
13.3	0.95	37	72	24	4	0	0	0	28	16000	
11.4	0.84	33	84	7	9	0	0	0	22	308000	
9.2	1.32	29	75	18	7	0	0	0			
10.7	0.82	30	76	11	13	0	0	0	22	230000	0
9.3	1.32	29	95	4	1	0	0	0	41	286000	
7	2.36	22	93	3	1	0	0	0	99	265000	
14.2	1.01	40	91	4	5	0	0	0	41	305000	
12.6	1.37	39	76	14	10	0	0	0	51		
	3.66										
7.9	1.14		93	4	3	0	0	0	22	98000	
12.8	0.83	40	90	5	5	0	0	0	25	255000	
		31	92	7	1					266000	0
11.8	0.75	33	87	4	9	0	0	0	32	443000	0
8.8	2.06	29	89	10	1	0	0	0	86	211100	
12.5	0.88	39	84	9	7	0	0	0		174000	

71.5	104	112	3.2	8.3	0.26	0.12	2	1	2	2	2
79.91	175	113	2.2	5.2	1.07	0.52	1	2	2	2	2
11.21	125	13	1.6	6.9	2.05	1.97	1	2	2	2	2
18.22	101	85	2.4	5.8	5.5	4.2	1	2	2	2	2
70.09	32	32	2.6	6.2	4.85	4.66	1	2	2	2	2
7.48	37	19	2.4	5	0.25	0.12	1	2	2	2	2
0	82	61	1.7	5.3	4.29	3.77	1	2	2	2	2
0	9	9	3.4	6.5	0.7	0.3	1	1	2	2	2
25.23	15	6	2.5	7.1	1.15	0.62	1	2	1	2	2
56.54	17	28	2.9	7.2	4.48	4.25	1	2	2	2	2
7.94	101	65	2.2	6.4	2.21	2	1	2	2	2	2
11.21	57	31	2.7	6.4	0.61	0.1	1	2	2	2	2
0	59	55	3.2	6.2	0.31	0.13	1	2	2	2	2
13.55	26	21	3.7	6.6	0.39	0.18	1	2	2	2	2
18.22	44	45	4.5	7.7	0.91	0.34	1	2			
35.51	119	49	1.8	3.8	3.49	3.26	1	2	2	2	2
14.49	11	16	3.2	5.5	3.2	0.42	1	1	2	2	2
25.23	14	18	2.4	6.8	0.92	0.71	1	2	2	2	2
67.76		11	8	5.2	0.34	0.23	1	2	2	2	2
48.6	15	14	2.1	7.9	0.2	0.1	1	2	2	2	2
20.09	37	19	2.3	5.6	2.38	1.37	1	2	2	2	2
12.15	41	33	3.4	7.1	0.52	0.21	1	2	2	2	2
19.16	55	44	3.5	6.9	1.45	0.61	1	2	2	2	2
11.21	55	39	3.5	6.9	0.72	0.36	1	2	2	2	2
0	355	454	2.8	7.3	7.3	6.68		2	2	2	2
0								2	2	2	2
40.19	32	21	2.3	6.1	1.08	0.83	1	2	1	2	2
20.09								2	2	2	2
19.16	19	18	3.3	6.8	0.68	0.37	1	2	2	2	2
7.01	28	48	3.2	7	0.58	0.42	1	1	2	2	2
84.58	19	19	3.6	7.4	0.35	0.19	1	2	2	2	2
7.94							1	2	2	2	2
18.22							1	2	2	2	2
0	45	21	3.2	7.8	0.89	0.38	1	2	2	2	2
22.43	11	18	3.5	6.9	0.41	0.21	1	2	2	2	2
0	21	13	4.1	7.6	0.82	0.25	1	1	2	2	2
0								2	2	2	2
45.79	14	15	2.5	6.1	2.31	2.19	1	1	2	2	2
12.15								2	2	2	2
61.68	16	17	2.8	6.3	1.07	0.78	1	2	2	2	2
0								2	2	2	2
14.49	17	23	2.2	6.7	0.37	0.18	1	2	2	2	2
69.63	32	42	3	7.1	0.27	0.16	1	1	2	2	2
18.69	31	18	2.7	5.1	0.27	0.17	1	2	2	2	2
0	69	47	3	6.1	1.09	0.68	1	2	2	2	2
0	67	44	3.3	6.7	1.12	0.85	1	1	2	2	2
0	18	17	2.5	7.1	0.38	0.24	1	2	2	2	2
17.29	20	17	2.3	5.7	0.58	0.32	1	2	2	2	2
25.23	45	26	2.9	7	1.29	1.11	2	1	2	2	2
13.55	14	12	2.9	7.1	0.65	0.26	1	1	1	1	2
0	3436	2258	2.9	5.3	2.29	1.48	1	2	2	2	2
13.08	251	72	3.3	6.6	1.16	0.41	1	2	2	2	2
10.28	36	32	3.5	6.9	0.78	0.35	1	2	2	2	2
0	24	22	4.2	7.8	0.5	0.24	1	2	2	2	2
10.28	19	19	3.4	7.4	0.69	0.34	1	2	2	2	2
19.16	23	23	87	5.2	0.41	0.29	2	2	2	2	2
46.26							1	2	2	2	2
19.16								1	2	2	2
23.83	7412	3163	3.2	5.6	1.76	1.36	1	1	2	2	2
0		21	21	0.4	0.24			2	2	2	2
10.28	205	132	3.1	7.5	3.91	3.56	1	1	2	2	2
11.68	18	42	3.9	6.2	1.14	0.47	1	2	2	2	2
0	40	17	2.8	6.9	0.48	0.26	1	2	2	2	2
14.95	8	9	2.9	8.3	0.32	0.16	1	1			
40.19							1	1			
0	28	27	3.7	7.7	0.73	0.34	1	1	2	2	2

bloodstap	bloodstrep	bloodent	Blood salm	Blood burkhol	Citrobacter	NFGNB	Alpha he	bloodother	bldsense	Urine	Enteroco	urikleb	uripseud	urivibrio	uristaph	uristrep	urisense	spuecoli	spukleb	spupseud	spuvibrio	spustaph	spustrep	spusense
2	2	2	2	2	2	2	2			2	2	2	2	2	2	2		2	2	2	2	2	2	
2	2	2	2	2	2	2	2			2	2	1	2	2	2	2	2	2	2	2	2	2	2	
1	2	2	2	2	2	2	2		6	2	2	2	2	2	2	2	1	2	2	2	2	2	2	
2	2	2	2	1	2	2	2	Burkholderia pseudomall		2	2	2	2	2	2	2	3	2	2	2	2	2	2	
2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2	2	2	2	2	2	2	
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2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
2	2	2	2	2	2	2	2			2	2	2	2	2	2	2		2	2	2	2	2	2	
2	2	2	2	2	2	2	2		1	2	2	2	2	2	2	2		2	2	2	2	2	2	
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2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	1	2	2	2	2	2		
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2	2	2	2	2	2	2	2			2	2	2	2	2	2	2		2	2	2	2	2	2	
	2	2	1	2	2	2	2	Salmonella		1	2	2	2	2	2	2	2	2	2	2	2	2		
2	2	2	2	2	2	2	2			2	2	2	2	2	2	2		2	2	2	2	2	2	
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2	2	2	2	2	2	2	2			2	2	2	2	2	2	2		2	2	2	2	2	2	
2	2	2	2	2	2	2	2			2	2	2	2	2	2	2	2	2	2	2	2	2		
2	2	2	2	1	2	2	2	Burkholderia pseudomall		2	2	2	2	2	2	2	2	2	2	2	2	2		
2	2	2	2	2	2	2	2			1	2	2	2	2	2	2	2	2	2	2	2	2		
2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		2	2	2	2	2	2	
2	2	2	2	2	2	2	2			2	2	2	2	2	2	2		2	2	2	2	2	2	
2	2	2	2	2	2	2	2		2	1	2	2	2	2	2	2		2	2	2	2	2	2	
2	2	2	2	2	2	2	2			2	2	2	2	2	2	2		2	2	2	2	2	2	
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