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Colistin Resistance in isolates from Cultures in a Tertiary Care Teaching Hospital: A One-year Patient Profile Study

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Abstract
Background
Antimicrobial resistance is among the top10 public health threats facing humanity[1]. Limited therapeutic options have led to resurgence in the use of older antibiotics once discarded because of their adverse affects. Colistin reuse began in the 1990s to tackle resistant gram negative bugs .Resistance to this mostly last resort drug has since emerged and is spreading quickly. Knowledge of local patterns of antibiotic resistance is vital to strategise management of severe resistant infections.
Methods
We conducted a retrospective observational study in our hospital from October 2020 to September 2021.We retrieved Colistin resistant isolates from Microbiology cultures over this period, reviewed case records and documented patient profiles.
Results
We found Colistin resistance in 39 out of 562 Cultures that isolated inherently susceptible GNB isolates over the one year study duration. The ICU mortality was 61.5%. The average LOS was very prolonged. The risk factors were elderly age and co morbidities especially Diabetes mellitus (74%) and Hypertension (58%)
Conclusion
Colistin Resistance is an emerging threat in health care settings. Robust antibiotic stewardship is the need of the hour.

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I. Background

Antimicrobial resistance is menacing and relentless. In 1937, sulphonamides were the first antibiotics introduced and resistance was documented by the late 1930s[2]. Penicillin was discovered by Alexander Fleming in 1928 and by 1940, bacterial penicillinases were observed[3] even before therapeutic usage .All old and new antibiotics have developed resistance. The clinical pipeline of new antibiotics is dry. The WHO identified 32 antibiotics in 2019 in clinical development to address the WHO list of priority pathogens[4], only six of which were innovative[1].The implications of AMR are manifold. It will lead to treatment failures, increase in mortality, morbidity and make surgeries, chemotherapy and other interventions riskier. It will also entail a higher financial burden to individuals and nations.[1]

The most common and preventable cause for AMR is misuse and overuse of antibiotics in humans and animals. A systematic review and periodical audit of antibiotic sensitivity patterns and usage at the local level will streamline optimal antibiotic usage and curb resistance.

Colistin was approved by the FDA in 1959 for use against gram negative bacterial infections[5]. It went out of use in the 1970s because of nephrotoxicity and neurotoxicity. There has been a renewed use of this drug starting in late 1990s to counter extensive antimicrobial resistance in GNB isolates. It is a last resort for life threatening multidrug resistant gram negative aerobic bacterial infections in many situations[5]. Resistance to Colistin started emerging very rapidly. The mechanisms are multiple with new genetic mechanisms being identified recently[6].

We noticed a surge in Colistin resistance in our hospital isolates in the recent years. Patients admitted to the intensive care unit with such infections seemed to have a dismal outlook. We wanted to study this cohort of patients in the ICU and wards to identify risk factors, patient characteristics and quantify outcomes. The last year was unique because of the COVID 19 pandemic. Our hospital was a designated COVID 19 centre in the

First and second waves and more than 12000 patients were treated. The overall number of Non COVID patients was decreased in comparison to previous years and so were the number of cultures.

II. Material and Methods

Aim of the Study

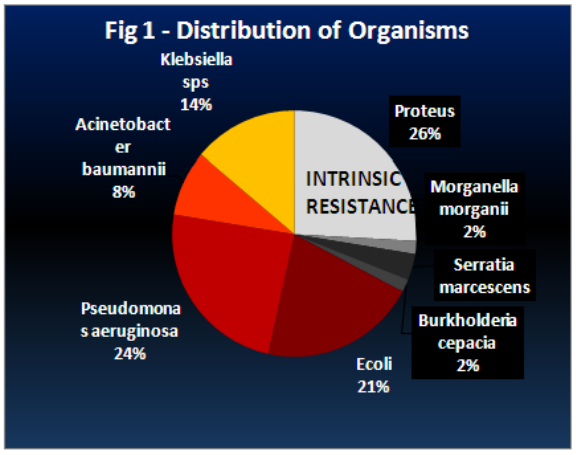
To study patient characteristics of Colistin resistant GNB isolates in our hospital inpatients

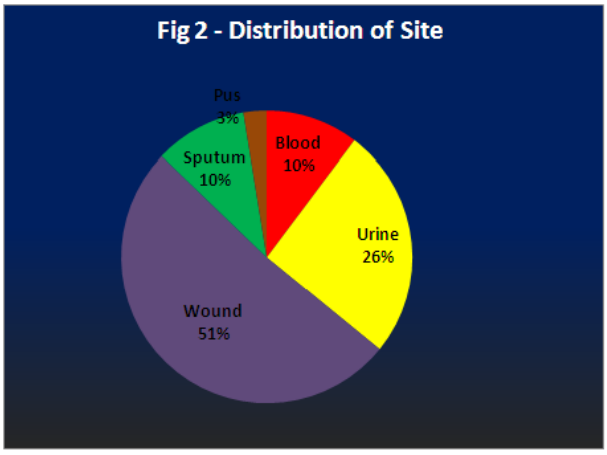
Methods

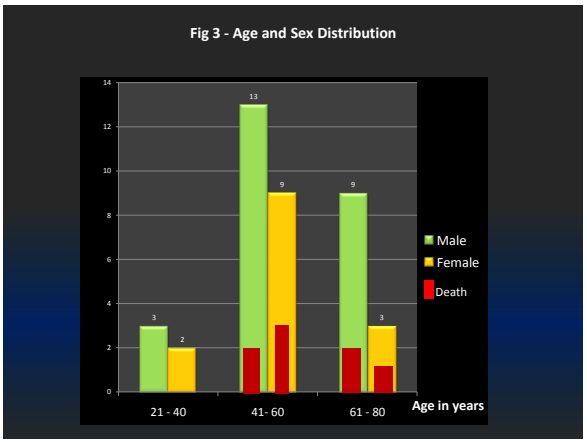
We conducted a retrospective observational study in our hospital from October 2020 to September 2021.
We retrieved Colistin resistant culture isolates from the register maintained by the Department of Microbiology at our hospital. Bacterial colonies were identified by VITEK 2 compact (Biomerieux, France) automation system and antimicrobial susceptibility testing was done with the same system to detect minimum inhibitory concentration (MIC). For this, antimicrobials used in the panel were tigecycline, cefoperazone/sulbactam, amikacin, aztreonam, piperacillin-tazobactam, ticarcillin clavulanic acid, cefepime, gentamicin, trimethoprim sulfamethoxazole, ceftazidime, levofloxacin, minocycline, ciprofloxacin, imipenem, doripenem, ceftriaxone and colistin. Interpretation of test was done as per Clinical and Laboratory Standard Institute 2017 guidelines. Colistin resistance was defined as MIC of ≥4 µg/ml. We then retrieved case records from the MRD. We documented demographic data, co morbidities, diagnosis and site of infection, surgical procedures, length of hospital and ICU stay and outcomes. We also noted the antibiotic utilized in the current admission before and after culture and sensitivity reports. We tabulated our findings.

III. Results

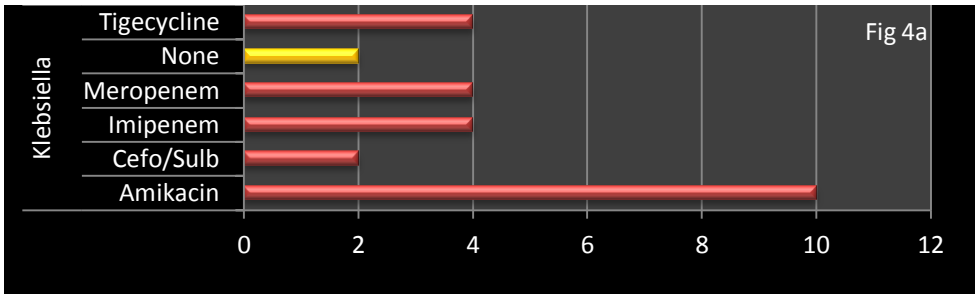
We retrieved a total of 54 culture isolates over the one-year period. 15 of these were bugs that are inherently resistant to Colistin (Proteus mirabilis (26%), Morganella morganii (2%), Serratia marcescens (4%) and Burkholderia cepacia (2%).We excluded them from further analysis. Of the 39 isolates, 13 were from ICU patients and 26 from wards. The distribution of various organisms is shown in Figure 1.The most common site of infection was wound followed by urine. The distribution of site of infection is depicted in Figure 2. In our study, 25 of the patients were male and 14 were female. The age and sex distribution are shown in Figure 3.

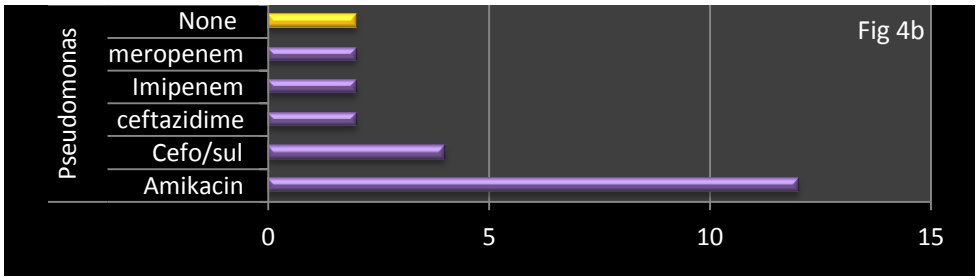


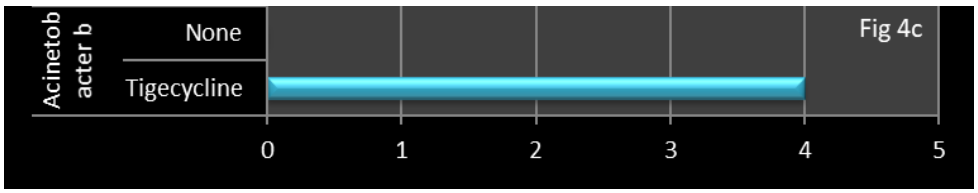




We found that 74% of the patients with colistin resistance were diabetic, 58% were hypertensive, 20% had chronic kidney disease, 15% had chronic lung disease and 2% had chronic liver disease. Most of the patients had multiple co morbidities. Coming to the patterns of resistance, out of 39, we found 4 cultures were pan drug resistant, meaning the bug was not susceptible to any of the drugs tested for, 14 cultures were extremely drug resistant, meaning that the bug was susceptible to only one of the drugs tested and 20 cultures were multidrug resistant meaning that the bud was resistant to all but two classes of drugs tested for. The patterns of resistance in individual organisms are depicted in figure 4.







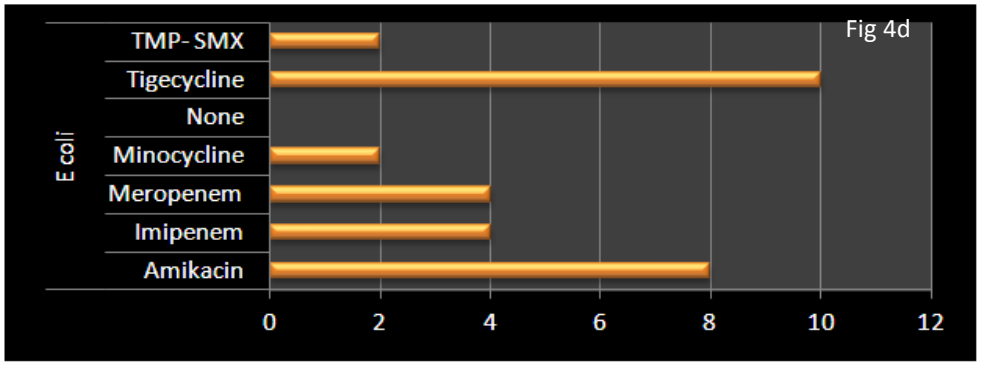
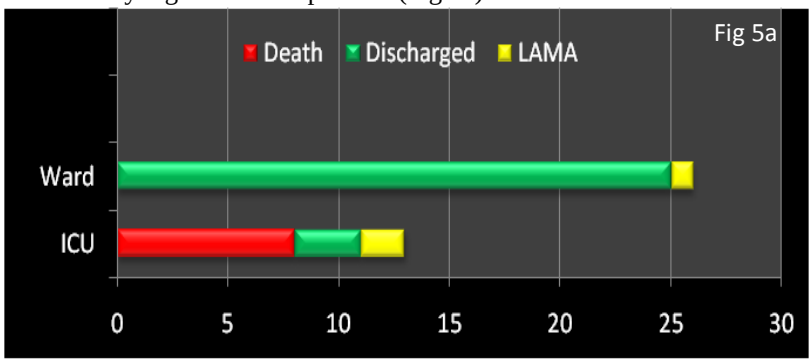
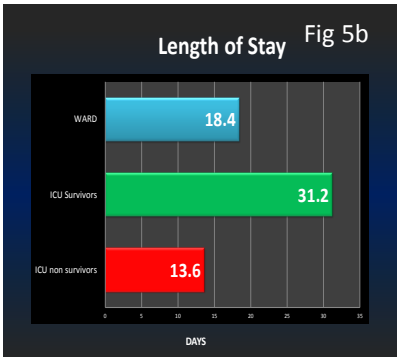


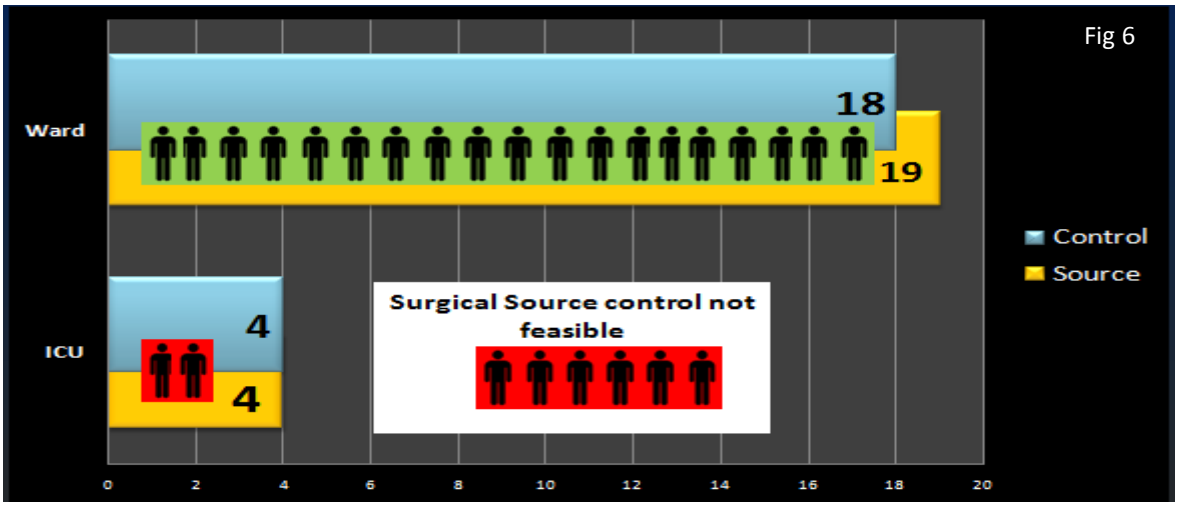
Fig 4 – Pattern of resistance in a- Klebsiella- Pseudomonas, c- Acinetobacter and d- E coli

The outcomes were very dismal in the ICU patients (Fig 5a). Out of thirteen patients, eight (61.5%) died and another two left against medical advice. Contrary to this, out of twenty six patients in the ward, twenty five (96.15%) were discharged alive and one patient left against medical advice. The length of stay was also substantially higher in these patients (Fig 5b).





Source control was attempted in all but one patient in the ward because the source was amenable to surgical debridement and other procedures. In the ICU on the other hand source control was attempted in 4 of the 13 patients. This seems to have a bearing on the outcomes. All patients who did not have source control measures instituted died in the ICU. The mortality was half in those who underwent source control. In the ward, all but one patient underwent source control. The same is depicted in figure 6.



IV. Discussion

Colistin is a polypeptide antibiotic of the group E, discovered in 1947 by Y. Koyama from Paenibacillus polymyxa subspecies colistinus cultures[7]. The polymyxins were deemed "miracle" antibiotics when they were first commercialized in the 1950s, with a bactericidal efficacy against Gram-negative bacteria and a low level of resistance[9]. Colistin was subsequently abandoned in the 1980s in favour of other less toxic broad-spectrum antibiotics. Therefore, the pharmacokinetic and pharmacodynamic properties, as well as the resistance mechanisms were understudied and poorly understood. In 2007, the World Health Organization (WHO) reclassified polymyxins as a major agent for the treatment of multidrug-resistant GNB infections[10] leading to renewed interest in clinical research on the drug. It is a bactericidal, narrow-spectrum molecule directed against most GNB, but ineffective against Gram-positive bacteria, anaerobic bacteria, and mycoplasmas. Gram negative bacteria such as Proteus, Burkholderia, Providencia, Morganella and Serratia species which add positively charged sugars such as 4-amino-L-arabinose, Ara4N or amino-alcohols such as ethanolamine to their Lipopolysaccharide, preventing polymyxin binding are inherently resistant[8].

The main target of the polymyxins is the lipopolysaccharide of GNB membranes. Colistin, a positively charged molecule has a strong affinity to the negatively charged Lipid A of the outer part of lipopolysaccharide, leading to a displacement of cations by electrostatic interaction. It results in a disorganization of the membrane

structure, with release of the lipopolysaccharide. Colistin is thus exposed to the outer membrane through its lipophilic acid-fat chain. Colistin then alters the permeability of the outer membrane, allowing it to insert itself and reach the inner membrane. A disorganization of this inner membrane is caused by breaking the integrity of the phospholipid bilayer. Finally, lysis of this membrane results in the release of intracellular contents and bacterial death. This process is the most commonly used mechanism to explain the antibacterial action of colistin, but the ultimate mechanisms leading to cell death are still not well understood [11].

The initial studies on resistance found in vitro resistant mutants[12].Colistin has been used for many decades in veterinary medicine to prevent infections in animals and as a growth factor in animal husbandry. There was also a poor understanding of Pharmacokinetics, pharmacodynamics and Minimum inhibitory concentrations which contributed to rapid development of resistance. Now, a multitude of genetic mutations have been identified that confer resistance by mechanisms including but not limited to mutation in LPS synthesis genes, efflux pumps, plasmid-mediated mcr-Like genes, chromosomal LPS membrane modulations and capsule changes[6]. A stagnant antibiotic pipeline in addition is making us defenseless against several superbugs.

Several studies have been done to quantify the problem of colistin resistance in gram negative bacteria[13].A study based on the SENTRY surveillance program data from 2006 to 2009 on polymyxins showed excellent in vitro activity against 40,625 isolates of Gram-negative bacteria collected worldwide. The overall resistance rates to the polymyxins were low but trended towards increasing resistance against Klebsiella spp. from the Asia Pacific and Latin American regions[14].The increased usage of colistin which accelerates resistance may be attributed to higher prevalence of MDR especially Carbapenem resistance in Gram negative bacilli in Asia Pacific regions. In a study from Egypt in 2019, 8.8 percent colistin resistance was reported in isolates from cancer patients[15].In India; several studies have reported high resistance rates. A study from a rural tertiary care centre in western India reported an alarming 9.98% colistin resistant Gram Negative bacterial isolates [16]. In a small study from Tamil Nadu among 94 isolates, 18.8% E Coli, 66.6% Klebsiella, 30% Pseudomonas and 50% Acinetobacter species were resistant to colistin[17].In another study from Punjab, over three years, a 5.6% resistance was reported among 533 isolates of Klebsiella species in patients admitted to intensive care unit[18].We found an incidence of 6.93% (39 of 562) of colistin resistance. We found 7.07% Klebsiella species, 8.77% of Acinetobacter species, 8.88% of pseudomonas and 4.66% of E coli were colistin resistant.

Colistin resistance portends a high mortality. In a Thai, study 70% of patients with Colistin resistant Acinetobacter Baumannii infection died[19].Another study among Colistin resistant Klebsiella bacteraemia patients reported a 60% 14day mortality and an 80% hospital mortality[20].Our population consisted of both ward and ICU patients. The mortality among ICU patients in our study was 61.5% while there was no hospital mortality in patients treated in wards. The site of infection was wound and urine in the ward while in the ICU; the sites were pneumonia, blood stream, urine and wound tissue. All but one of the patients in the wards underwent source removal by way of wound debridement and daily wound care. In the ICU, on the other hand, source was amenable to debridement in 4 of the 13 patients of which 2 patients survived. Patients also had multiple co morbidities, were elderly and sicker. Antibiotic options were very limited including high dose Carbapenem, Tigecycline and Trimethoprim Sulfamethoxazole.

Limitations of our study

Our study was retrospective. We were not able to study the mechanisms of resistance in our patients. We did not have data on prior antibiotic usage. We did not follow up patients post discharge from the hospital.

V. Conclusions

Colistin Resistance is a serious problem resulting in high patient mortality, morbidity and length of stay. A near dry new antibiotic pipeline leaves very few treatment options. Hence a robust antibiotic stewardship program which will ensure appropriate and timely usage in terms of indications, dosage, duration, Pharmacokinetic and pharmacodynamic considerations is the need of the hour. Early and effective source control prevents deaths and cannot be overemphasized.

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