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Antibiogram Analysis and Altering Antimicrobial Susceptibility Pattern of Multidrug Resistant Pathogens

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Abstract- *Introduction:* In the current situation of escalating antibiotic resistance it is essential to identify and report sensitivity pattern of these MDR bacteria in order to tailor empirical therapy and hygienic measures. Because there will be hardly any new antibiotics in the near future, a better understanding is needed on the how to optimize the use of existing antibiotics, alone and in combination with other drugs. To achieve this, periodic monitoring and surveillance of hospital antibiogram is mandatory.

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Keywords: *antibiogram, surveillance, changing trends, MDR pathogens.*

GJMR-C Classification : *NLMC Code: QW 1*

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Results: The most prevalent MDR gram negatives at our centre were ESBL *E.coli* & ESBL *Klebsiella pneumonia* (73% & 61% respectively) and MRSA among Gram positives at 24.5%. *Pseudomonas* was the most predominant Imipenem resistant gram negative bacilli. Uropathogenic *E.coli* strains had better sensitivity to Nitrofurantoin at 63%. Imipenem showed 90-100% sensitivity to *E.coli* & *Klebsiella* and 70-80 % to *Pseudomonas*. MRSA was predominantly from soft tissue infection showing 100% sensitivity to Linezolid & 99% to Vancomycin.

Conclusion: During the study period a narrow spectrum of sensitivity was observed for commonly used antibiotics. An empirical antimicrobial Guideline was drafted following the Antibiogram Surveillance. Infection control measures & antimicrobial stewardship had proven to be modestly effective in our study.

Keywords: antibiogram, surveillance, changing trends, MDR pathogens.

I. Introduction

The bacterial disease burden in India is among the highest in the world [1, 2, 3]; consequently, antibiotics are playing a critical role in limiting morbidity and mortality in the country. But unfortunately antibiotic resistance which is a global concern now, has reached a pandemic proportion fuelled by human need, greed and irresponsibility [4]. This is particularly pressing in developing nations, including India, where the burden of infectious disease is high and healthcare spending is low. And the worst consequence is that , the bacterial strains that acquire resistance to one or more first-line antimicrobials pose numerous challenges to healthcare, including: increased patient morbidity and mortality, increased drug costs, prolonged illness duration, and more expensive disease control measures. The overall take-home message from studies of resistant infections is that resistance levels have been worryingly high wherever studies have been conducted [3, 4]. Management of common and lethal bacterial infections has been critically compromised by the appearance and rapid spread of these antibiotic-resistant bacteria. This resistance is affecting patients and therapeutic outcomes, with concomitant economic consequences. Because the anti Microbial Resistance (AMR) genes can be readily transmitted through a bacterial population, surveillance of AMR trends is critical for the rapid detection of new isolates and continuous monitoring of disease prevalence [5]. Surveillance is central to the control of antimicrobial resistance. Data generated by surveillance activities can be used to guide empirical prescribing of antimicrobial agents, to detect newly emerging resistances, to determine priorities for research and to evaluate intervention strategies and potential control measures aimed at reducing the prevalence of resistant pathogens [6-10].

Antibiogram pattern with specific reference to MDR Organisms is increasingly reported in Indian hospitals [11-15] and worldwide [16-21]. Therefore it is crucial to monitor emerging trends in drug resistance at local level to support clinical decision making, infection control intervention and antimicrobial resistance containment strategies.Antibiogram surveillance and changing trends in antimicrobial resistance at our healthcare setting is monitored periodically by annual cumulative antibiogram.The cumulative antibiogram is done as per the consensus guidelines from CLSI[22]. This report provides an overview of surveillance information on multidrug resistant pathogens at our tertiary care centre for a five year period from 2008 to 2012, and also

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presents data on Sensitivity rates of these drug resistant pathogens, highlighting the probable effective pathogen-drug combinations for most common infections.

II. Materials and Methods

Our super speciality hospital is a 300 bedded tertiary care Post graduate teaching centre with CTVS, Cardiology, Urology, Ophthalmology and orthopaedic units. We analysed antibiogram surveillance reported during the five year period from Jan 2008 to December 2012.The following indices were monitored.

1. Prevalence rates: The number of MDR Organisms-MDR O (as a percentage of all specimens received by our Lab) was determined annually and analysed longitudinally for the five year period. Most of the clinical specimens were urine specimens and predominantly from Urology outpatient Unit. And we specifically looked for
   - Prevalence of ESBL *E.coli* & ESBL *Klebsiella pneumoniae*
   - MRSA Prevalence rate
   - Imipenem resistant *Pseudomonas*, ESBL *E.coli* & ESBL *Klebsiella*
2. Antibiogram: The sensitivity pattern as determined by Kirby bauer disc diffusion for all isolates from all clinical samples was used and interpretation of sensitivity was as per updated CLSI Guidelines (years 2007 to 2011).
3. We analysed the changing sensitivity pattern of most prevalent pathogens of Urinary tract infection , soft tissue infection, and Ventilation associated pneumonia (VAP) during the study period as defined by standard surveillance criteria[1,5].
4. We also analyzed the Antibiotic Sensitivity pattern of Imipenem resistant gram negative bacilli strain(*Pseudomonas aeruginosa*, ESBL *E.coli,* ESBL *Klebsiella pneumoniae*)
5. We documented modifications in the hospital infection control measures and Empirical antimicrobial Guideline was drafted following the Antibiogram Surveillance for Infections from specific bodily sites.

III. Our Hospital Antibiogram Software

Our Hospital cumulative Antibiogram is framed periodically using a Software (LIS) from CSC (previous iSOFT). The data entry and analysis is done by a report generator using this isoft software (based on WHONET 5.6). The generated report is based on consensus guidelines given by CLSI [22].

IV. Results

Table: 1a shows the most prevalent MDR-O at our tertiary care centre and which are *ESBL E.coli, ESBL K. pneumoniae* among Gram negative bacilli and *MRSA* among Gram positive cocci.

Table 1a : Prevalence rates of selected Multi Drug Resistant Pathogens

	ESBL *E.coli*	ESBL.*K. pneumoniae*	*MRSA*
2008	67.3%	61.5%	40.9%
2009	73%	55.5%	11.1%
2010	72.3%	63.5%	34.7%
2011	73%	64.5%	25%
2012	74%	61%	19.3%
Overall Prevalance %	**73%**	**61%**	**24.5%**

Table 1b shows the frequency of Imipenem resistance among selected Gram negative bacilli (*Pseudomonas, ESBL E.coli, ESBL Klebsiella pneumoniae*) at our tertiary care centre.

Table 1b : Percentage if Imipenem Resistance isolates among selected Gram negative bacilli

	ESBL *E.coli*	ESBL *Kleb. pneumoniae*	*Pseudomonas*
2008	1 isolate (1/372) 0.3%	0.00%	37 isolates(37/159) 23.3%
2009	14 isolates(14/527) 2.7%	1 isolate(1/50) 2%	40 isolates(40/166) 24%
2010	6 Isolates(6/440) 1.4%	5 isolates(5/171) 3%	15 isolates (15/128) 11.7%
2011	5 Isolates(5/397) 1.3%	3 Isolates)(3/71) 2.8 %	30 isolates(30/153) 19.6 %
2012	18 Isolates(18/759) 2.4%	8 Isolates (8/116) 6.7%	74 isolates(74/292) 25%
TOTAL	**44 Isolates(44/2496)1.7 %**	**17 isolates(17/359)4.7 %**	**196 isolates(196/899)22 %**

Fig-1: The most frequently isolated pathogen from the urine samples at our centre are ESBL *E.coli*, ESBL *Klebsiella pneumoniae* & *Pseudomonas spp*. The change in antibiotic sensitivity during the five year of all the above mentioned three Uropathogens are analysed in the Fig 1a,1b, and 1c.

Fig-1a shows change in Uropathogenic *E.coli* sensitivity pattern over the time frame for important groups of Antibiotics. Sensitivity to Ciprofloxacin remains constantly low at less than 20% throughout the study period.

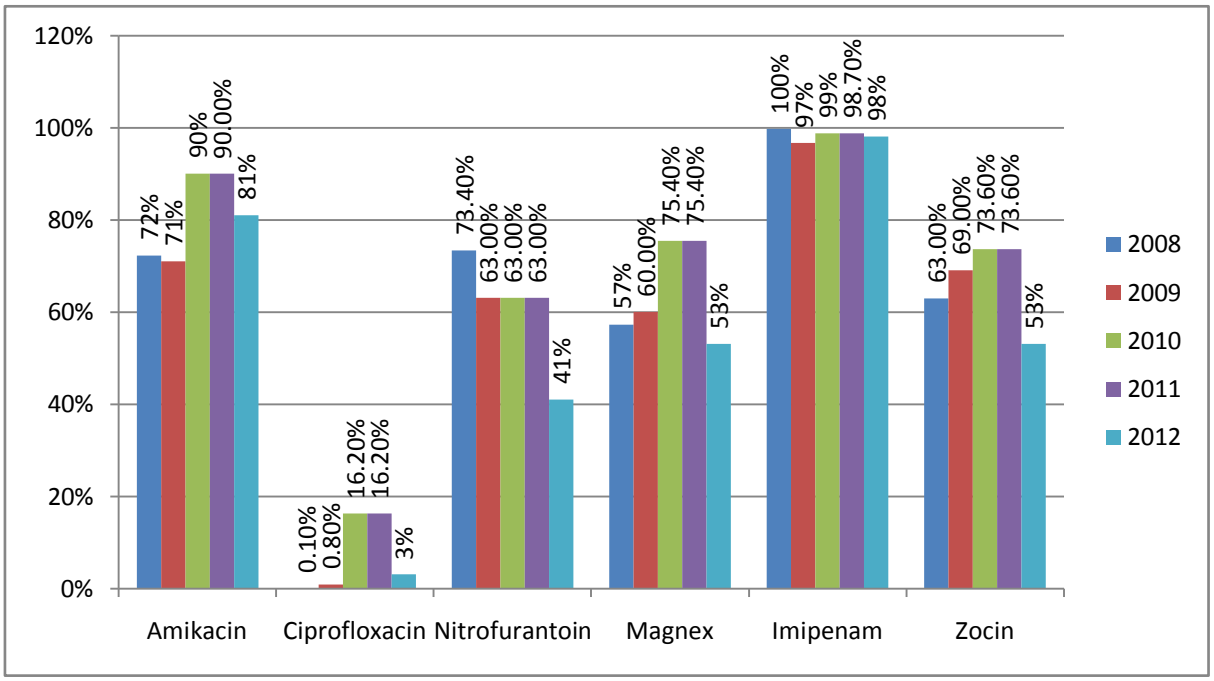


Fig 1 a : Antibiotics percentage sensitivity of ESBL E.coli isolates from urine

Fig-1b shows changes in Uropathogenic Esbl *Klebsiella pneumoniae* sensitivity pattern over time. Sensitivity to Ciprofloxacin and Nitrofurantoin remains constantly low at less than 20% throughout the study period.

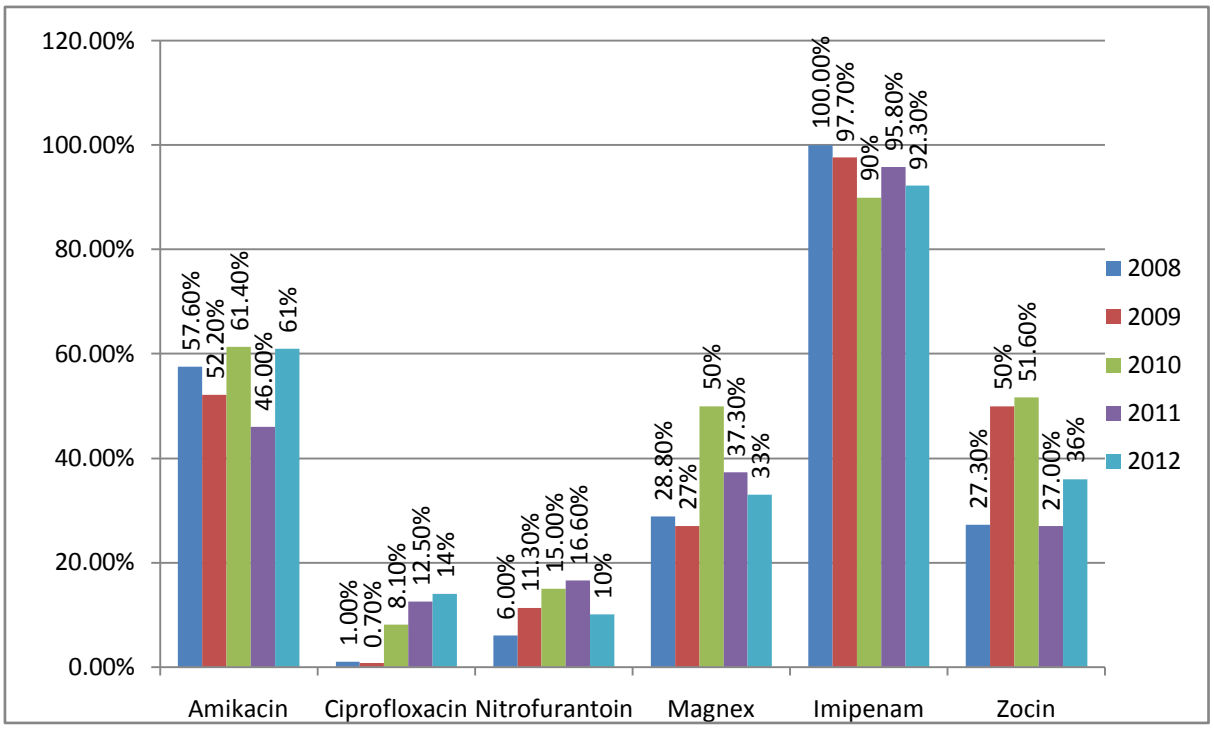


Fig-1c shows Uropathogenic *Pseudomonas spp* sensitivity pattern over time. Sensitivity to ciprofloxacin was at a range between 20-40% and Nitrofurantoin less than 10%

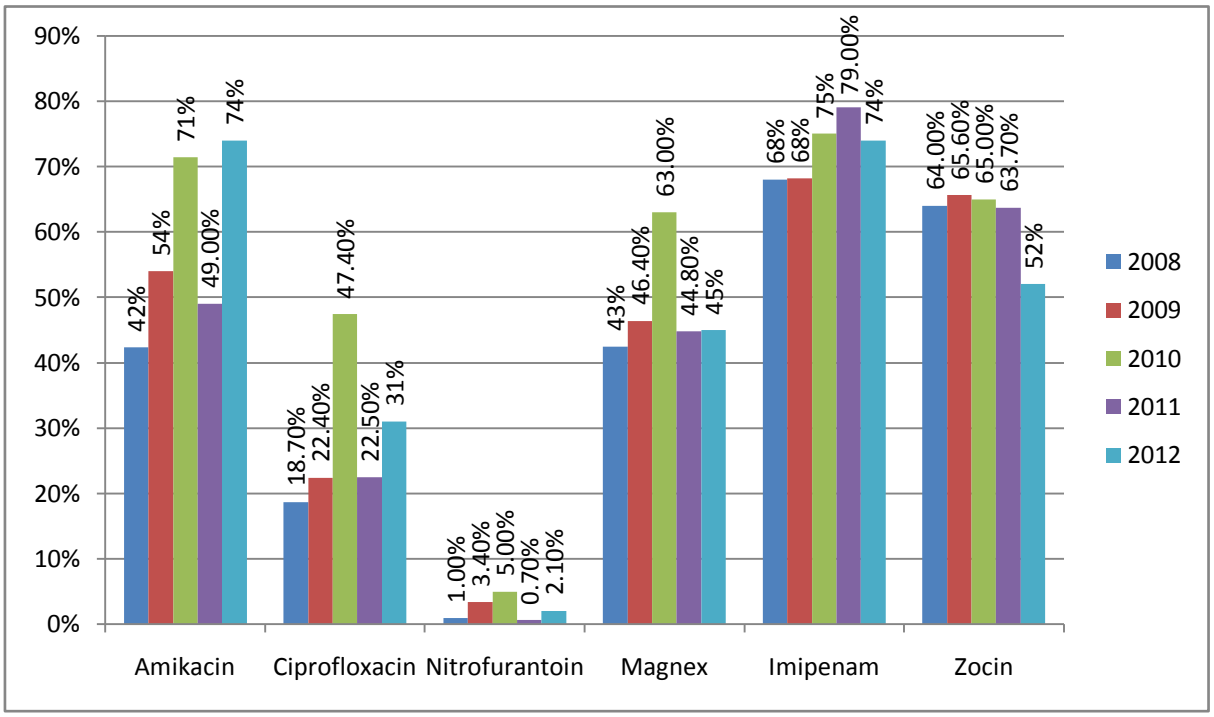


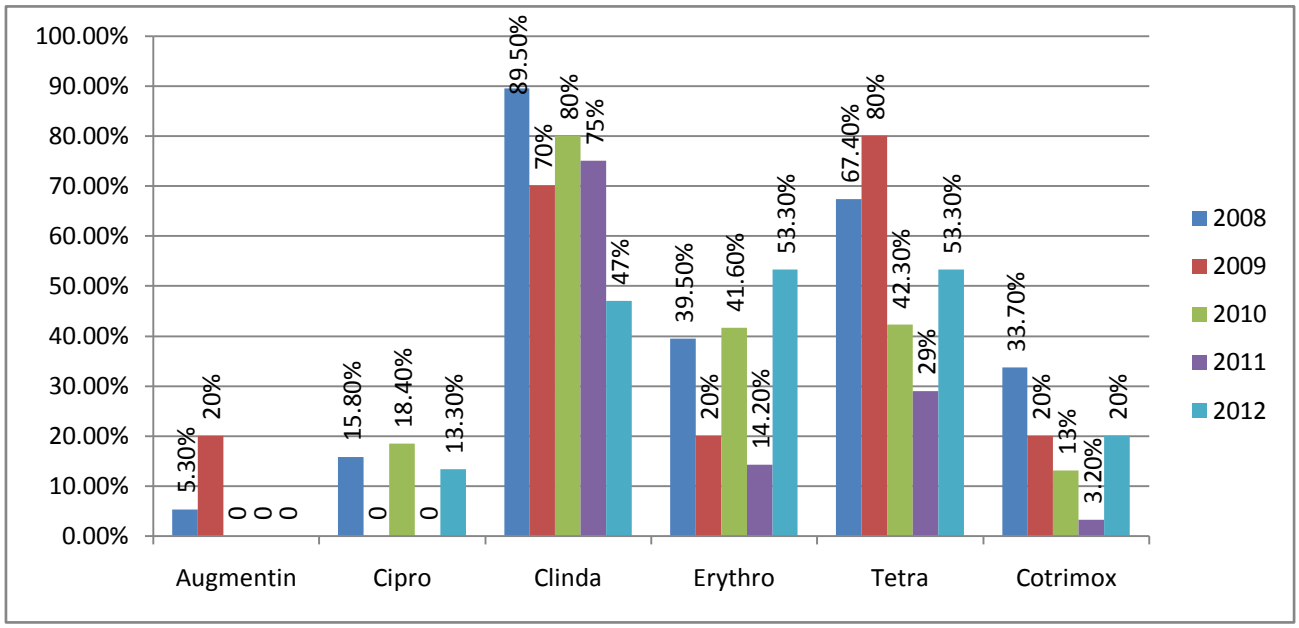
Fig 1c : Antibiotics percentage sensitivity of P.aeruginosa isolated from urine

Table: 2 represent the overall sensitivity rate of *MRSA* isolates from all types of clinical specimens to different class of Antibiotics. Of the Beta lactum groups, Penicillin showed 0% sensitivity throughout the study period.Ampicillin was less than 10% and Augmentin (betalactum+beta lactamase inhibitor) less than 20%

Table 2 : % Sensitivity pattern of MRSA against various antimicrobials

	Sensitivity Percentage				
	2008	2009	2010	2011	2012
Cipro floxacin	11.1	0	13.9	0	8
Ampi cillin	3.7	0	0	9	0
Augmentin	14.8	16.7	0	10	0
Tetra cycline	69.2	76	71.4	68.2	50
Co-Trimxazle	23	16.6	19.4	9	17
Imipenem	88	75	97.2	100	NT
Erythro mycin	42.8	20	48.5	38.1	41
Penicillin	0	0	0	0	0
Vanco mycin	100	100	100	100	96%
Linezolid	100	83.3	100	100	100
Rifampicin	96.3	100	100	100	82%
Clinda mycin	92.5	75	82.3	77.2	50%
Oxacillin	0	0	0	4.5	0
Nitro furantoin	83.3	66.6	NT	14.3	20

Fig-2 shows the changing sensitivity pattern of *MRSA* isolated from wound specimens (MRSA was most frequently isolated from Wound specimens). Augmentin & ciprofloxacin sensitivity percentage consistently declined and came down to 0% during the five year study period. Antibiotics with good sensitivity percentage for Clindamycin, Vancomycin, Linezolid.



**Linezolid 100% throughout the study period & Vancomycin 99.8 %*

Fig 2 : Antibiotic sensitivity % of MRSA from Pus swab/aspirates*

Fig-3: The most frequently isolated pathogen from endotracheal aspirate was *Pseudomonas aeruginosa*. The changing trends in sensitivity pattern of this pathogen in Endotracheal aspitates is shown in Fig-3

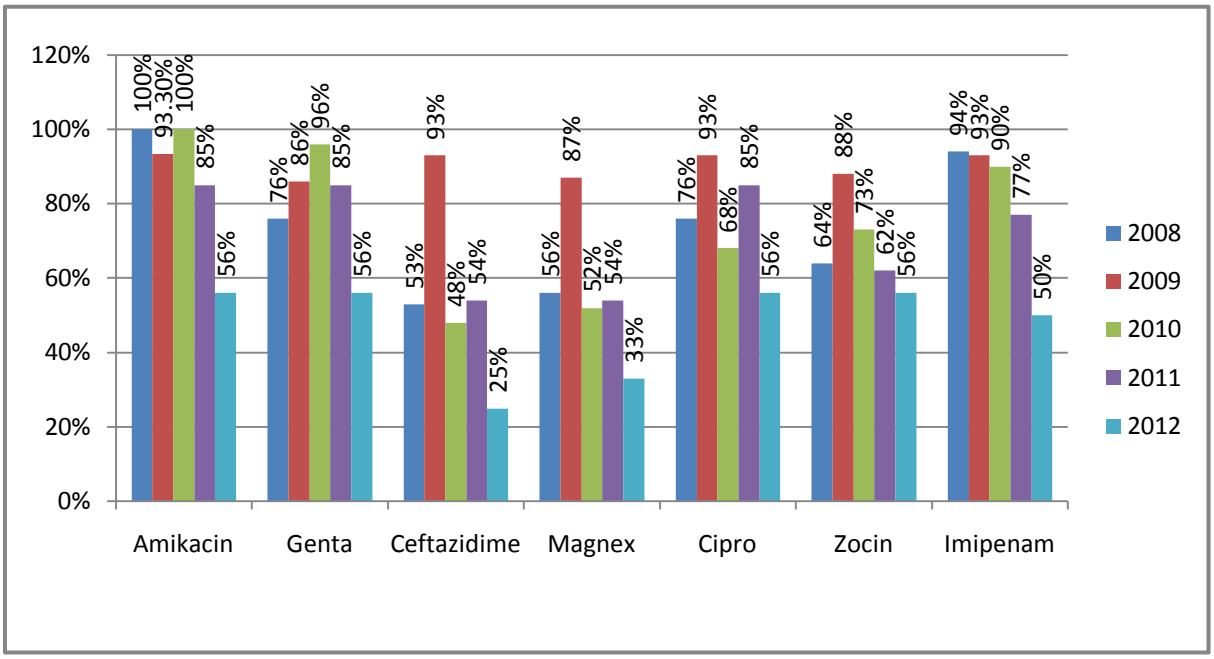


Fig 3 : Antibiotic sensitivity % of Pseudomonas from Endotracheal apirates

Table -3 shows Imipenem sensitivity percentage among selected Gram negative bacilli. Fig-4a & 4b shows Imipenem resistant Gram negative bacilli sensitive to other antibiotics.

Table 3 : Antibiotic Sensitivity pattern of Imipenem resistance strain

	Total no of Imipenem resistance isolates	% of Pan resistant isolates	% of Imipenem resistant isolates showing sensitivity to other antibiotics
ESBL *E.Coli*	44- isolates	47.60%	52.4%-Senitive to other antibiotics* fig -1
ESBL *Kleb. pneumoniae*	17 -isolates	83.30%	16.3%- Sensitive to Amikacin, Nitrofuratoin
Pseudomonas aeruginosa	196-Isolates	68.50%	31.5%- Sensitive to other antibiotics* fig-2

V. Discussion

a) Multi Drug Resistant Pathogens at our tertiary care centre

Our study shows that ESBL producers are the most prevalent Gram negative MDR organism at our tertiary care centre and MRSA is the most prevalent Gram positive pathogen as shown in the Table-1a. Urine samples are the predominantly received clinical sample for culture & sensitivity at our diagnostic microbiology division and the ESBL producers are frequently isolated from all types of Urine specimens submitted at our laboratory. ESBL production among *E.coli* was greater than 70% and *Klebsiella* greater than 60% throughout our study period. This data is consistent with many other centres from India & worldwide [23]. MRSA's are prevalent pathogen from wound specimens. The prevalence percentage of MRSA ranged from 11% - 40% during the study period at our Institute. Literature evidence indicates that the prevalence can range from 3-66% [24, 25] .The prevalence rate started to decline from 2010 in relation to enhanced hospital wide MRSA screening and contact isolation.

Imipenem resistant *Pseudomonas spp* was the next serious Gram negative MDR pathogen as shown in Table 1b.It shows an overall prevalence rate of 22 % during the five year study period. Even though there was a low prevalence rate of Imipenem resistance seen among ESBL *E.coli & ESBL Klebsiella* (1.7% and 4.7% respectively), it is still a matter of concern. And these three Imipenem resistant pathogens were frequently isolated from urine specimens (41% from mid stream urine, 44 % from catheterised urine). There was gradual increase in the prevalence rate of Imipenem Resistance among *ESBL E.Coli & ESBL Klebsiella* during this five year period from 2008 till 2012(Table-1b). But a gradual decrease in the Prevalence of *Pseudomonas* from 23.3% in 2008 to 19.6 % in 2011 and a sudden increase to 25% in 2012 was documented.

b) Analysis of Sensitivity pattern of ESBL Producers causing Urinary Tract Infection

Ciprofloxacin sensitivity percentage was very low at less than 15% for ESBL producers and at a range of 18-25% for *Pseudomonas spp* among the Urine specimens as shown in Fig 1a, 1b & 1c. This essentially rules out Fluoroquinolones as empiric antimicrobial therapy for Severe & Complicated urinary tract infections at our tertiary care centre.

Nitrofurantoin had a better sensitivity for ESBL *E.coli* at 63%, but a very low percentage for *Klebsiella* & *Pseudomonas* at less than 15% and 10% respectively. Hence a recommendation to use Nitrofurantoin as empiric therapy for Urinary tract infection was kept under reserve.

Carbapenam the drug of choice for ESBL producers showed 95% - 100% sensitivity in *E.coli* & *Klebsiella* UTI and 68-80 % in *Pseudomonas* infections. This emergence of Imipenem resistance among Gram negative UTI is a matter of concern and hence strict antibiotic policy was implemented for the use of Imipenem as empiric therapy for UTI. It was reserved only for clinically severe UTI like Pyelonephritis.

The Beta lactum + Betalactamase inhibitors combination like Magnex(cefaperazone & sulbactum) & Zocin (Pipericillin+ Tazobactum) showed a considerable sensitivity percentage for Esbl *E.coli* at 60-75% AND 73% respectively as shown in Fig-1a. But both the drugs had low percentage sensitivity for ESBL *Klebsiella pneumoniae* at 27%-50% as shown in Figure1b. *Pseudomonas spp* had good sensitivity pattern for Zocin at 65% when compared to Magnex which is around 45% -63%. Hence these two drugs remained useful against *E.coli* UT infection when compared to *Klebsiella & Pseudomonas.*

As the predominant pathogen causing UTIs, empiric treatment strategies generally target *E.coli*. Nitrofuratoin remains effective for *E.coli* isolates with 76% showing susceptibility. This is reassuring as 85% to 90% of all uncomplicated UTI infections are caused by *E. coli*. In brief, the overall better sensitivity pattern for all the three frequent pathogens causing UTI is noted with Amikacin & Imipenem. Amikacin was recommended for patients with good renal parameters. Since emerging resistance was noted with Imipenem, this was reserved for severe upper UTI with compromised renal parameters. Hence the urologists were left with Betalactum and betalactamase inhibitor combination like Magnex & Zocin. These drugs retains value as workhorse dry force , especially for less severely ill UTI and play a valuable role as Carbapenam sparer's in Antimicrobial stewardship programme. The following empiric guidelines were recommended for patients with UTI.

- For Uncomplicated UTI,Ciprofloxacin PLUS Nitrofurantoin

- Complicated UTI (related to instrumentation, ie. catheter, percutaneous nephrostomy (PCN), ureteral stent, and/or recurrent infection with the same organism) amikacin PLUS ciprofloxacin for outpatient OR amikacin q24h if patient can come daily to the hospital for therapy.
- For Pyelonephritis, Amikacin OR Imipenem OR Piperacillin/tazobactam 6'TH hourly. Recommended imaging of upper genitourinary tract with Ultrasound to look for hydronephrosis, obstructing stone, renal or perinephric abscess. To De-escalate to peroral therapy IF possible once fever has resolved.
- Other Infection control measures critical to limiting the spread of ESBL-producing organisms were also addressed (i.e.) Protocols to limit the use of indwelling Foley catheters and protocols for regular catheter changes when they are needed,

c) Analysis on MRSA sensitivity pattern (Most prevalent pathogen causing Soft tissue infection)

As discussed before the most prevalent Gram positive pathogen at our centre was MRSA and the prevalence rate ranged from 11% to 40%. Predominantly 79% of MRSA were from wound swabs, 13% from urine and 9% from Endo tracheal secretions & blood. The overall sensitive pattern of MRSA from all clinical isolate was analysed in TABLE-2. When we look into overall sensitivity pattern both in wards and OPD together, sensitivity to penicillin was Zero percent throughout our study period from 2008 to 2012.This is in accordance with a study by Bandaru etal [26]. Sensitivity to Ampicillin was lowest next to penicillin, followed by Ciprofloxacin, Cotrimoxazole and Erythromycin. Analysis of the changing pattern of Antibiotics for MRSA isolates for the five year period indicated that, the sensitivity percentage for all the above mentioned antibiotics was declining from 2008 to 2012.Ampicillin, Ciprofloxacin & Cotrimoxazole had less than 25 % sensitivity. Erythromycin and Tetracycline percentage was varying during this period. The sensitivity percentage of Clindamycin slowly declined from 92.5 % in 2008 to 50% in 2012 and Rifampicin to 82%.Linezolid had 100 % sensitivity.

In our study 60.5% of MRSA isolates were found to be multidrug resistant, to more than three antimicrobials which are similar to two other studies [25, 27]. Other studies which show less than 50% MDR resistant strains are Majumdar et al (23.2%) [28] And Bandaru et al [26] (32.09%).All the MRSA strains were sensitive to Vancomycin except one in the present study which is in accordance with other studies. [29-31]

Maximum MRSA positive wound specimens were from Ortho department (57%) followed by CTVS (20.4%) and then Plastic surgery (14 %) and Urology (10 %).Wound specimens sent from Orthopedics were predominantly from outpatient clinic. When the sensitivity percentage of MRSA's isolated from pus/ wound aspirates were analysed as shown in Fig-2, a better sensitivity pattern was observed for Erythromicin and ciprofloxacin during the study period. There was a fluctuation in Tetracycline & Cotrimoxazole sensitivity percentage. It consistently decreased to 29% and 3.2% respectively during the year 2011, but an improved sensitivity percentages was observed in 2012. Sensitivity to Clindamycin percentage reduced from 89 %(2008) to 49 % in 2012. Eighty seven percent of non hospitalized MRSA isolates were presumptively identified as CA-MRSA based on Clindamycin susceptibility- a surrogate marker of CA-MRSA. As a result, admission screening for MRSA colonization has been implemented in 2011 in addition to routine infection control measures.

Guidelines & empirical antimicrobial choice for soft tissue/wound infections from different source were recommended based on the above mentioned analysis along with adequate drainage/wound debridement/ cleaning.

- Simple Skin and Soft Tissue Abscess: For Outpatients, Doxycyline OR Clindamycin & For Inpatients, Vancomycin PLUS piperacillin/ tazobactam .
- Cellulitis: Outpatient therapy with clindamycin OR doxycycline
- Traumatic Wounds: Outpatients to start with Doxycycline PLUS Clindamycin PLUS consideration of Amikacin OR Gentamicin. Inpatient with Piperacillin/ tazobactam PLUS Vancomycin OR Ciprofloxacin PLUS Vancomycin .Therapy depends on severity and nature of wound. All wounds should receive adequate cleaning
- Prosthetic Joint Infections: Vancomycin AND Piperacillin/tazobactam OR Vancomycin AND Imipenem.
- PostOperativeSternotomy/SurgicalSiteInfection: VancomycinANDPiperacillin/tazobactam OR Vancomycin AND Imipenem pending cultures.

d) Analysis on sensitivity pattern of Pseudomonas aeruginosa (Most prevalent pathogen causing Ventilation associated Pneumonia)

The most prevalent pathogen from ETA was *Pseudomonas aeruginosa* throughout the study period. Analysis on changing sensitivity pattern of Pseudomonas is as shown in Fig-3. There was a fluctuation in sensitivity percentage of Aminoglycosides, ceftazidime, Beta lactum+ Beta lactum inhibitor combination like Magnex & Zocin till 2010.But the sensitivity percentage started to decline in 2011 and further more in 2012. Imipenem sensitivity alarmingly declined to 50% in 2012.The MDR % ranged more than 60% during this study period , which is low when compared to other studies [32].In a study by Koirala et al [33], *Pseudomonas* had Zero percent sensitivity to Ceftazidime, Amikacin at 22% and Gentamicin at 18%. Sensitivity to ciprofloxacin was at 19% which is very low when compared to our study. Overall ciprofloxacin & Zocin was showing

around 60% sensitivity rate when compared to other antibiotics as shown in FIG: 3.

Pipericillin-tazoactum, Ciprofloxacin, and Imipenem were proposed as empirical antimicrobial choice for patients diagnosed with clinical Ventilation associated pneumonia or Ventilation associated Tracheobronchitis at our centre. These empirical antibiotics were recommended to be given alone or in combination depending on severity of Patient's clinical condition and renal parameters. Also recommendations were made such that antibiotic therapy should be changed and deescalated based on Culture identification report and a specific antibiotic should be chosen based on sensitivity pattern. An Active Surveillance for VAP was also initiated as a measure of Hospital Infection control at our tertiary care centre.

e) Analysis on sensitivity pattern of Imipenem resistant Gram Negative Bacilli

In this study 83.3 % of ESBL *Klebsiella pneumoniae* isolates, 47.60% of ESBL *E.Coli* & 68.50% of *Pseudomonas* isolates were Pan resistant (Table-3). Among the Imipenem resistant *Pseudomonas* strains 21.7 % isolates were sensitive to Amikacin & Zocin (Pipericillin+Tazobactum) as shown in Fig-4a and among Imipenem resistant ESBL *E.coli*strains 33.3 % were sensitive to Nitrofurantoin & Magnex (Cefepe-razone+Sulbactum)as shown in Fig-4 b. This is almost similar to two other studies, Taneja et al[34] and Sasikala et al [35]where in the Imipenem resistant *Pseudomonas* strains had the best in vitro susceptibility to Amikacin and Pipericillin.

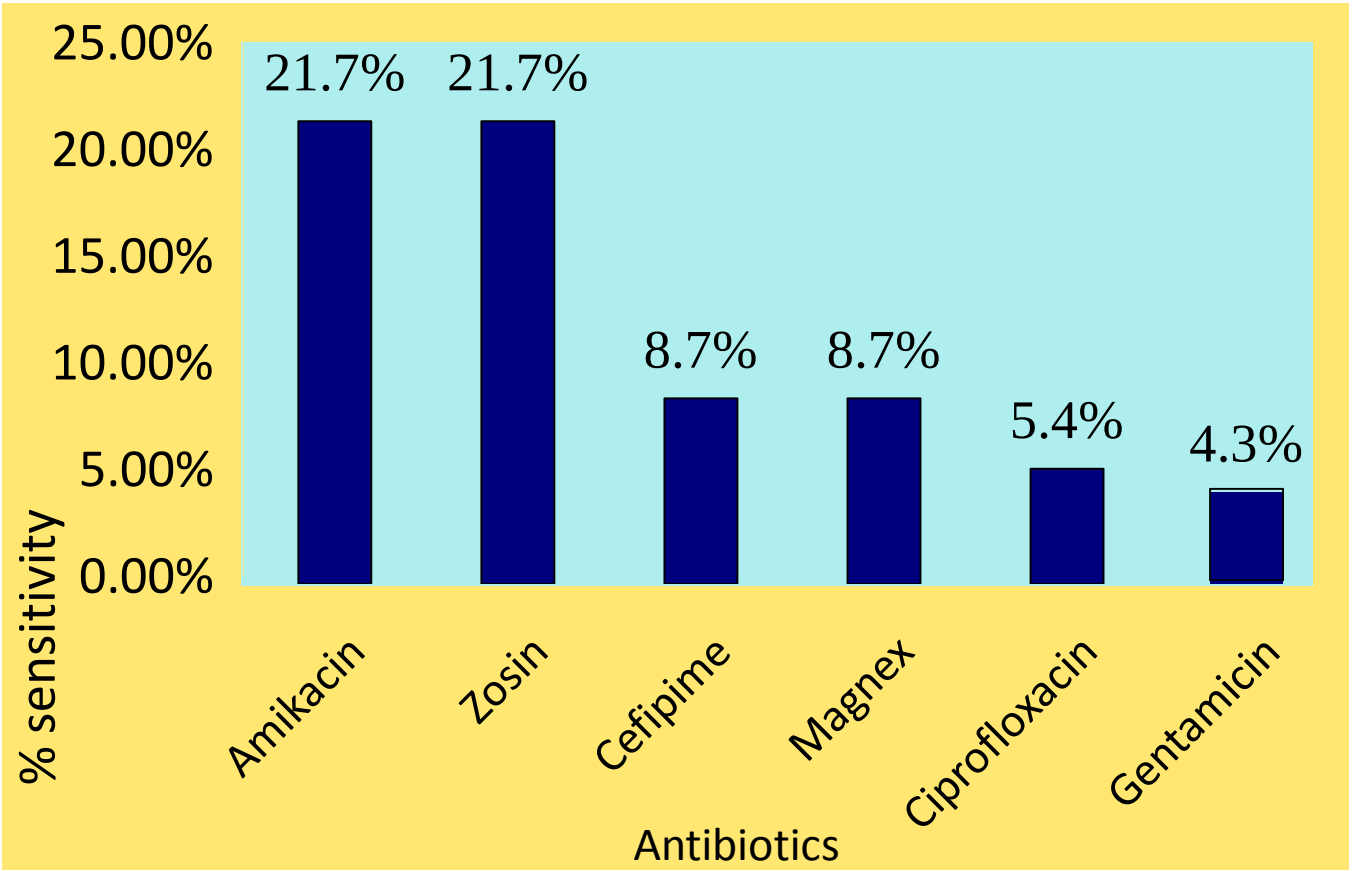


Figure 4 a : Imipenem resistant Gram negative bacilli sensitive to other antibiotics

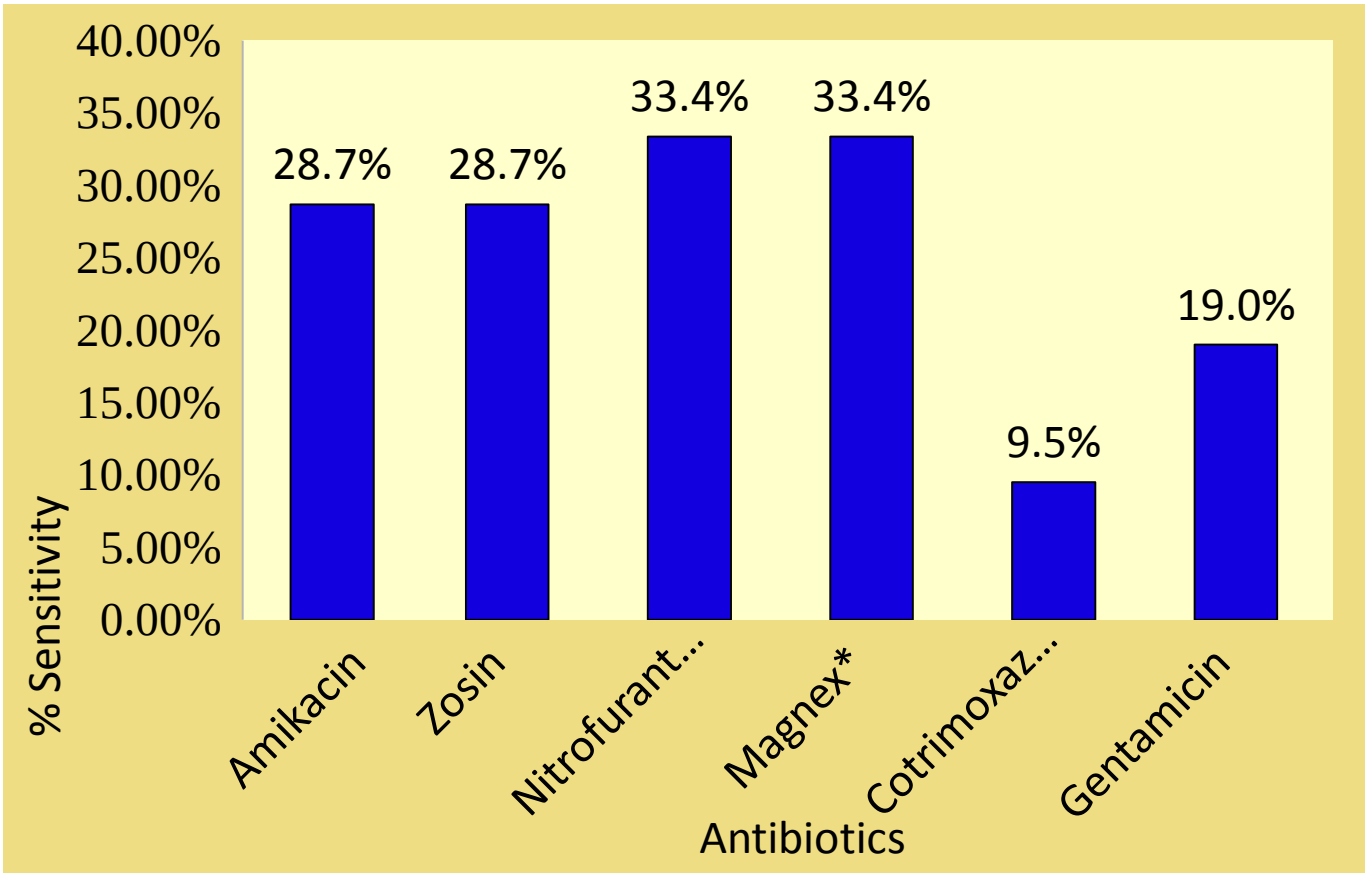


Figure 4 b : Imipenem resistant Gram negative bacilli sensitive to other antibiotics

VI. Conclusions

Our findings suggest that there is a definite increase in the multidrug resistant organisms. This Surveillance study showed that the most prevalent Multidrug resistant Uropathogen at our centre was ESBL producers (E.coli & *Klebsiella pneumoniae*). *MRSA* was the predominant MDRO causing soft tissue infections & *Pseudomonas* prevalent in VAP. We believe that the data analysis on the changing trends in antibiotic resistance from most frequently received clinical samples, is an important pillar in our efforts at improving infection control practices. We proposed a draft Antibiotic guideline in 2012 based on the analysis on the data. The guideline provided recommendations for empiric antimicrobial therapy based on susceptibility pattern and relevant infection control practices for Complicated & Uncomplicated UTI's, for soft tissue infections, VAP's and Blood stream infections. We acknowledge the limitation of disc diffusion antimicrobial susceptibility testing as our tertiary care centre is a charitable institution. Infection control measures including Hand hygiene, antimicrobial stewardship, MRSA screening and restricted use of second line antibiotics had proven to be modestly effective in our study. But still it appears that our MDR Organism antibiograms were largely uninfluenced by infection control measures including institution of Antimicrobial Guidelines in spite of our clinicians adhering to protocols. Probable reasons might be widespread prevalence rates in the community and importation of cases harbouring partially/untreated Multi drug resistant pathogens from other referral hospitals to our tertiary care centre may have negated efforts within our centre.

VII. Acknowledgements

1. Our Heartfelt thanks to Dr.Ramya Gopinath, Infectious Disease Consultant, Howard County General Hospital, Maryland, USA, for helping us draft our Institute's empirical antimicrobial Guideline.
2. We Acknowledge Mr.Ramprasad Gaddam, Senior Manager, and Mr.Kannan, HOD, Information Technology Department, SSSIHMS-PG, Puttaparthy, AP, India.

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