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RESEARCH ARTICLE
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ASSESSMENT OF VANCOMYCIN MIC CREEP PHENOMENON IN METHICILIN-RESISTANT STAPHYLOCOCCUS AUREUS ISOLATES IN A TERTIARY CARE HOSPITAL OF SURAT.

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ABSTRACT

Background: The "Methicillin-resistant *Staphylococcus aureus* (MRSA) is regarded as a major public health concern worldwide, as it is associated with severe infections, elevated mortality rates, and limited treatment options, particularly in healthcare settings."Vancomycin remains the primary therapeutic agent for MRSA infections; however, increasing concern has arisen regarding vancomycin treatment failures despite isolates falling within the susceptible range. This phenomenon, termed "MIC creep," refers to the gradual rise in vancomycin MICs over time and is associated with poorer clinical outcomes.

Methods: The current analysis was designed as cross sectional, retrospective, observational study over a three-year period, from January 2021 to December 2023. A total of 881 non-duplicate *Staphylococcus aureus* isolates resistant to methicillin (MRSA) were recovered from various clinical specimens, including blood, pus, wound swabs, tissue, and urine. Following the clinical and laboratory standards institute (CLSI) 2023 guidelines bacterial determination and antimicrobial susceptibility testing was performed. By employing the E-Test method vancomycin (MICs) were evaluated. Statistical analysis was done by using the annual trends in MIC values.

Results: Of the 881 MRSA isolates, the majority were from females (64.02%) with a mean age of 52.3 years. Wound swabs (51.31%) and surgical wards (35.30%) were the predominant sources. A gradual increase in vancomycin MIC values was observed from 2021 to 2023. Isolates with MIC ≤0.5 µg/mL decreased from 72.82% to 64.17%, while those with MIC ≥1.5 µg/mL increased from 6.16% to 7.82%. The arithmetic and geometric mean MICs rose significantly ($p < 0.0001$), confirming the presence of MIC creep.

Conclusion: The study demonstrates a statistically significant vancomycin MIC creep among MRSA isolates, underscoring the need for continued antimicrobial surveillance and judicious vancomycin use to prevent therapeutic failure.

KEYWORDS:- Vancomycin, Methicillin-resistant staphylococcus aureus (MRSA), Creep, minimum inhibitory concentration (MIC).

INTRODUCTION:-

MRSA is recognized as a significant severe pathogenic infection responsible for both hospital-acquired and community-acquired infections across the globe caused by Methicillin-Susceptible *S. aureus* (MSSA). [1-2] Data from The Surveillance Network (TSN), which gathers microbiological information from 300 laboratories in the United States, highlights the high prevalence of *S. aureus* infections in both inpatient (18.7%) and outpatient (14.7%) settings. [3-4] MRSA infections are associated with increased morbidity, the need for prolonged antibiotic treatment, longer hospital stays, and higher mortality rates.

Vancomycin a glycopeptide antibiotic, being the most widely used for serious MRSA infections. [5] However, there is growing concern about treatment failures with vancomycin, even when the bacterial isolates fall within the susceptible range based on standard testing. Numerous studies have demonstrated that an elevated MIC of vancomycin, even within the susceptible range, may negatively affect clinical outcomes in patients with MRSA bacteremia. [6-7] Specifically, higher vancomycin MIC values have been linked to persistent bacteremia and increased mortality rates.

A phenomenon known as “MIC creep” has been observed in various parts of the world. This refers to the gradual increase in the MIC of vancomycin against MRSA over time. For example, a study by Chang CNet al. identified a rise in vancomycin MICs among both MSSA and MRSA isolates over a five-year period, with MIC values increasing from less than 0.5 µg/mL to 1.0 µg/mL. [8-9] Additionally, the proportion of isolates with an MIC greater than 1 µg/mL increased markedly from 19% to 70.4% during the same time frame.

Recognizing the potential clinical implications of increased vancomycin MICs, both the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) addressed this issue in their clinical practice guidelines published in 2011 and 2016, respectively. [10]

Despite these findings, MIC creep is not a universally observed trend. For instance, larger surveillance programs such as the SENTRY antimicrobial surveillance program have not consistently demonstrated an upward shift in vancomycin MICs over time. [11] It is important to consider that these large-scale data collections involve multiple institutions with varying levels of vancomycin usage and methodological differences, which may dilute or mask localized increases in MIC values.

Nevertheless, when managing MRSA infections, it is essential to focus on the patient's clinical and microbiological response rather than relying solely on the MIC value. If there is evidence of clinical improvement and microbiological clearance, continuing treatment with vancomycin is considered appropriate for isolates with MIC values less than 2 µg/mL, which fall within the susceptible range.[12-13] "Thus, our present investigation aims to evaluated the vancomycin MIC creep phenomenon in MRSA isolated.

Methodology:-

Data were obtained from clinical specimens processed in the Department of Microbiology over a three-year period, for 2years. Purposive sampling was employed to include MRSA isolates derived from various clinical samples, such as blood, pus, wound swabs, tissue, urine, and collected from hospitalized patients.

To prevent duplication, only the first MRSA isolate from each patient was included in the analysis. The study encompassed 881 MRSA isolates, with the sample size calculated using the formula $4pq/L^2$. Clinical specimens were cultured on blood agar and incubated aerobically at 35–37°C for 24 hours. Preliminary identification of *Staphylococcus aureus* was based on colony morphology, Gram staining, and catalase testing, and was subsequently confirmed using coagulase tests. Methicillin resistance was determined phenotypically by the modified Kirby-Bauer disc diffusion method, employing 30 µg cefoxitin discs, and interpreted according to the CLSI 2023 guidelines.

MICs for vancomycin were assessed using E-test strips, with MIC interpretations also based on CLSI standards. The described protocol accurately reflects the standardized methodology for determining vancomycin MICs using the E-test (E-strip) method: a 0.5 McFarland inoculum

(~1×10^8 CFU/mL) is lawn-inoculated onto Mueller–Hinton agar, followed by placement of a vancomycin gradient strip. The plate is incubated aerobically at 35–37 °C for 18–24 hours, after which the MIC is visually read at the intersection of the inhibition ellipse with the strip's scale. Results are interpreted using CLSI breakpoints: MIC ≤ 2 µg/mL (susceptible), 4–8 µg/mL (intermediate), and ≥ 16 µg/mL (resistant). Quality control was maintained using MRSA ATCC 43300 and MSSA ATCC 29213 strains. Data collection spanned two months, followed by two months each for analysis and manuscript preparation, resulting in a total study duration of six months. Only MRSA isolates from accepted clinical samples were included, with specimens failing to meet laboratory acceptance criteria excluded from the study.

RESULT AND OBSERVATION

Table-1: Demographic Characteristics of Patients with MRSA Isolates (N = 881)

Variables	**No of cases**	**%**
Male	317	35.98%
Female	564	64.02%
Age (Mean ± SD)	52.3 ± 24.9	

A total of 881 MRSA isolates were included in the study. Among the patients, 317 (35.98%) were male and 564 (64.02%) were female. The mean age of the study population was 52.3 years with a standard deviation of ± 24.9.

Table-2: Distribution of MRSA Isolates by Specimen Source and Clinical Department (N = 881)

Specimen Source	Blood	144	16.35%
	Pus	205	23.27%
	Wound swab	452	51.31%
	Tissue	32	3.63%
	Urine	48	5.45%
Clinical Department	Medicine Ward	157	17.82%
	Surgical Ward	311	35.30%
	Pediatrics Ward	21	2.38%
	Obstetric and gynecological ward	77	8.74%
	Orthopedic Ward	164	18.62%
	All ICUs	98	11.12%
	OPD	53	6.02%

Among the 881 MRSA isolates, the most common specimen source was wound swab, accounting for 452 isolates (51.31%), followed by pus (205, 23.27%), blood (144, 16.35%), urine (48, 5.45%), and tissue (32, 3.63%). In terms of clinical departments, the highest number of isolates was from the surgical ward (311, 35.30%), followed by the orthopedic ward (164, 18.62%), medicine ward (157, 17.82%), obstetric and gynecological ward (77, 8.74%), ICUs (98, 11.12%), OPD (53, 6.02%), and pediatric ward (21, 2.38%).

Table-3: Year-wise Distribution of Vancomycin MIC Values Among MRSA Isolates (N = 881)

Year	**No. of Isolates**	**≤ 0.5 µg/mL**	**0.75 µg/mL**	**1 µg/mL**	**≥ 1.5 µg/mL**
2021	276	201 (72.82%)	15 (5.43%)	43 (15.58%)	17 (6.16%)
2022	298	204 (68.46%)	18 (6.04 %)	55 (18.46%)	21 (7.05%)
2023	307	197 (64.17%)	23 (7.49%)	63 (20.52%)	24 (7.82%)
Total	881	602 (68.33%)	56 (6.36%)	161 (18.27%)	62 (7.04%)

Over the three-year period, a gradual increase in vancomycin MIC values among MRSA isolates was observed. In 2021, 72.82% of isolates had MIC ≤0.5 µg/mL, which decreased to 64.17% by 2023. Conversely, isolates with MIC ≥1.5 µg/mL rose from 6.16% in 2021 to 7.82% in 2023. The proportion of isolates with intermediate MICs (1 µg/mL and 0.75 µg/mL) also showed a slight increase over time, indicating a subtle MIC creep trend.

Table-4: Year wise* MIC by E test and arithmetic/geometric Mean Tabulation.

Year	Total	MIC				
		0.5	0.75	1	1.5	2
		n (%)	n (%)	n (%)	n (%)	n (%)
2021	58	8 (13.79%)	10 (17.24%)	24 (41.38%)	13 (22.41%)	3 (5.17%)
2022	66	9 (13.64%)	11 (16.67%)	29 (43.94%)	14 (21.21%)	3 (4.55%)
2023	72	10 (13.89%)	12 (16.67%)	30 (41.67%)	15 (20.83%)	5 (6.94%)
Total	**196**	**27 (13.78%)**	**33 (16.84%)**	**83 (42.35%)**	**42 (21.43%)**	**11 (5.61%)**

A total of 196 MRSA isolates were analyzed year-wise for vancomycin MIC using the E-test method. In 2021 (n = 58), the most common MIC observed was 1 µg/mL in 24 isolates (41.38%), followed by 1.5 µg/mL in 13 isolates (22.41%), 0.75 µg/mL in 10 (17.24%), 0.5 µg/mL in 8 (13.79%), and 2 µg/mL in 3 (5.17%). In 2022 (n = 66), 29 isolates (43.94%) had an MIC of 1 µg/mL, followed by 14 (21.21%) with 1.5 µg/mL, 11 (16.67%) with 0.75 µg/mL, 9 (13.64%) with 0.5 µg/mL, and 3 (4.55%) with 2 µg/mL. Similarly, in 2023 (n = 72), the majority again showed MIC of 1 µg/mL in 30 isolates (41.67%), followed by 15 (20.83%) at 1.5 µg/mL, 12 (16.67%) at 0.75 µg/mL, 10 (13.89%) at 0.5 µg/mL, and 5 (6.94%) at 2 µg/mL. Overall, across the 3 years, 1 µg/mL was the most prevalent MIC (83 isolates, 42.35%), indicating a gradual upward shift in MIC values.

Table-5: Yearly MIC Mean Values and Statistical Significance in MRSA Isolates (2021–2023)

Arithmetic Mean ± SD	95% CI (Mean)	Geometric Mean ± SD
0.96 ± 0.34	0.91–1.02	0.85 ± 1.36
1.04 ± 0.38	0.98–1.10	0.98 ± 1.40
1.09 ± 0.35	1.03–1.15	1.33 ± 1.44
1.03 ± 0.36	1.00–1.07	0.97 ± 1.40
P-value	f-test=9.72, p<0.0001	f-test=9.28, p<0.0001

The mean MIC values showed a rising trend from 2021 to 2023. The arithmetic mean increased from 0.96 to 1.09, while the geometric mean rose from 0.85 to 1.33. This upward shift was statistically significant (f-test $p < 0.0001$), indicating the presence of MIC creep among MRSA isolates over the study period.

DISCUSSION:-

Globally, MRSA has been recognized as a significant public health threat. Vancomycin remains one of the primary therapeutic agents for the treatment of MRSA infections. However, the emergence of reduced susceptibility to vancomycin among MRSA strains has raised serious concerns over the past several decades, posing challenges to effective clinical management and infection control. [14]
The present study analyzed 881 MRSA isolates collected over a three-year period (2021–2023) to evaluate the demographic characteristics of affected patients, sources of specimens, clinical department distribution, and trends in vancomycin MIC. Female predominance (64.02%) was observed in the present study. Wound swabs were the most common specimen source (51.31%), followed by pus (23.27%) and blood (16.35%). Most MRSA isolates were obtained from the surgical ward (35.3%), with orthopedic (18.62%) and medicine wards (17.82%) also contributing significantly.

Specifically, the proportion of isolates with MIC ≤0.5 µg/mL declined from 72.82% in 2021 to 64.17% in 2023, while those with MIC ≥1.5 µg/mL rose from 6.16% to 7.82%. In the study by Arshad F. et al. (2016–2019), vancomycin MICs of 0.5 µg/mL and 0.75 µg/mL were exceptionally uncommon among MRSA isolates, indicating that most had MICs higher than these values. Conversely, a large multicenter investigation conducted across multiple U.S. medical centers from 2002 to 2006 found that MRSA isolates with vancomycin MIC values exceeding 1 µg/mL were rare, and there was no evidence of a rising MIC trend, challenging the hypothesis of an emerging vancomycin MIC creep. [14-16]

In the analysis done by the Kshetry A.O. et al. in Nepal, vancomycin MIC values for MRSA isolates ranged from 0.125 µg/mL to 1 µg/mL, demonstrating that the strains remained fully susceptible to vancomycin.Data from E-tests further showed that 1 µg/mL was the most frequently observed MIC across all three years. Additionally, both the arithmetic and geometric mean MIC values demonstrated a statistically significant upward trend ($p < 0.0001$). [13,15]

In the present investigation, a gradual increase in vancomycin MIC values was observed over the study period, indicating a trend of MIC creep.A study conducted by Cheema et al. reported that 71% of MRSA isolates exhibited a vancomycin minimum inhibitory concentration (MIC) of 2 µg/mL, while the remaining 29% had MIC values of 1 µg/mL. In contrast, findings from a study by Ejaz et al. demonstrated that all MRSA isolates were susceptible to vancomycin. [17-18]

The clinical significance of rising vancomycin MIC values within the susceptible range, known as the MIC creep phenomenon, has been highlighted in several studies, warning that even slight MIC increases below the breakpoint can lead to therapeutic failure. A study from Barcelona reported higher rates of treatment failure and mortality in MRSA bacteremia cases when vancomycin was used empirically for strains with MIC ≥1.5 µg/mL. [19-20]

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A study conducted by Arshad F. evaluated vancomycin MIC trends in MRSA isolates from 2016 to 2019. Prior to that, Aljohani S. et al. assessed vancomycin MIC values from 2013 to 2018. [14,16] However, no relevant studies were identified beyond 2019, highlighting a critical gap in recent data. The present study addresses this gap by analyzing vancomycin MIC trends from 2021 to 2023.

CONCLUSION:-

The study demonstrates a statistically significant upward trend in vancomycin MIC values among MRSA isolates from 2021 to 2023, indicating a clear MIC creep phenomenon. Although the MIC values remained within the susceptible range, the gradual increase, reflected in both arithmetic and geometric means, raises concern for potential therapeutic failure. This highlights the need for continuous antimicrobial surveillance and cautious use of vancomycin in clinical settings.

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