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RESEARCH ARTICLE

INCIDENCE OF INDUCIBLE CLINDAMYCIN RESISTANCE IN CLINICAL ISOLATES OF STAPHYLOCOCCI AND THEIR ANTIBIOTIC SENSITIVITY PATTERN.

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Abstract

The grassland resource could be better managed if the effect of different defoliation regimes on the amount of the dry matter and nutritive value was known. Consequently, 9 accessions of Andropogon gayanus Kunth were evaluated in south region of Benin with an average 1100 mm annual rainfall during 3 years for ley pasture without any fertiliser input. Three cutting regimes (3-10-3, 5-6-5 and 6-4-6-week) were tested for dry matter production (DM), crude protein (CP) content, CP production and mineral (Ca, Mg, P, K, Na, Zn, Mn, Cu and Co) contents. Significant differences were observed between accessions ($p<0.05$), cutting regimes ($p<0.05$) and years ($p<0.05$) for DM and CP production. Accession and cutting regime influenced significantly CP content ($p<0.05$) but year had no influence. Forage harvested from 3-10-3-week regime produced significantly ($p<0.05$) more DM (4742 kg $DMha^{-1}$) than 5-6-5-week (3635 kg $DMha^{-1}$) or 6-4-6-week cutting regime (3789 kg $DMha^{-1}$). But the reverse effect was observed for CP content as 3-10-3-week regime (5.68 gkg^{-1} DM) had significantly ($p<0.05$) lower CP than those of 5-6-5-week (8.55 gkg^{-1} DM) or 6-4-6-week cutting regimes (7.15 gkg^{-1} DM). Mineral concentrations varied between accessions but not by cutting regimes and years. Three accessions (n° 1, 4 and 5) consistently outproduced than others and can be harvested through 5-6-5-week cutting regime. P, Na, Zn and Cu deficiencies were the most common detected in the cropped forages.

Introduction:-

Methicillin Resistant *Staphylococcus aureus* (MRSA) and Methicillin Resistant Coagulase Negative Staphylococci (MRCoNS) are prevalent worldwide and are an important cause of nosocomial infection resulting in increased morbidity, mortality, length of hospital stay, and health care costs. [1]

Coagulase-Negative Staphylococci (CoNS) represent a group of opportunistic microorganisms that are common inducing agents of bacteraemias and other hospital infections, particularly in the patients with medical implants (

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central and peripheral venous catheters, valvular prostheses, artificial heart valves, pacemaker and orthopedic prosthesis), as well as in immunocompromised subjects. [2]

Methicillin resistance in *Staphylococcus aureus* and MRCoNS is due to the expression of the penicillin binding protein 2a (PBP2a), which is a transpeptidase with a low affinity for β-lactams, encoded by the *mecA* gene. The mobile genetic element, the staphylococcal cassette chromosome (SCCmec), is responsible for transmission of the *mec* genes determining the resistance to methicillin and almost all β-lactam antibiotics. The horizontal transmission of the resistance genes from MRCoNS onto *Staphylococcus aureus* has been confirmed, contributing significantly to the development of methicillin-resistant *Staphylococcus aureus.* [2]

The increasing prevalence of methicillin resistance among *Staphylococci* is an increasing problem. This had led to renewed interest in the usage of Macrolide-Lincosamide-Streptogramin B (MLS_B) antibiotic to treat *S. aureus* infections with Clindamycin being the preferred agent due to its excellent pharmacokinetic properties.[3]

However, widespread use of MLS_B antibiotics has led to an increase in the number of Staphylococcal strains acquiring resistance to MLS_B antibiotics. Strains with inducible resistance to Clindamycin are difficult to detect in the routine laboratory as they appear erythromycin-resistant and Clindamycin sensitive in *vitro* when not placed adjacent to each other. In such cases, in *vivo* therapy with Clindamycin may select mutants leading to clinical therapeutic failure.[3] Most common mechanism for such resistance is target site modification mediated by *ern* gene which can be expressed either constitutively (constitutive MLS_B phenotypes) or inducible (inducible MLS_B phenotype).[4-8] Clinical and Laboratory Standard Institute recommends the double disk diffusion test (D-test) to detect the presence of phenotypic inducible Clindamycin resistance.[9]

The presence study was undertaken to find the incidence of inducible clindamycin resistance using D-test amongst clinical isolates of *Staphylococcus aureus and* Coagulase-negative staphylococcus and to know there antibiotic sensitivity pattern.

Material and methods:-

After the permission from institutional ethical committee, present study was conducted at Department of Microbiology. A total of 368 non repetitive *Staphylococcus aureus* isolates form various clinical specimens like pus, blood, body fluids, sputum, and urine were included in the study.

Isolation and Identification of Staphylococcus[9]:

Culture and microscopy :

All samples were inoculated on Blood agar and MacConkey's agar. The plates were incubated at 37^{o} C in for 18 hours and staphylococcus was identified by standard bacteriological procedures like grams staining, colony characters and biochemical testing.

Identification of Staphylococcus aureus and Coagulase Negative Staphylococci (CoNS) [9]

All staphylococci were subjected first to slide and tube coagulase test and manitol fermentation on manitol salt agar (MSA). A isolate was labeled as S. aureus if positive for slide and/or tube coagulase positive and manitol fermenting (yellow colonies on MSA). Isolate with negative coagulase test and maintol non fermenting (Pink colonies on MSA) was labeled as coagulase negative staphylococci.

Detection of Methicillin resistance in S. aureus and Coagulase Negative Staphylococci.

Methicillin resistance was detected by performing cefoxitin disc diffusion test as per CLSI 2016 guidelines. For this a 30 µg cefoxitin disc was placed on Muller Hinton agar (MHA) inoculated with the staphylococcus isolate. A isolate was considered as MRSA if it was resistant to cefoxitin i.e. having a zone of inhibition of ≤ 21 mm diameter and MRCoNS if having a zone of inhibition of ≤ 24 mm diameter.[10]

Detection of Inducible Clindamycin resistance: **D-test[11]**

All MRSA and MRCoNS isolates exhibiting erythromycin resistance and clindamycin susceptibility on primary antibiotic susceptibility testing were further subjected to D-test, to detect inducible clindamycin resistance.

D-test:
For this Erythromycin (15µg) disc was placed at a distance of 15 mm (edge to edge) from Clindamycin (2 µg) disc on Mueller Hinton agar plate previously inoculated with 0.5 McFarland suspension of the isolate and incubated at 37^{o}C for 16 to18 hrs.

Three different phenotypes were appreciated.

1. MS Phenotype- Staphylococci isolates exhibiting resistance to erythromycin (Zone size <13mm) while susceptible to clindamycin (zone size > 21mm) and giving a circular zone of inhibition around Clindamycin were labelled as having this phenotype.
2. Inducible MLSB(iMLSB) Phenotype - Staphylococcal isolates showing resistance to erythromycin (zone size ≤13 mm) while being susceptible to clindamycin (zone size ≥21 mm) and giving a D shaped zone of inhibition around clindamycin with flattening towards erythromycin disc were labelled as having this phenotype.
3. Constitutive MLSB (cMLSB) Phenotype - this phenotype was labelled for those staphylococcal isolates which showed resistance to both erythromycin (zone size ≤13 mm) and clindamycin (zone size ≤14 mm) with a circular shape of zone of inhibition if any around clindamycin.

Antibiotic Sensitivity Testing:
All MRSA and MRCoNS isolates were also subjected to antibiotic susceptibility testing by Kirby Bauer's disc diffusion methods. The antibiotics tested were Gentamycin -30µg (GEN), Norfloxacin-10µg (NX),Tetracycline-30µg (TE),Teicoplanin-30µg (TEI), Linezolid-30µg (LZ), Co-trimoxazole-25µg (COT), Clindamycin-2 µg (CD), Erythromycin15µg (E).[10]

Quality control:
For AST testing *Staphylococcus aureus* ATCC-25923was used for quality control. For D test ATCC BAA-977 was used as the positive control for iMLSB.

Results:
A total of 368 isolates of Staphylococci from various clinical samples were included in the present study. The clinical samples were Pus 117, Blood 158, Urine 30, Sputum 20, ET secretion 20, CSF 5, Body Fluid 18.

Table 1:-Distribution of Methicillin Resistance in Staphylococci

Methicillin Resistance	**Number of isolates**
MRSA	79 (21.46%)
MSSA	93 (25.27%)
MRCoNS	147 (39.94%)
MSCoNS	49 (13.31%)
Total	368

Out of the total 368 Staphylococci isolates included in this study 79 isolates were MRSA. Thus the incidence of MRSA in the present study was 21.46 %. While 147 isolates were MRCoNS giving an incidence of 39.94 % respectively. The total incidence of methicillin resistance in Staphylococci is 61.41% i.e 226 isolates out 368.

Table 2:-Erythromycin-Clindamycin Sensitivity pattern for MRSA & MRCoNS

	MRSA	**MRCoNS**	**TOTAL**
E Resistant & CD Sensitive	40 (50.63%)	104 (70.74%)	144 (63.71%)
E Sensitive & CD Sensitive	36 (45.56%)	40 (27.21%)	76 (33.62%)
E Resistant & CD Resistant	03 (3.79%)	03 (2.04%)	06 (2.65%)
TOTAL	79 (34.95%)	147 (65.04%)	226 (61.41%)

In the present study the total number of MRSA and MRCoNS were 226. Amongst these the total number of staphylococci which were erythromycin resistance and clindamycin sensitive were 144. These included 40 MRSA and 104 MRCoNS. The number of isolate which were erythromycin sensitive & Clindamycin sensitive were 76. Of

these 36 were MRSA and 40 MRCoNS. There were 6 isolates which were Erythromycin resistance and Clindamycin resistant. Of these 3 isolates were MRSA and 3 were MRCoNS.

Table 3:-MRSA & MRCoNS resistant phenotypes on D test

Staphylococci	MS phenotypic	iMLSB	cMLSB	TOTAL
MRSA	08 (20%)	26 (65%)	06 (15%)	40 (27.77%)
MRCoNS	56 (53.84%)	18 (17.30%)	30 (28.84%)	104 (72.22%)
TOTAL	64 (44.44%)	44 (30.55%)	36 (25%)	144 (63.71%)

For the 40 MRSA isolates the incidence of iMLSB phenotype, cMLSB phenotype was 8 (20%), 26 (65%), 6 (15%) respectively. For the 104 isolates of MRCoNS the incidence of MS phenotype, iMLSB phenotype, cMLSB phenotype was 56 (53.84%), 18 (17.30%), 30 (28.84%) respectively.

Table 4:-AST pattern of MRSA isolates

Antibiotics	MRSA (n=79)		
	Sensitive	Intermediate	Resistant
GEN	57 (72.15%)	3 (3.79%)	19 (24.05%)
NX	26 (32.91%)	9 (11.39%)	44 (55.69%)
TE	52 (65.82%)	0 (0.0%)	27 (34.17%)
TEI	55 (69.62%)	4 (5.06%)	20 (25.31%)
LZ	66 (83.54%)	0 (0%)	13 (16.45%)
COT	40 (50.63%)	4 (5.06%)	35 (44.30%)
E	36 (45.56%)	0 (0%)	43 (54.43%)
CD	40 (50.63%)	0 (0%)	39 (49.36%)

The AST pattern of 79 MRSA isolates in the present study showed the highest sensitivity of 83.59 % to Linezolid followed by 72.15 % to Gentamycin. The least sensitivity was for Norfloxacin (32.91%). For teicoplanin, erythromycin and co-trimoxazole there was moderate sensitivity of 69.62%, 45.56%, and 50.63% respectively.

Table 5:-AST pattern of MRCoNS isolates

Antibiotics	MRCoNS (n=147)		
	Sensitive	Intermediate	Resistant
GEN	92 (62.58%)	10 (6.80%)	45 (30.61%)
NX	58 (39.45%)	18 (12.24%)	71 (48.29%)
TE	86 (58.50%)	01 (0.68%)	60 (40.81%)
TEI	93 (63.26%)	11 (7.48%)	43 (29.25%)
LZ	118(80.27%)	0 (0.0%)	29 (19.72%)
COT	49 (33.33%)	04 (2.72%)	94 (63.94%)
E	40 (27.21%)	0 (0%)	107(72.78%)
CD	144(97.05%)	0 (0%)	03 (2.04%)

For 147 isolates of MRCoNS the AST pattern showed the best sensitivity for Clindamycin (97.95%) followed by Linezolid (80.27%). Teicoplanin and Gentamycin gave a similar sensitivity of 63.26 % and 62.58 % respectively. For norfloxacin and co-trimoxazole was 39.45% and 33.33%respectively. Least sensitivity of 27.21 % was for erythromycin.

Table 6:-Antibiotics susceptibility percentage for all phenotypes

Antibiotics	MRSA			MRCONS		
	iMLSB	MS phenotype	cMLSB	iMLSB	MS phenotype	cMLSB
GEN	18 (69.23%)	4 (50%)	4 (66.66%)	14 (77.77%)	36 (64.28%)	18 (60%)
NX	18 (69.23%)	6 (75%)	0 (0%)	10 (55.55%)	22 (39.28%)	14 (46.66%)
TE	14 (53.84%)	6 (75%)	2 (33.33%)	04 (22.22%)	32 (57.14%)	14 (46.66%)

TEI	08 (30.76%)	2 (25%)	6 (100%)	06 (33.33%)	30 (53.57%)	16 (53.33%)
LZ	20 (76.92%)	2 (25%)	4 (66.66%)	16 (88.88%)	50 (89.28%)	22 (73.33%)
COT	12 (46.15%)	2 (25%)	4 (66.66%)	04 (22.22%)	08 (14.28%)	16 (53.33%)

If the AST pattern for the MRSA isolates only having the iMLSB phenotype is studied the best sensitivity is for Linezolid (76.92%) followed by 69.23 % for Gentamycin as well as Norfloxacin. Least sensitivity of 30.76 % was for Teicoplanin. If the sensitivity of only iMLSB MRCoNS is studied the best sensitivity was for Linezolid (88.88%) followed by Gentamycin (77.77%). Least sensitivity of 22.22 % was seen for Tetracycline as well as for Co-trimoxazole.

For MS phenotype in MRSA isolates the best sensitivity was for tetracycline and norfloxacin of 75 % followed by gentamycin (50%). Linezolid, teicoplanin and co-trimoxazole had a similar sensitivity of 25 %. For MRCoNS with MS phenotype linezolid was with highest sensitivity of 89.28 % followed by 64.28 % for Gentamycin, tetracycline and teicoplanin had a showed a decent sensitivity of 57.14 % and 53.57 % respectively. Co-trimoxazole was least sensitive with 14.28%.

The AST pattern of MRSA isolates with cMLSB phenotype showed 100 % sensitive to teicoplanin. The next best sensitivity was of 66.66 % for gentamycin, linezolid and co-trimoxazole not isolates were sensitive to norfloxacin. For MRCoNS having cMLSB phenotype the highest sensitive of 73.33 % was for linezolid followed by gentamycin 60 % other antibiotics had a decent sensitivity from 46 % to 53 %.

Discussion:-

The increasing prevalence of methicillin resistance among staphylococci is an increasing problem[13] Macrolide lincosamide-streptogramin B (MLSB) family of antibiotics is a choice of treatment of staphylococcal infection strains. [14] Clindamycin is frequently used to treat skin & soft tissue infections because of good oral bioavailability, low cost, excellent penetration and the fact that it accumulates in abscesses.[15] There is concern about the use of these antibiotics in the presence of erythromycin resistance because of the possibility of induction of cross resistance among members of the MLSB phenotype. [16]

Inducible MLSB resistance is not recognized by using standard susceptibility test methods. The strains appear resistance to erythromycin and sensitive to clindamycin by routine susceptibility testing. In such cases in vivo therapy with clindamycin will lead to clinical therapeutic failure.[17,18] Clinical and Laboratory Standards Institute (CLSI) recommends routine testing of all Staphylococcal isolates for iMLSB by D Test. [11]
The incidence of MRSA in the present study of 21.46% is similar to the study by Abhishek M et al from Uttar Pradesh India of 20%.[19] Among foreign study Ratna et al from Nepal has reported a higher incidence of 41%. [20] Similarly Eman M et al has also reported a incidence of 21.05% from Egypt. [21] In the present study incidence of MRCoNS was 39.94%. This is similar to study of Khadri H et al from Saudi Arabia who has reported a incidence of (39.4%).[22]

For MRSA isolates in the present study the incidence of iMLSB was 65 % i.e. 26 isolates out of 40 MRSA isolates. Thus if the D test is not included in routine testing for detection of iMLSB phenotype these isolates will be reported as clindamycin susceptible and would have resulted in therapeutic failure with MLSB antibiotics. The incidence of iMLSB in the present study of 65% is similar to the study by Angel et al from Vellore India of 64%.[23] Among foreign study Fasih N et al from Pakistan has retorted a higher incidence of iMLSB phenotype of 70%.[24] Similarly Mshana et al has also reported a incidence of 61.5% from Tanzania. [25] For MRCoNS the incidence of iMLSB was found to be 17.30 %. I.e. 18 out of 104 isolates. The incidence of 17.30% in the present study is similar to a study from Brazil by Leandro R et al of 18.5%.[12] From India Angle et al has reported a incidence of 10%, Eman et al from Egypt has reported a incidence of of 2.99%.[23,21]

Amongst the MRSA isolates the incidence cMLSB phenotypes on D testing in the present studies is 15 % i.e. 06 isolates. But there were 3 isolates which were cMLSB on the primary antibiotic testing. It has been proposed that isolates showing resistance to both erythromycin and clindamycin are constitutive types of MLSB resistance. [20] Thus the total constitutive resistance in the present study is 22.55% i.e. 9 isolates. Our finding is similar to the findings of Lyall KS et al from Punjab who has reported an incidence of 22.1% for cMLSB phenotype. [26] Similarly for

MRCoNS There were 3 isolates with cMLSB types of resistance on the primary antibiotic testing. On adding these 3 to the 30 cMLSB on D testing the true incidence of cMLSB amongst MRCoNS would be 31.73%. Level of constitutive resistance depends on the use of clindamycin in a particular setup. Over use of the drug may lead to development of constitutive mutants during therapy.[21]

For the present study the incidence of MS phenotype for MRSA isolates was 20% i.e 8 out of 40 isolates. For MRCoNS it was 53.84% i.e 56 out of 104 isolates. These MS phenotype isolates indicate true sensitivity to clindamycin and there for clindamycin can be used for treatment of infection with such isolates. With a combined sensitivity of 44.44% for MRSA and MRCoNS clindamycin definitely has a role in treatment of staphylococcal infections empirically. The finding of 20% MS phenotype for MRSA in the present study correlates well with the studies of 19.31% by Jadhav S et al from Pune and 22.8% by Lall M et al Pune. [27,15]

In the present study for MRSA incidence of iMLSB was more than the incidence of cMLSB and MS phenotypes. For MRSA the incidence of iMLSB being more than cMLSB is similar to the finding of study by Lall M et al al. [15] However Yilmaz etal have reported a higher incidence of cMLSB than iMLSB.[13] For MRCoNS in the present study the incidence of cMLSB was more as compared iMLSB. Similar was the findings for studies of Angle et al al and Eman et al al.[23,21]

In the present study iMLSB was more frequent in MRSA (65%) than in MRCoNS (17.30%). Similar were the findings of the study by Eman et al 2017 who has reported a incidence of 13.46% for MRSA and 2.99% for MRCoNS. [21] Similar higher iMLSB incidence was reported by Angle et al for MRSA 64% as to 10% for MRCoNS. [24]However in a study by Yilmaz G et al the iMLSB incidence was slightly more for MRCoNS (25.7%) than in MRSA isolates (24.4%).[13] Incidence of MS phenotype in our study is more in MRCoNS than in MRSA and is similar to the findings in studies of Yilmaz G et al, Angle et al and Eman et al.[13,23,21] The incidence of cMLSB was more in MRCoNS then in MRSA. In a study by Eman et al 2017 who reported cMLSB type of resistance of 42.31% for MRSA and 47.76% for MRCoNS. [22] In another study by Date et al 2012 who found cMLSB to be more frequent in MRSA (52.63%) than MRCoNS (78.95%).[28]

AST pattern for MRSA isolates is shows the best sensitivity for linezolid of 83.54 %, followed by Gentamycin 72.15 %. A 100% sensitivity for linezolid was reported by Shetty J et al, Bansal et al.[29,30]Hatkar et al has reported a sensitivity of 73.86 %.[31] Pai et al has reported a sensitivity of about 40% for gentamycin, which is less as compared to our study. [32] For clindamycin sensitivity was 50.63% i.e. 40 out of 79 isolates. From the result of the D test it is evident that of these 40 isolates, 26 isolates were iMLSB and 6 were cMLSB and thus should be considered clindamycin resistant or may lead to therapeutic failure, Thus the true effective sensitivity would be only 8 isolates i.e. 20 %. These are the MS phenotype isolates.

For MRCoNS highest sensitive was for clindamycin 97.05 % followed by linezolid 80.27 %. But for clindamycin after doing the D test there were 18 iMLSB and 30 cMLSB resistance phenotypes identified. If this result of D test is taken into consideration the true effective sensitive for clindamycin would be 53.84 % i.e. 56 sensitive isolates in 104 MRCoNS. These are the MS phenotype isolates. Thus performing D test is important for picking all resistant phenotypes. The overall clindamycin sensitivity in all 226 methicillin resistant staphylococci is 61.94% (140 isolates). These 140 isolates include 64 isolates having MS phenotype and 76 isolates which were erythromycin sensitive and clindamycin sensitive on primary AST testing.

If we analyze the susceptibility of the isolates as per the phenotypes, linezolid and gentamycin were uniformly having the best sensitivity for all phenotypes except for MRSA isolates having the MS phenotype which showed lower susceptibility rates. Teicoplanin resistance is 100% only for MRSA isolates having constitutive phenotype. For other phenotypes in MRSA and MRCoNS the teicoplanin susceptibility ranges from 25% to 53.57%. For norfloxacin, tetracycline, teicoplanin, co-trimoxazole there is a mixed susceptibility pattern with no single drug having uniformly good susceptibility in all the phenotypes. These drugs have shown moderate sensitivity and thus can be used for empirical treatment in patents not having serious infections. Knowing the antibiotic sensitivity pattern of these antibiotics will play an important role in treatment of infections with MRSA and MRCoNS.

The D test is usually done on erythromycin resistant and clindamycin sensitive isolates, as is the case in the present study. This would take another day or 18 hours for the result of the D test to be available and thus delay in reporting to the clinician. For this studies should be correct out to see whether the D test can be performed on the primary

AST plates with erythromycin and clindamycin being placed adjacent to each other at appropriate distance. This would enable the laboratory in giving the results of the AST and D test a day earlier.

Conclusion:-

In the present study the incidence of methicillin resistance in Staphylococci was high. Therefore performing the D test is must for identifying true clindamycin resistance to bring out beneficial treatment out comes in the patients. D test is a simple, reliable, inexpensive and easy to interpret option for detecting iMLSB resistance. The AST pattern in the present study indicates linezolid to have the best sensitivity. Thus should be used as reserved drug for patient with severe infections with methicillin resistance strains.

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