Original Article

Superiority of D-zone Testing Method over Standard Method to detect Rnducible Resistance in Gram Positive Bacteria: a Prospective Surveillance from a Teaching Hospital in Saudi Arabia

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Abstract
Objective: In this prospective study, we determined phenotypic resistance to erythromycin among gram positive bacteria.
Methods: Bacterial isolates were identified by conventional methods and by the MicroScan: D-test zone was performed according to the Clinical and Laboratory Standards institutes (CLSI) recommendations to determine inducible resistance to clindamycin on gram positive bacteria isolated from different clinical specimens .Bacterial isolates included : group A streptococci (GAS), group B streptococci (GBS), viridans streptococci, *S.pneumoniae, Staphylococcus aureus* (*S.aureus*) (both methicillin susceptible *(MSSA*) and methicillin resistant (*MRSA)* .
Results: A total of 1072 gram positive bacterial isolates were tested .The majority was from swabs collected from outpatient clinics. Erythromycin resistance was 8/23 (35%) for *S. pneumoniae*, 12/91(13%) for GAS and 17/300(5.7%) for GBS. All GAS and viridans streptococci possessed the efflux phenotype only, 8(8.8% and 1(20%), respectively. For GBS, $cMLS_B$ was 11(3.7%), 3 (1%) $iMLS_B$ and 2(0.33%) were of efflux phenotype. All *S.pneumoniae* strains possessed $cMLS_B$ phenotype. Seventy five isolates (16.3%) of *MSSA* were resistant to erythromycin compared to 160(83%) of *MRSA*. The majority of *MSSA*, 31/460 (6.7%) had an efflux phenotype while 26/460(5.6%) were of $cMLS_B$ and 19/460(4%) $iMLS_B$ phenotypes. Constitutive MLS_B was the most predominant resistant phenotype, 152/193(78.8%) among *MRSA*.
Conclusion: D-test zone should be considered for routine testing to detect inducible clindamycin resistance among significant gram positive bacteria.
Keywords: Inducible resistance, constitutive resistance, efflux, erythromycin, clindamycin.

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Introduction

Macrolides and clindamycin are chemically distinct antimicrobial agents but share a similar mode of action. For years, both drugs have been used as a major alternative for penicillin and cephalosporin-allergic patients infected with gram positive bacteria (staphylococci and streptococci) and as empiric therapy for community acquired pneumonia. In addition, clindamycin has been used for treating infections caused by anaerobic gram positive bacteria and is recommended for patients with life threatening soft tissue infections[1]

Over the past decade, there have been several reports of a global rise of macrolide resistance among clinical isolates of gram positive bacteria with wide geographic variations[2-5] Data from the USA revealed that 18-22% of *S .pneumoniae* and 5% of GAS isolates exhibited decreased susceptibility to macrolides[6-7] In Spain, 35% of *S .pneumoniae* and 20% of S. *Pyogenes* (*S. Pyogenes*) were resistant to erythromycin[8] Macrolide resistance in *S. pyogenes* was 42% in Poland while more than 90% in Taiwan[9-10] Rates of resistance among *MSSA* range from 30-46% in North America, 14.5% in Scotland and 37% in Korea[11-13] Reports from the Middle East countries are few. A study involving major hospitals in Saudi Arabia has shown that 6.3% of *S.pyogenes* and 18.8% of *S.pneumoniae* were resistant to macrolides[14]

There are three mechanisms of resistance to macrolides and lincosamide antibiotics: (1) target –site modification (2) efflux and (3) inactivation[7] Target site modification encoded by an *erm* gene also refer to as MLS_B (involving macrolides , lincosamides and streptogramin B) resistance and can be consitiutive ($cMLS_B$) or inducible ($iMLS_B$) and occurs in most *Streptococcus* and *Staphylococcus* species. Efflux of the antibiotic encoded by a *mef* gene refer to as M phenotype, occurs in *Streptococcus* species and resistant only to macrolides. Efflux has been described for *Staphylococcus* species. It is encoded by *msr*A, *msr* B and refer to as MS_B phenotype and affects macrolides only[7]

Due to the multiplicity of macrolide resistance and their diversity in phenotypic expression, resistance could be missed or in vitro interpretation of erythromycin resistance -clindamycin susceptibility may be difficult that may have important therapeutic implications particularly in situations where clindamycin is prescribed empirically. Strains that demonstrate constitutive resistance to clindamycin can easily be detected by disc diffusion test. However, strains with inducible resistance to clindamycin may go unrecognized without induction test. The D-zone test (or double disc induction test) was originally proposed in 2003 for this purpose[15] It identifies inducible resistance that might presage mutational clindamycin constitutive resistance[16]

In this study, we aimed to determine the distribution of erythromycin resistance phenotypes among gram positive bacterial isolates. To our knowledge, no similar study was carried out from our institutions.

Methods

Bacterial strains

This study was carried out at King Khalid University hospital in Riyadh, Saudi Arabia, during the 1st of January to 28th December 2007. Gram positive bacteria included in the study were GAS and GBS, *S. Pneumoniae*, viridans Streptococci and *S. Aureus* (both *MSSA* and *MRSA*) routinely isolated from different clinical specimens that were resistant to erythromycin but susceptible to clindamycin. Identification of bacterial isolates was

done by conventional methods and by the MicroScan Walk Away 96 system (Dade Behring Inc., West Sacramento CA 95691 USA) and susceptibility testing was performed by disc diffusion method and MicroScan. No duplicated isolate was involved in the study.
D-zone test
The test was performed according to CLSI (2008) instructions on all selected gram positive strains that were erythromycin resistant (or intermediate) but susceptible to clindamycin on Mueller Hinton blood (MHB) agar plate supplemented with 5% sheep blood (Becton Dickinson Microbiology systems ,Cockeysville, Md) using erythromycin 15µg and 2µg clindamycin discs (Becton Dickenson)[17] A suspension of isolated colonies of each test strain was prepared in sterile saline equivalent to a 0.5 McFarland standard. Using a sterile cotton swab, standardized organisms were inoculated onto an MHB agar plate and streaked over the entire agar surface. Using sterile forceps, erythromycin and clindamycin discs were applied onto the agar 15 mm apart. Plates were incubated in ambient air with CO2 at 35^{o}C for 18 hours. *S. aureus* control strain *ATCC 25923* was used. After incubation, plates were examined using transmitted light to detect any flattening or blunting of the shape of the clindamycin zone[17]
Interpretation of the results
Organisms that showed flattening or blunting of the clindamycin zone adjacent to the erythromycin disc (D- shape) were interpreted as D-zone test positive and indicated inducible clindamycin resistance (iMLS$_B$ phenotype) and reported as erythromycin and clindamycin resistant. If there was no zones or intermediate zone appear for both discs a constitutive (cMLS$_B$ phenotype) is indicated and both are reported as resistant. If erythromycin zone was resistant and clindamycin was susceptible without D-zone, an efflux phenotype is indicated and erythromycin reported as resistant and clindamycin as susceptible.

Results
A total of 1072 erythromycin – resistant- clindamycin susceptible gram positive bacterial isolates were included in the study .The majority of bacterial isolates resistant to erythromycin were from different swabs of outpatients (except *MSSA* and *MRSA*), Table 1.
Table 1: Sources of different gram positive bacterial isolates resistant to erythromycin

Organisms	Blood N (%)	Respiratory N (%)	Swabs N (%)	Urine N (%)	Inpatients N (%)	Outpatients N (%)	Total N
GAS	0(0)	0(0)	12(100)	0 (0)	14(15)	77(85)	91
GBS	0(0)	0(0)	13(76.4)	4(23.5)	100(33)	200(66.7)	300
S.pneumoniae	1(12.5)	2 (25)	5(62.5)	0(0)	9 (39)	14(60.9)	23
Viridans streptococci	1 (20)	0(0)	0 (0)	0)0(	1(20)	4(80)	5
MSSA	1(1.3)	8(10.7)	64(85)	2(2.7)	291(63)	170(37)	460
MRSA	10(6.2)	22 (13.8)	123(77)	5(3)	166(86)	27(14)	193

All *GAS* was isolated from pharyngeal swabs 12 (100 %). The main source of GBS was vaginal swabs from antenatal clinics 13(76.4%). *S.pneumoniae* were common from eyes

and ear specimens, 5(62.5%) while only 1(12.5%) and 2(25 %) isolates were from blood and respiratory infections, respectively. *MSSA* 64(85%) and *MRSA* 123(77%) were most commonly isolated from different wound and skin swabs of inpatients compared to outpatients. The only isolate of viridans streptococci resistant to erythromycin was from blood culture and considered insignificant.

Table 2 summarizes the incidence of erythromycin resistance and distribution of different resistant phenotypes of tested bacteria. A total of 8(35%) of *S.pneumoniae* were unsusceptible to erythromycin and 12(13%) GAS whereas it was 160(83 %) for *MRSA* compared to 75 (16.3%) of *MSSA*.

Table 2: Incidence of erythromycin resistance and distribution of different resistance mechanisms among gram positive bacterial isolates

Organisms	**ER-R N(%)**	**Resistant phenotypes N (%)**			**D-zone test not done***
		$cMLS_B$	**$iMLS_B$ (+ve D-test)**	**Efflux (-ve D-test)**	
GAS n=91	12 (13)	0(0)	0 (0)	8 (8.8)	6 isolates
GBS n=300	17 (5.7)	11 (3.7)	3(1)	2(0.33)	1 isolate
S.pneumoniae n=23	8 (35)	8 (35)	0 (0)	0(0)	All isolates
Viridans streptococci n=5	1 (20)	0(0)	0 (0)	1 (20)	-
MSSA n=460	75 (16.3)	26 (5.6)	19 (4)	31(6.7)	7 isolates
MRSA n=193	160 (83)	152 (78.8)	5(2.5)	1(0.5)	5 isolates

ER; erythromycin resistant.

D-zone test not done; isolates failed to grow for further testing . All S. pneumoniae strains were resistant to both erythromycin and clindamycin.*

None of the GAS and viridans streptococci showed any MLS_B resistant phenotypes and efflux phenotype was the only mechanism of resistance, 8(8.8%) and 1(20%) respectively. For GBS, $cMLS_B$ phenotype was most predominant than other phenotypes [11(3.7%)]. All erythromycin resistant isolates of *S.pneumoniae* were resistant to clindamycin so they only possessed $cMLS_B$ phenotype. Ninteen isolates (4%) of *MSSA* showed blunting of clindamycin zone adjacent to erythromycin indicative of $iMLS_B$ phenotype whereas only 5 isolates (2.5 %) of *MRSA* possessed $iMLS_B$ phenotype and the majority (78.8%) was of $cMLS_B$ phenotype. Efflux mechanism accounted for 31 (6.7%) of *MSSA* and only one isolate (0.5%) of *MRSA*.

Discussion

This study revealed that the incidence of erythromycin resistance among GAS and *S.pneumoniae* was similar to the results from Spain[8] M phenotype was the only resistant mechanism among our GAS strains. This is in agreement with studies from North America, UK, and Australia[18-20] However, a discrepant results have been obtained from other study from our region with lower erythromycin resistance and the presence of M

and efflux phenotypes among both GAS and *S. pneumonia*[14] A study from Ottawa has shown that 67% of GAS isolates had M phenotype of resistance[21] In the USA, 38 % of resistance among community GAS isolated from children were due to strains carrying the *mef* (A) gene[22] Reports of inducible resistance phenotype was low among GAS as well as among other streptococcal species (3.1%) [2,4,22,24] Our results may have an important impact on the treatment of GAS infections since clindamycin can be used for the treatment of serious GAS soft tissue infections.

GBS exhibited multiple patterns of erythromycin resistance in our study. The majority were resistant by $cMLS_B$ mechanism. This is consistent with other reported studies where $cMLS_B$ ranged from (12.8% - 47%), $iMLS_B$ phenotype (5.9% - 40%) and M phenotype (1.3% - 13%) [7,25]

Although viridians streptococci are part of the normal human flora and the number of isolates in this study was very small in addition to that erythromycin is not widely used for the treatment of genuine infections caused by these bacteria. However, selection of resistant strains can occur in this bacterium by exposure to antimicrobials. Since viridians streptococci carried M phenotype of resistance in the current study, this could have been be transmitted to GAS.

Results of the present study indicated that $cMLS_B$ was the only macrolide resistant phenotype among *S. pneumoniae* surveyed. This indicates that *S. pneumoniae* strains resistant to erythromycin as well as to lincosamides and steptogramin B. Report from Spain and Italy observed the predominance of $cMLS_B$ (76.5% and 94% respectively) over *mef* phenotype in *S. pneumoniae* [8,26] In Spain, efflux (M type) was encountered in 5% of *S.pneumoniae* isolates [8] However, none of *S. pneumoniae* strains reported from France possessed an efflux phenotype [27] Inducible resistance is rarely reported in *S. pneumoniae* [26,27] Of note is the report by Montanari et al that erythromycin- clindamycin double disc test is less applicable to erythromycin resistant *S. pneumoniae* because the constitutive or inducible character of MLS in the test was inferred from the response to clindamycin and that *S. pneumoniae* with MLS resistance when tested by the double disc test are almost invariably assigned to the $cMLS_B$ phenotype[26] This could explain why all our *S.pneumoniae* strains had $cMLS_B$ phenotype. Furthermore, the majority of our pneumococcal isolates were from outpatients with eye and ear infections and erythromycin is commonly used topically for pneumococcal eye infections. Other macrolides are commonly used empirically for community acquired respiratory tract infections.

Several studies have related the consumption of antibiotics (including erythromycin) and widespread of resistance which was true for *S.pneumoniae* that showed coresistance to penicillin, macrolides and several other antibiotics [5,8,28] However, this relation was not found in GAS which developed resistance to macrolides following increased consumption but remained susceptible to penicillin[29]

Despite the presence of different mechanisms of resistance to erythromycin among streptococcal species, use of different macrolides for different streptococcal infections, different patient populations and community factors ,a temporal factor has been reported to exist or interaction of streptococci with other organisms which aids the evolution of erythromycin resistance among GAS and *S.pneumoniae* or among streptococcal species [8,24] Robinson et al demonstrated that macrolide resistance was acquired by GAS via

independent genetic events and genetic diversification of resistant clones has occurred by mutation along with global dissemination of resistance clones[5]

With regards to *MSSA* and *MRSA*, only 4% and 2.5 % of our strains had $iMLS_B$ phenotype, respectively. Much higher rates of inducible resistance were reported among *MSSA* (63%) and *MRSA* (50%) [30] Furthermore, all *MRSA* isolates in other study expressed $iMLS_B$ phenotype [31] For *MRSA* strains with $iMLS_B$ phenotype, there is a high rate of mutation to constitutive resistance which would be selected during clindamycin therapy [32] This is could be true for our *MRSA* strains where 78.8% expressed $cMLS_B$ phenotype compared to the other phenotypes .The incidence of inducible or constitutive resistance among *S.aureus* varies by geographical regions, patient age and bacterial species.[15,16] Investigators reported clindamycin treatment failure in infections due to $iMLS_B$ *MSSA* and *MRSA* [16,30] Therefore, clindamycin should not be used for the treatment of serious *S. Aureus* (or *Streptococcus*) infections expressing $iMLS_B$ resistant phenotype. For strains of *MRSA* that harbor an efflux pump, clindamycin can be used for therapy.

Our study did not use any of the molecular methods to detect the genes responsible for macrolide resistance for two reasons; first, it is unavailable in our laboratory as is the case in most laboratories in developing countries. Second, we felt that phenotypic methods gave reproducible results and are concordant with established and standardized methods in detecting this mechanism of resistance.

In conclusion, due to the multiple resistance mechanisms and diverse phenotypic expression of macrolide - clindamycin resistance among gram positive bacteria, clindamycin may appear susceptible when tested by standard disc diffusion method and inducible resistance can be detected by D-zone induction test . Although the number of bacterial strains with positive D-zone test was small in the current study which might reflect the status of use of macrolide in our community, we suggest that all clinical microbiology laboratories should be aware of the different macrolide - clindamycin resistance phenotypes and recommend routine D-zone testing of clinically significant gram positive bacterial isolates that display different susceptibility patterns to erythromycin and clindamycin to identify potential clindamycin resistance and avoid ineffective therapy .

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