Susceptibilities of Common Bacterial Isolates from Oman to Old and New antibiotics

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Abstract

Objectives: The purpose of this study is to compare the antimicrobial activity of linezolid and tigecycline with other commonly used antibiotics against a variety of clinical isolates at Royal Hospital, Muscat.

Methods: Clinically-significant bacterial isolates in Royal hospital during the period from 1st of March to 30th of June 2007 were collected, stored and finally tested to determine their susceptibility to different antibiotics by broth microdilution (microscan panels).

Results: Two hundred ten bacterial strains were collected and tested including *Staphylococcus aureus* (29), Group B *ß-haemolytic Streptococcus* (10), *Streptococcus pneumoniae* (15), *Enterococcus spp.* (16), *Haemophilus spp.* (15), *Escherichia coli* (26), *Klebsiella spp.* (26), *Enterobacter spp.* (25), *Serratia spp.* (10), *Acinetobacter baumannii* (17) and *Pseudomonas aeruginosa* (21). All strains except P. aeuginosa were susceptible to tigecycline. All gram-positive strains were susceptible to linezolid. Meropenem and piperacillin-tazobactam showed good activity against most organisms tested including *P. aeruginosa* and *Acinetobacter baumannii*. Levofloxacin showed 100% activity against *K. pneumoniae* and 61% activity against *E. coli*. The activity of 3rd generation cephalosporins against **E.coli** and *K. pneumoniae* ranged from 76% to 100%.

Conclusion: Tigecycline and linezolid showed excellent activity against microorganisms in their relevant spectrum of activity. However, they should be used wisely and judiciously.

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Introduction

Microorganisms have virtually unlimited capacity to develop resistance to all antimicrobial agents. Hospitals provide the ideal environment for the evolution and dissemination of antibiotic resistant bacteria as a result of selective pressure caused by antibiotic overuse and spread of resistant bacteria.[1] In our hospitals and particularly intensive care units, there is a steady increase in multi-resistant bacteria.[2, 3] This ever developing antimicrobial resistance among hospital as well as community bacterial strains presents a serious therapeutic problem.[4] Therefore development of novel antimicrobial agents effective against such multi-resistant bacteria has been sought. Several novel antimicrobial agents such as oxazolidinones and glycylcyclines have been developed and introduced to clinical practice.

The purpose of this study was to test and compare the antimicrobial activity of the newly introduced linezolid and tigecycline with other commonly used antibiotics against a wide variety of clinical isolates from patients in the Royal Hospital, Muscat.

Bacterial strains

Clinically significant bacterial strains isolated from different body sites during the period 1st March to 30th June 2007 were collected. They were then stored in trypticase soya broth with glycerol at -80° C until tested. Duplicate microorganisms were excluded from the study.

Isolation and identification of microorganisms

Clinical specimens were inoculated onto blood agar, chocolate agar and MacConkey agar and incubated at 37o C for 24 hours. Significant isolates were then picked and identified according to standard microbiological procedures,[5] and further identified to the species level by Phoenix system (Becton Dickenson).

Antibiotic susceptibility testing

Antibiotic susceptibility testing was performed by broth microdilution using MicroScan (Siemens) either Gram-positive or Gram-negative panel. Gram-positive panel consisted of penicillin (0.06-8µg/ml), ampicillin (0.06-16µg/ml), augmentin (0.03-8µg/ml), Piperacillin-tazobactam (0.25-16µg/ml), cefotaxime (0.03-64µg/ml), levofloxacin (0.06-32µg/ml), linezolid (0.5-8µg/ml), minocycline (0.25-8µg/ml), vancomycin (0.12-32µg/ml), tigecycline (0.008-16µg/ml) and meropenem (0.12-16µg/ml). Gram-negative panel consisted of ampicillin (0.0.5-32µg/ml), augmentin (0.12-32µg/ml), piperacillin/tazobactam (0.06-

128µg/ml), cefotaxime (0.06-64µg/ml), cefepime (0.5-32µg/ml), ceftazidime (8-32µg/ml), levofloxacin (0.008-8µg/ml), amikacin (0.5-64µg/ml), minocycline (0.5-16µg/ml), tigecycline (0.008-16µg/ml) and meropenem (0.06-16µg/ml). Using an inoculum loop, 5-10 morphologically similar colonies were picked from the agar plate and emulsified in 3 ml of inoculum water. The final turbidity was adjusted to 0.5 McFarland Standard. 0.1 (100 µg) of the standardized suspension were added to 25 ml of broth. *H. influenzae* strains were inoculated into *Haemophilus* test medium broth, while *S. pneumoniae* and *S. agalctiae* were inoculated into Mueller-Hinton broth with 5% lysed horse blood. The remaining microorganisms were inoculated into cation adjusted Mueller-Hinton broth. Rehydration and inoculation were performed using the Renok system for MicroScan panels (Siemens). The following control bacterial strains were also tested: *E. coli* ATCC25922, *P. aeruginosa* ATCC27853, *S. aureus* ATCC29213, *E. faecalis* ATCC29212, *S. pneumoniae* ATCC49619 and *H. influenzae* ATCC49766. The panels were then incubated at 35°C without CO_2 for 20-24 hours. The panels were read manually using the microdilution viewer. Minimum inhibitory concentration (MIC) for each antibiotic was recorded as the lowest antibiotic concentration showing inhibition of growth. CLSI criteria were used to interpret MIC values except for tigecycline where FDA susceptible breakpoint of ≤ 0.5mg/L was used.

Results

Bacterial strains

Bacterial strains isolated from different clinical specimens are shown in Table 1. A total of Two hundred and ten bacterial strains were collected including *Staphylococcus aureus* (29), Group B ß-haemolytic *Streptococcus* (10), *Streptococcus pneumoniae* (15), *Enterococcus spp.* (16), *Haemophilus species* (15), *Escherichia coli* (26), *Klebsiella spp.* (26), *Enterobacter species.* (25), *Serratia species.* (10), *Acinetobacter baumannii* (17) and *Pseudomonas aeruginosa* (21).

S. aureus, P. aeruginosa, Enterobacter spp. and *Acinetobacter spp.* were mostly isolated from skin infections, while *S. pneumoniae* and *Haemophilus species* were recovered from sputum. Group B β-haemolytic *Streptococcus* was isolated only from genital specimens and *E. coli* and *Klebsiella spp.* mostly from urine. *S. aureus, S. pneumoniae, Enterococcus spp.* and *Serratia spp.* were the most frequent blood isolates.

Table 1: Counts of bacterial isolates by clinical specimen

Organisms	Blood	Sputum	Abscess	IV catheter	Urine	Wound and skin	GU	Other*	Total
S. aureus	5	1	5		2	9		7	**29**
S. pneumoniae	5	8						2	**15**
S. agalactiae					3		7		**10**
Enterococcus spp.	5		1	2	3	4		1	**16**
E.coli	2	2	1		12	6		3	**26**
Klebsiella spp	1	5	2	1	7	7		3	**26**
Haemophilus spp	1	12						2	**15**
P. aeruginosa	1	3	2	3	4	7		1	**21**
Serratiaspp	5	1	1		1	2			**10**
Acinetobacter baumannii	2	4			2	6		3	**17**
Enterobacter spp	1	5	1		6	10		2	**25**
Total	**28**	**41**	**13**	**6**	**40**	**51**	**7**	**24**	**210**

*Others: Ear, Eye, unspecified

GU : Genitourinary, S: Streptococcus, spp: species, P: Psuedomonas

Antibiotic susceptibilities

Antibiotic susceptibilities of tested organisms are shown in tables 2 and 3. All strains, except *P. aeruginosa* were susceptible to tigecycline with MIC range of 0.12 to 1 mg/L. and susceptibilities to amikacin ranged from 90% to 100%. All Gram positive bacteria were susceptible to linezolid with MIC90 (MIC required to inhibit the growth of 90% of organisms) ranging from 1 to 2 mg/L. *Enterococcus spp* except one *E. faecium* strain were susceptible to ampicillin and vancomycin.

Table 2: Antibiotic susceptibilities of Gram-positive bacterial isolates

Antimicrobial	MIC90* (mg/L)	Susceptible (%)	Intermediate (%)	Resistant (%)
S. pneumoniae				
Penicillin	2	50	20	30
Ceftriaxone	1	80	20	
Levofloxacin	1	100		
Linezolid	1	100		
Meropenem	0.5	60		40
Minocycline	2	90	10	
Tigecycline	0.03	100		
Vancomycin	0.25	100		
S.agalactiae				
Penicillin	0.12	100		
Ampicillin	0.12	100		
Ceftriaxone	0.12	100		
Levofloxacin	1	100		
Linezolid	1	100		
Meropenem	≤ 0.12	100		
Minocycline	> 8			
Tigecycline	0.12	100		
Vancomycin	0.5	100		
Enterococcus spp				
Ampicillin	1	93.75		6.25
Levofloxacin	32	62.5		37.5
Linezolid	2	100		
Minocycline	8	43.75	56.25	
Tigecycline	0.12	100		
Vancomycin	2	93.75		6.25
*S. aureus***				
Penicillin	32	10.3		89.7
Amoxicillin Clavulanic Acid	1	93.1		6.9
Levofloxacin	o.5	100		
Linezolid	2	100		
Minocycline	≤ 0.25	100		
Tigecycline	0.12	100		
Vancomycin	1	100		

*MIC90: Minimum Inhibitory Concentration required to inhibit the growth of 90% of organisms.
** 29 isolates including 4 methicillin resistant *S. aureus* (MRSA)

Table 3: Antibiotic susceptibilities of Gram-negative bacterial isolates

Antimicrobial	MIC90* (mg/L)	Susceptible (%)	Intermediate (%)	Resistant (%)
E. coli				
Amikacin	4	100		
Amoxicillin Clavulanic Acid	16	65.38	26.92	7.69
Ampicillin	> 32	30.77	3.85	65.38
Cefepime	16	84.62	7.69	7.69
Ceftazidime	≤ 8	96.15	3.85	
Ceftriaxone	> 64	76.92		23.08
Levofloxacin	8	61.54		38.46
Meropenem	≤ 0.06	100		
Minocycline	16	73.08	15.38	11.54
Piperacillin Tazobactam	8	92.31		7.69
Tigecycline	0.25	100		
Klebsiella spp				
Amikacin	2	100		
Amoxicillin Clavulanic Acid	8	92.3	3.85	3.85
Ampicillin	> 32		3.85	96.15
Cefepime	≤ 0.5	100		
Ceftazidime	≤ 8	100		
Ceftriaxone	≤ 0.06	96.15		3.85
Levofloxacin	0.06	100		
Meropenem	≤ 0.06	100		
Minocycline	4	92.3	3.85	3.85
Piperacillin Tazobactam	2	100		
Tigecycline	0.5	100		
Enterobacter spp				
Amikacin	2	100		
Amoxicillin Clavulanic Acid	> 32	4.35	4.35	91.3
Ampicillin	> 32			100
Cefepime	16	86.96	4.35	8.7
Ceftazidime	16	82.61	8.7	8.7
Ceftriaxone	64	78.26	4.35	17.39
Levofloxacin	8	86.96		13.04
Meropenem	0.12	95.65	4.35	

Table 3. continued

Antimicrobial	MIC90* (mg/L)	Susceptible (%)	Intermediate (%)	Resistant (%)
Minocycline	4	91.30	8.7	
Piperacillin Tazobactam	4	86.96	8.7	4.35
Tigecycline	1	100		
Serratia spp				
Amikacin	2	100		
Amoxicillin Clavulanic Acid	> 32	10		90
Ampicillin	> 32	10		90
Cefepime	≤ 0.5	100		
Ceftazidime	≤ 8	100		
Ceftriaxone	1	100		
Levofloxacin	0.12	100		
Meropenem	0.06	100		
Minocycline	4	100		
Piperacillin Tazobactam	4	100		
Tigecycline	1	100		
Haemophilus spp.				
Amoxicillin Clavulanic Acid	1	100		
Ampicillin	1	90.9		9.1
Cefepime	≤ 0.5	100		
Ceftazidime	≤ 8	100		
Ceftriaxone	≤ 0.06	100		
Levofloxacin	0.015	100		
Meropenem	0.12	100		
Minocycline	≤ 0.5	100		
Piperacillin Tazobactam	≤ 0.06	100		
Tigecycline	0.25	100		
Acinetobater baumannii				
Amikacin	8	94.12		5.88
Cefepime	32	82.35	5.88	11.76
Ceftazidime	> 32	82.35		17.65
Ceftriaxone	> 64	41.18	41.18	17.65
Levofloxacin	4	70.59	23.53	5.88
Meropenem	2	100		
Minocycline	4	100		
Piperacillin Tazobactam	128	82.35		17.65
Tigecycline	0.5	100		
P. aeruginosa				
Amikacin	4	90.48	9.52	
Cefepime	16	85.71	14.29	
Ceftazidime	16	95.00	5.00	
Ceftriaxone	> 64	9.52	47.62	42.86
Levofloxacin	> 8	80.00	5.00	15.00
Meropenem	16	80.00	5.00	15.00
Minocycline	> 16			100
Piperacillin Tazobactam	32	95.00		5.00
Tigecycline	> 16			100

*MIC90: Minimum Inhibitory Concentration required to inhibit the growth of 90% of organisms. spp: species

Only 30% of *E. coli* isolates were susceptible to ampicillin, 96.15% to ceftazidime, 76.9% to each of ceftriaxone and cefepime and 61% to levofloxacin. On the other hand 100% of *Klebsiella spp.* were susceptible to levofloxacin, while susceptibilities to other antibiotics ranged from 92% to 100%. 95.65% and 86.96% of *Enterobacter spp.* were susceptible to meropenem and piperacillin-tazobactam respectively. 82.6% of them were susceptible to ceftazidime, but only 78.26% were susceptible to ceftriaxone. All tested *A. baumannii* strains were susceptible to meropenem, minocycline and tigecycline. 82.75% of them were susceptible to ceftazidime and cefepime, but only 41.18% were susceptible to ceftriaxone. All *Serratia spp.* were susceptible to all tested antibiotics except augmentin, where only 10% were susceptible. *P. aeruginosa* was universally resistant to tigecycline with MIC range 8-16 mg/L. Over 90% of *P. aeruginosa* were susceptible to amikacin and piperacillin-tazobactam and 80% were susceptible to meropenem and levofloxacin. *Haemophilus species* were susceptible to all tested antimicrobial agents except ampicillin where 9.1% were resistant.

Four strains (12.12%) of *S. aureus* were found to be oxacillin resistant (MRSA). The remaining strains were susceptible to all other antibiotics except penicillin, to which 10% were susceptible. All strains of *S. agalactiae* were susceptible to all antibiotics. 50% of *S. pneumoniae* were resistant to penicillin 20% of which were intermediately sensitive and 30% were fully resistant. 80% were fully susceptible to ceftriaxone and 20% showed intermediate susceptibility.

Discussion

We tested a wide variety of commonly encountered microorganisms in clinical practice. This selection represents the types of bacteria isolated from patients in Oman, since the Royal hospital is the main tertiary referral hospital, where patients from different parts of Oman are treated. All tested strains were susceptible to tigecycline, except *P. aeruginosa*, which is known to be resistant to glycylcycline due to efflux pump (MexXY-OprM) mediated resistance mechanism.[6,7,8] Similarly all Gram positive organisms were universally susceptible to linezolid. This oxazolidinone antibiotic is known to be effective against all Gram positive bacteria. It binds to the 50S subunit of the bacterial ribosome via interaction with the 23S rRNA, thereby blocking protein synthesis.[9] Tigecycline and Linezolid should however be kept as reserve antibiotics and used only when other antibiotics are not effective. Their use should be restricted and only permitted when approved by the hospital microbiologist or infectious disease physician as unrestricted use will lead to development of resistance to these valuable antibiotics. Hence, establishing antimicrobial stewardship program in each hospital is highly desirable and would ensure judicious use of antibiotics as well as evidence-based, safe and effective antimicrobial therapy. On the other hand all *E. coli* strains were susceptible to meropenem and amikacin. Susceptibilities to 3rd generation cephalosporins varied. While only 4% were resistant to ceftazidime, 24% were resistant to ceftriaxone. This is most probably due to the prevalence of CTX-M type extended spectrum β-lactamase (ESBL) producing strains, known to mostly hydrolyze cefotaxime and ceftriaxone, but to a less extent ceftazidime.[10, 11] Indeed most of our recent ESBL producing *E. coli* isolates have been shown to belong to type CTX-M (unpublished data). CTX-M type ESBL producing strains are spreading rapidly worldwide and are increasingly dominant.[12] Because of the increasing significance of multi-resistant ESBL producing *E. coli* in the community, clinicians should be aware of the possibility of treatment failure associated with infections caused by such organisms.[13] We also found wide prevalence of levofloxacin resistance among *E. coli* stains. Quinolone resistance among *E. coli* has been reported worldwide and believed to be due to acquisition of *qnr* gene that protects DNA from binding to gyrase and topoisomerase.[14] This has been reported to occur more frequently among ESBL producing strains.[15] Indeed this correlates with the high prevalence of ESBL producers among our isolates.

Although *A. baummanni* is known as one of the most resistant Gram negative bacteria that can acquire resistance by multiple mechanisms, all strains isolated during the study period were highly susceptible to antimicrobial agents.[16, 17] On the other hand, about 4% and 13% of *Enterobacter spp*. were resistant to meropenem and piperacillin-tazobactam respectively. This could be due to production of a carbapenemase or efflux pump.[18, 19] Similarly 20% of *P. aeruginosa* were resistant to meropenem, which can also be explained by the above mechanisms. However, since the same meropenem resistant strains were also resistant to levofloxacin, it is more likely that this was an efflux mechanism. Overproduction of the efflux system Mex AB-OprM confers resistance to meropenem as well as quinolones and may result in treatment failure.[20] Piperacillin-tazobactam, however showed high activity against *P. aeruginosa*. This may be considered as the drug of choice for treating infections with *P. aeruginosa* in our setting.

Only four *S. aureus* strains (12.12%) were methicillin resistant. Although this is consistent with previous findings (unpublished data), it appears much lower than that reported in other GCC countries and in some European countries.[21,22,23] On the other hand all strains were susceptible to linezolid and tigecycline, a finding consistent with other studies.[24] Although all *S. pneumoniae* strains were also susceptible to linezolid and tigecycline, 50% of them were not susceptible to penicillin and 20% were intermediately resistant to ceftriaxone. This represents a significant increase in the rate of resistance to penicillin and ceftriaxone as compared to a previous report from Oman.[25] A similar trend has also been reported in other neighboring countries.[26] It is imperative, therefore, to consider adding vancomycin in empirical treatment of serious pneumococcal infections. The only isolate of *E. faecium* was resistant to vancomycin. Although we rarely encounter vancomycin resistant *Enterococcus* (VRE) in our region, it is often reported from some parts of North America and Europ.[27] However, *E. faecalis*, the dominant strain remained to be susceptible to commonly used anti-enterococcus agents.

In our hospital we have been experiencing mechanisms of resistance as these reported worldwide, as a result of increasing antibiotic pressure. However new antimicrobial agents, linezolid and tigecycline, seem to be effective agents against all clinical isolates in the Royal Hospital, only they need to be restricted and used judiciously and only when approved by microbiologist or infectious diseases physicians so that these valuable drugs continue to be effective in the future.

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Transparency Declarations

None to declare.

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