Original Article

Update on the resistance pattern of common multidrug resistant pathogens to the common end resort antibiotics

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Objective: To review across the globe resistant trends of commonly isolated Gram positive and Gram negative microorganisms against four end resort antibiotics e.g. Vancomycin, Linezolid, Carbapenems, and Colistin.

Methodology: Web based Medical literature search was done using keywords. Extensive search was done to retrieve surveillance studies data from PubMed/Medline, WHO databases, Health Surveys, google scholar and grey literature until December 2018.

Results: Resistance pattern to end resort antibiotics is increasing worldwide and is regionally variable. There had been a rapid increase in carbapenem resistance in gram negative organisms across the globe in many countries, with very high rates of >25% in some. Colistin resistance in gram negative bacteria is so far less than 10% worldwide. There is an increasing incidence (approx.7% worldwide) of Vancomycin intermediate resistant in Staphylococcus aureus (VISA) and hetero-resistant Staphylococcus aureus (hVISA), which may lead to therapeutic failure with Vancomycin. Fully resistant Staphylococci aureus (VRSA) remains low with sporadic reports. Similarly Linezolid resistance in Staphylococcus aureus and Enterococci is also generally low<1% with sporadic reports only.

Conclusions: Since empiric therapies in hospitals are based on data regarding resistance pattern, there is a crucial need to determine current resistant rates at a global scale. (Rawal Med J 202;45:737-745).

Keywords: Vancomycin resistant Staphylococcus aureus, Vancomycin resistant Enterococci, Carbapenem resistant Enterobacteriaceae, Linezolid resistant Staphylococcus aureus, Linezolid resistant Enterococci, Colistin resistant gram negative bacteria, antibiotic resistance.

INTRODUCTION

End resort antibiotics are the miracle and the wonder drugs used to treat infections under situations when all other alternatives fail. These severe infections are caused by microorganism that have been labeled as superbugs. As bacteria grow more and more resistant fewer choices have been left as last resort antibiotics and humanity is on the verge of facing an antibiotic apocalypse foretold by the father of antibiotics Alexander Fleming as "public will demand then an era will begin of abuses."

Since the discovery of penicillin by Sir Alexander Fleming in the last century, antimicrobials have transformed modern healthcare and helped save millions of lives . However, bacterial resistance to almost all available antimicrobials and drying up of antibiotic pipeline, due to no newer antibiotics being introduced, has threatened many of the advances of the previous century. The failure to discover newer antibiotics brings about the threat of untreatable infections raising their ugly heads taking us back to the pre antibiotic era. It is predicted that resistance will cause three hundred million deaths by 2050, and 100 trillion dollars loss to the economy of the world.[1]

Ever since its introduction into clinical practice in 1972, Vancomycin has stood the test of time as a last resort in the treatment of methicillin resistance *S. aureus* (MRSA).[2]It was so hard to induce resistance against vancomycin in vitro that it was considered highly unlikely that true resistance will occur in clinical practice. However, VRSA is a reality now and Vancomycin resistant enterococci (VRE) is a substantial clinical problem .[3]

Reliability on Vancomycin to treat gram positive bacteria as end resort was shaken by strains of

bacteria resistant to this class, so newer classes like linezolid is a welcome option. Linezolid has been approved since 2000, to treat infections caused by gram positive bacteria. It has unique features that were thought to prevent development of resistance against it. First, it inhibits protein synthesis in bacterial ribosomes, and there is no shared cross resistant mechanisms with other ribosomal agents. Second it is a synthetic agent therefore there is less chance of pre-existing intrinsic resistance mechanisms. Lastly, it binds to 23S rRNA encoded by multiple copies of bacterial genome.[4] Mutation in these genes is difficult since it will require multiple mutations. In vitro studies proved that resistance against linezolid is difficult and slow to emerge.[4] There was no documented resistance until 2005, but in 2006 resistant strains arose at low rates among Staphylococci and Enterococci.[5]

Carbapenems are an important member of our antimicrobial armamentarium. This group of beta lactam drugs is unique because they are not only more resistant to breakdown by β-lactamases but may also have a value added feature of inhibiting β-lactamases. Carbapenems are broadest spectrum beta lactam group with great potency against Gram-negative bacteria. They are often used as last-line weaponry in critically ill patients with gram negative infections. The emergence of carbapenemase producing gram negative bacteria seriously threatens this weapon of mass destruction as several studies around the world demonstrated that resistance against this group is increasing.[6]

A rise in multidrug resistant Gram-negative bacteria producing carbapenemase gene, has resulted in increased reliance on use of another last resort antibiotic, Colistin. Although introduced much earlier in 1959, it fell into disfavor because of its toxicity profile. The need to treat carbapenemase producing Gram-negative bacteria has reintroduced Colistin into clinical use. Previously, Colistin resistance in gram negative bacteria was chromosomally mediated slowly transmissible and was a rare occurrence. However, since 2016, newer plasmid-mediated resistance gene known as, mobilized colistin resistance (*mcr*)-*1*, and *mcr-2* have emerged, resulting in MDR gram negative bacteria developing resistance to this valuable antibiotic.[7]

METHODOLOGY

Web based Medical literature search was done using keywords. Extensive search was done to retrieve surveillance studies data from PubMed/Medline, WHO databases, Health Surveys, google scholar and grey literature until December 2018. Global Resistance pattern of common gram negative and gram positive organism against 4 common last resort antibiotics i.e Vancomycin, Linezolid, Carbapenems and Colistin was searched and summarized. Vancomycin and Linezolid vs *Staphylococcus aureus* and *enterococci* was investigated and global efficacy of Carbapenem and Colistin against gram negative microorganisms was analyzed.

RESULTS

Vancomycin

There are three types of resistance mechanisms shown by *Staphylococcus aureus* to Vancomycin. The first type is labeled VISA with a *Staphylococcus aureus* strain with minimum inhibitory concentration to vancomycin of 8 mg/l to 16 mg/l. The second type is hetero resistant –VISA(hVISA). These are sensitive to Vancomycin with MIC < 4 mg/l but contain subpopulations of organisms that sustain Vancomycin concentration ≥8 mg/L. These lead to therapeutic failure during treatment. The third type is high level resistance in S *aureus* with MIC ≥32 μg/ml.[8]

Disk diffusion, and automated testing methods such as Vitek and Microscan misidentify VISA, hVISA and VRSA strains.[9] Therefore the Vancomycin resistance in staphylococcus aureus has to be identified using a reliable method like screen agar, broth or agar diffusion methods according to CLSI guidelines and a molecular testing method.

VISA and hVISA: Zhang et al conducted a systemic review of literature regarding the world wide prevalence of VISA and hVISA reviewing 91 published studies in Embase and Pubmed. They calculated a worldwide prevalence of 7.01% for hVISA and 7.93% for VISA from 2010-2014. In Asia, the hVISA was 6.81% and VISA was 3.42%. In America/Europe, hVISA was 5.60% and VISA 2.75%.[10]

VRSA: High level VRSA incidence worldwide is

low with approximately 20 confirmed strains described worldwide.[11] In USA alone, 14 case have been reported until now.[12,13] In Europe, only one case has been reported from Portugal.[14] However, there are more than 100 published studies from Middle east, South Asia, North Africa and Latin America reporting VRSA. It seems that most of these studies did not follow set guidelines on VRSA identification reporting and confirmation. We only selected studies that detected VRSA through both molecular method and recommended MIC determination method. Table 1 summarizes VRSA confirmed by molecular methods and acceptable as true vancomycin resistant through international standards.[12-36]

Table 1. Credible articles based on CLSI criteria & molecular confirmation for high level VRSA identification.

Reference	Place of isolation	Date of isolation/ Publication	MIC*Value	*vanA*/B Detection Based on PCR Results	No of isolates
12	USA	2002-2013	different	*van a (+)*	13
13	USA	2015	512	*van a(+)*	1
14	Portugal	2013	256[a]	*van a (+)*	1
15.	Egypt	2014	≥ 16 [c]	*vanA*, (+)	1
16	Iran	2013	ND[b]	*vanA*, (+)	1
17.	Iran	2008	64/512[d]	*vanA*, (+)	2
18	Egypt	2008	33/50[d]	*vanA*, (+)	2
19	Pakistan	2011	16	*vanA*, (+)	1
20	Iran	2011	ND	*Van A (+)*	1
21	Iran	2012	512[d]	*vanA*, (+)	1
22	Iran	2012	512[b]	*vanA*, (+)	1
23	Egypt	2012	32[e]	*vanA*, (+)	1
24	Iran	2012	different	*Van A(+). Van B(+*	3
25	Iran	2013	ND	*3 vanA*, (+)2 Van B (+) 1 van A & B(+)	6
26	Egypt	2015	different[c]	*vanA*, (+)	5
27	Brazil	2015	256	*vanA*, (+)	1
28	India	2008	64	*Van A(+)*	1
29	india	2008	different	*Van A(+)*	5
30	India	2011	different	*Van A(+)*	6
31	India	2011	different	*Van A(+)*	4
32	Brazil	2014	>32	*Van A(+)*	1
33	India	2017	ND	*13 van A(+) 2 Van B(+)*	15
34	India	2016		*Van A(+)*	2
35	Nigeria	2018	ND	*Van A (+)*	2
36	Egypt	2014	ND[b]	*Van A (+)*	14

[a]Method of detection not elaborated. [b]E-test. [c]Agar dilution method. [d]Broth microdilution method. [e]Broth macrodilution method.

Rahimipour et al scanned 100 articles overreporting VRSA from middle East and selected 26 genuine reports and concluded that until 2016, 13 VRSA had been reported from Egypt, 5 from Iran, and 1 from Pakistan.[37] Askari et al reported that until 2012 thirty three credible VRSA strains had been reported, 16 from India,13 from the USA, 3 from Iran, and 1 from Pakistan.[38]

Vancomycin resistance in enterococci (VRE): O'Driscoll and Cranket followed publications on the worldwide epidemiology of VRE and found that it was high (35%) in United states 4% in

Europe,11.9% in Asia pacific and 12.9% in Latin America. There was low incidence of VRE (<1%) in Spain and France but high (>20%) in UK, Ireland, Greece, and Portugal.[39]

Linezolid

Gu et al summarized global surveillance data and stated that worldwide linezolid resistance in *Staphylococcus aureus* (LRSA) was <1%.[40] Two surveillance groups called ZAAPS (Zyvox Annual Appraisal of Potency and Spectrum) and the united states based LEADER (Linezolid Experience and Accurate Determination of Resistance) regularly monitor Linezolid susceptibility against gram positive organisms worldwide and in USA, respectively. From 2002 to 2010 ZAAPS documented 1 LRSA among 8122 *Staphylococcus aureus* (0.14% resistance rate). LEADER identified 13 LRSA among 23077 *Staphylococcus aureus* (0.05% resistance rate) (Table 2).[40] *Linezolid resistant enterococci* Global LRE prevalence is generally <1%.[45] Linezolid resistance pattern against enterococci conducted by ZAAPS 2004 and 2016 are shown in Table 3.

Table 2. LRSA surveillance from ZAAPS global (2002–2016) and LEADER USA (2004–2016) programs.[40-44]

	Total No of isolates		Number of resistant isolates	
Year	ZAAPS	LEADER	ZAAPS	LEADER
2002	502	-	0	-
2003	373	-	0	-
2004	1422	2872	0	0
2005	1416	3021	0	1
2006	2276	2913	0	1
2007	3000	3318	1	2
2008	3240	3156	0	3
2009	2958	3257	0	5
2010	2875	4540	0	1
2011	3884	3025	0	3
2012	4077	2980	3	1
2013	3885	3035	1	2
2014	3560	3106	0	1
2015	3627	3031	1	1
2016	3990	-	0	-

Table 3. LRE surveillance from ZAAPS global (2004–2016).[40-43]

Year	Number of isolates	Number of resistant isolates
	ZAAPS	ZAAPS
2004	719	0
2005	718	0
2006	-	-
2007	906	1
2008	-	-
2009	744	4
2010	787	4
2011	760	3
2012	797	2
2013	-	-
2014	813	1
2015	772	2
2016	854	2

Carbapenems

Gram-negative bacteria resistant to Carbapenem are escalating worldwide. We reviewed the prevalence of Carbapenem-resistant Enterobacteriaceae and Carbapenem resistant *Acinetobacter* and *pseudomonas Aeruginosa*, among major populations centers across the world despite data gaps and deficiency of surveillance programs in most of the countries.

Carbapenem resistant Enterobacteriaceae (CRE) in Asia: Hsu et al followed published data from Nepal ,Pakistan and India and reported a prevalence rate of > 10% in these countries and calculated a prevalence rate of 5-10% for Indonesia and Vietnam and 1-5% for Thailand and Malaysia.[46] Zhang et al conducted study in 27 provinces around China between 2014–15 and reported carbapenem resistance in *E coli and K pneumoniae* of 2% and 8%, respectively with wide regional variations. Large population centers like Shanghai and Beijing recorded higher rates 20% and 19%, respectively.[47]

Infectious agent's surveillance report (IASR) of National Institute of infectious diseases of Japan, stated that so far the prevalence of CRE in Japan was less than 1%.[48] Bae et al found that prevalence of CRE in South Korea was <1%.[49] Israel successfully

controlled its high prevalence rate of 12.1 % in 2008 to 3.8% in 2013.[50] Hammoudi et al reported isolation rate of 1.2% across 10 hospitals in Lebanon.[51] Baran and Aksu from Turkey reported 181 CRE (2.82%) cases.[52] There is sparse and limited information about the prevalence of CRE in rest of the middle East and Arabian peninsula.

CRE in Europe: The European center for disease prevention and control (ECDC) published a report on CRE prevalence among European countries in 2016 from 947 hospitals. Highest percentage of 39.9% was reported from Greece, Italy and Slovakia reported >20% CRE, Portugal, Bulgaria, Hungry and Poland had CRE prevalence of 5-10%, Spain, Germany, France, UK, Ireland, Austria, Czechia and Finland had prevalence of 1-5% and Norway, Iceland, Latvia, Estonia, Croatia and Slovenia had a CRE prevalence of <1%.[53]

CRE in North America: Centers of disease control and prevention USA in its report published in 2013 stated that there were 140,000 Enterobacteriaceae infections in US every year; of which about 9,300 were CRE associated (6.6%) and percentage of CRE among E coli and K pneumonia in USA was 2% and 11%, respectively.[54]

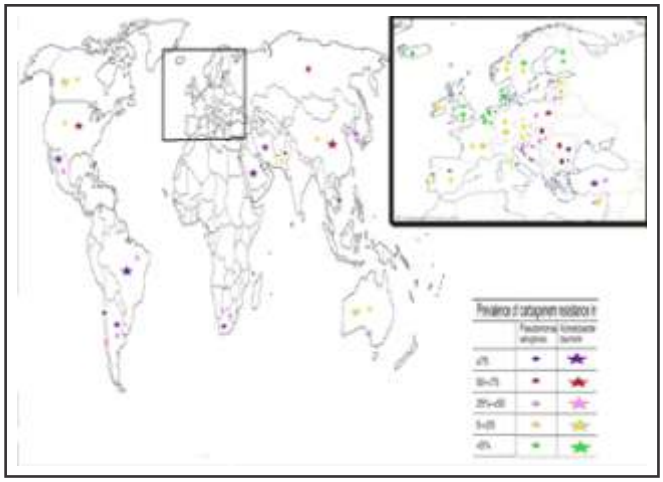
The CRE in Canada is rare. The Canadian Nosocomial Infection Surveillance Program for Carbapenem Resistant Gram- Negative (CNISP-CRGN) identified 0.1% CRE in 2010 report.[55]

Sampaio and Gale reported an alarming increase in the CRE isolation rates in Brazil, from 6.8% in 2011 to 35.5% in 2015.[56] SENTRY Antimicrobial Surveillance Program results during 2011-14 from Latin America, reported 6.3%, 0.4%, and 0.7% CRE isolation rate in Argentina, Chile and Mexico respectively.[57]

CRE in Africa: Mitgang et al analyzed 494 studies regarding CRE in Africa and found generally low (0-1%) to moderate (1- 5%) prevalence in Africa. Exceptions included over 5% in Uganda and Madagascar, South Africa, Cameroon, Nigeria, Ethiopia, Kenya, and Mauritania has a moderate CRE burden, whereas Algeria, Senegal, Namibia, Gabon, Tanzania, Ghana and Togo had a low CRE burden.[58]

Carbapenem resistant Pseudomonas and Acinetobacter species: There was higher resistance rates to carbapenems in *Pseudomonas aeruginosa* in Eastern Europe (66% in Romania) & Southern Europe countries as compared to Western Europe (0% in Iceland). (Figure). The resistant rate was very high in Russia (50-75%). Carbapenem resistance in *Pseudomonas aeruginosa* isolates from South America is about 40%. In USA, Australia & China it is 5–25%. Average resistant rates in Asian pacific countries is 10-50%.[59] Similarly, worldwide Carbapenem resistance in *Acinetobacter* is high. There is very high resistant rate in Eastern & Southern Europe (exceeding 75% in Greece , Turkey, Romania and Italy), and lower in western European countries with clear east and west divide. In South America, resistant rates exceed 80%. In USA and China the rate is 50 -75%. The rates are also high in middle eastern countries like Saudi Arabia and Iran (>75%).[59]

Figure. Carbapenem resistant Pseudomonas and Acinetobacter species.



Colistin

Colistin resistant gram negative organisms

There is only scarce published data on prevalence of Colistin resistance in gram negative organisms. This might be due to i) limited interest in this regard ii) lack of well-defined cut off values for determination of resistance and iii). Some countries do not have access to colistin. Also, most of the published work targeted only one type of organism like Pseudomonas, Acinetobacter or Klebsiella species. In some cases the sample size is very small so true prevalence is difficult to determine.

Bialvaei et al reviewed published data from across the world and concluded that the global prevalence of Colistin resistance in gram negative organisms was so far less than 10%.[60] SENTRY surveillance program, conducted between 2006 to 2009 among Gram-negative organisms from across the world described resistance to the Colistin's was low; 0.9% among Acinetobacter spp. 0.4% in Pseudomonas aeruginosa, and 1.5% in Klebsiella spp.[61] Rossi et al conducted a study in São Paulo, Brazil, over five years (2010-2014) among 33,765 Gram-negative organisms and noted that only 1346(4%) were Colistin resistant.[62] Maalej et al from Tunisia over five years found only 93(0.5%) out of 18791 Enterobacteriaceae were Colistin resistant.[63] Prim et al from Spain from found that there were 13579 Enterobacteriaceae, of which 91(0.7%) were resistant to Colistin.[64] Bianco et al reported 90 Colistin resistant (0.4%) out of 19053 Enterobacteriaceae, in a study conducted in Northern Italy.[65]

DISCUSSION

Emergence of resistant microorganisms to last resort antimicrobials is a huge concern, especially in third world countries, where treatment alternatives and newer antibiotics are not available or costly.

Our study highlights rising trend of resistance against vancomycin and carbapenem which is a likely outcome of compromised infection control in hospitals, local treatment practices and changing antibiotic policies. Therefore, we strongly recommend a rational use of these two antibiotics, especially to prevent further deterioration of situation.

Compromised infection control measures are adding fuel to the fire. The importance of infection control measures in this regard cannot be over emphasized. Therefore, compliance with hand hygiene and isolation of patients may prevent spread of organisms resistant to these antibiotics. Our study also shows that so far the resistance against linezolid and colistin is low worldwide (less than 1% and 10%, respectively). But, If we continue with our irrational prescribing practices this silently spreading slow moving crisis may prove disastrous.

CONCLUSION

Resistance to last resort antibiotics is increasing all around the world. There is a crucial need to use antibiotics judiciously.

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