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Clinical Factors Associated with Bacterial Resistance Derived from Health Care in Chihuahua, Mexico

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ABSTRACT

Abstract: Objective: Describe the profile of Multidrug Resistance (MDR), Extended Resistance (XDR) and Pan-Resistance (PDR) to antibacterials and identify the associated clinical factors in a hospital in Chihuahua, Mexico.

Materials and methods: An observational, analytical, case-control study was carried out during the period from January 2018 to December 2020. From 308 clinical records, 506 bacteria were isolated, the variables included previous admission and treatment, days of hospital stay, site of infection, days of antibiotic use, use of 2 or more antibiotics, relationship with nosocomial infection, coinfection, admission service, and reason for admission. Descriptive analysis, Xi2 and logistic regression were performed to search for association with bacterial resistance.

Results: 56 and 44% of the isolates were gram negative and positive. Significant risk factors were days of hospital stay, previous antibiotic use, nosocomial infection, antibiotic use for more than 10 days, use of two or more antibiotics, and coinfection; the latter four being an independent risk factor for bacterial multiresistance.

Conclusion: The surgery, internal medicine and pediatric services deserve special attention due to the high proportion of multi-resistant isolates and the presence of pan-resistance, in the same way, previous admission, previous treatment and days of antibiotic use were identified as risk factors for multi-resistance. derived from the prescription and therefore, subject to modification.

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INTRODUCTION

Bacterial resistance, known as the bacteria's capacity to survive medication used in the treatment, represents a global public health issue. The World Health Organization warned about the arrival of a post antibiotics era, in which despite counting with over 200 antibiotics none shows enough efficiency.[1] In some countries bacteria's response level represents a big impact in the use of antibiotics, for example, the use of fluoroquinolones becomes inefficient in more than 50% of the patients with urinary tract infection, likewise, 3rd generation cephalosporins failure in gonorrhea confirmed by over 10 countries.[2]

Bacterial resistance comprehends a spectrum of complications, in mortality terms it's been reported 2000 dead people every day due to an infectious disease with a resistant bacterium,[3] in the same way, an estimated of over 64% of the patients infected by methicillin resistant S. *aureus* (MRSA) are more likely to pass away compared to those infected by sensitive *S. aureus*; [2] in economic terms the total spent accumulated for world economy due to the resistance is estimated around 100 trillion dollars per year,[4] also, bacterial resistance it's so immediate that some pharmaceutical industries have deflected their resources to infectious diseases units due to viral etiology or cardiometabolic diseases, where

the return of investment is assured given the chronicity oh the pathologies.[5]

On the other hand, to this day we find ourselves in the middle of COVID-19 pandemic, and because of the initial ignorance on the treatment, antibiotics misuse occurred, which according to a study, will take us into an exponential increase on resistance levels in a near future,[6] however, previous the pandemic's start it has already been documented the appearance of pandrug-resistant bacteria,[7] because of it, the infectious diseases specialists must prescript according to the local context, therefore, it is indispensable to know the resistance patterns of your community, as much as clinical factors associated to bacterial resistance so that the measures be direct and appropriated.[8]

METHODS AND MATERIALS

An observational study was made, analytic, cases and control kind, during the time between January 2018 till December 2020 in a second-level attention public hospital, located in Chihuahua, Chihuahua, Mexico. The size of the sample was calculated supported by Epidat 4.2 statistical software, 506 bacteria was isolated, which were classified by their resistance level according to the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) definitions, meaning, multidrug-resistance (MDR), extensively drug-resistant (XDR) and pandrug-resistance (PDR), additionally information it's been extracted from the patients through clinical history, that is to say, bacterial resistance related variables, said information was registered into a database, such as what was done in the previous studios.[7,9] In the same way, the cases and controls were classified according to the methodology used in the previous studio,[9] obtaining a relation 1:1 of the cases and controls. The simple and comparative proportion of the variables were calculated, just like central tendance and dispersion measures, comparisons between the studied variables were made and the Odds Ratio (OR) that calculated within its respective confidence interval (IC) at 95% and a significative *p* value of <0,05. Finally, a logistic regression was made with the significant variables according to the Hosmer-Lemeshow Criterion (p <0.25) to obtain the model that explains better the associations of the variables of the study with the event. This approved by the Research Committee from Medicine and Biomedical Science Faculty (CI-057-19), no personal data from the patients was used.

RESULTS

A total of 308 clinical expedients from hospitalized patients were studied, 154 patients with an infectious disease not multidrug-resistant (controls) and 154 patients with an infectious disease multidrug-resistant (cases). Likewise, a total of 407 clinic samples of various biological fluids were cultivated: urine (n= 113), exudate from wound or eschar (n= 71), blood culture or catheter (n=96), expectoration or bronchial secretion (n= 86), and others (for example, cerebrospinal fluid, peritoneal fluid, lung fluid; n=41). From this samples 506 bacterial strains were characterized due to the fact some of the samples analyzed isolated more than one type of bacteria. (Table 1)

56% (285/506) of the bacteria were gram negative, the most frequent found: *Escherichia coli* (80/506), *Pseudomonas aeruginosa* (60/506), *Klebsiella pneumoniae* (40/506); in the gram positive (221/506) most common found: *Staphylococcus aureus* (48/506), *Staphylococcus epidermidis* (47/506), *Enterococcus faecalis* (23/506) (Table 2).

As in the bacteria classification according to their sensitivity profile to antibiotics, figure 1 shows 193 gram negative bacteria (38%) presented some level of multidrug-resistance: finding 99 MDR, 52 XDR y, notoriously, 42 PDR. On the other hand, 85 (17%) gram positive bacteria isolates showed some level of multidrug-resistance. The characterization per specie and its MDR level shows on chart 3. The whole 506 bacteria belonged to one on 61 different species, where 20 of the 61 isolated species did not present any MDR level, as shown on chart 3. Three bacteria species presented all three resistance levels (*Pseudomonas aeruginosa, Acinetobacter baumannii, Enterobacter cloacae*).

On its part the biological type of sample and resistance level (table 1), stands out that in all types of samples exist isolated from the three resistance levels, finding the most on wound exudate, followed by blood culture and expectoration.

On figure 2 are shown seven species of the most frequent on each level of multidrug-resistance within the different types of samples, being able to observe that it exists the presence of PDR bacteria in each of them, finding more an equal quantity in wound exudate (9/33) as in expectoration (9/33), corresponding mostly to *Pseudomonas aeruginosa.* As supplementary material, on appurtenant 1 are detailed all microorganisms isolated by specie, the sample where they come from, and their resistance level (MDR, XDR OR PDR).

In addition, with the purpose of exploring the magnitude of the problem of multidrug-resistance in distinct sections of the hospital, the isolated were classified according to the service and multidrug-resistance level (table 4). Was found 17% to 70% of isolated with some level of multidrug-resistance on the multiple services, being intensive therapy services (70%), surgical services (62%), and pediatric services (58%) being the most affected inasmuch as isolated on multidrug-resistance proportion. Urgency and gynecology and obstetrics services were the only exceptions by not presenting XDR and PDR isolations, the rest of the services were found within all three levels of resistance.

On the other hand, from the 308 clinical charts analyzed were found a similar distribution per sex (p= 0.25), 56% (91) of the patients were men; the age range was 43 (DE 24) for the

control group and 41 (DE 25) for the study group, without distinction between groups (p=0.35), shown on table 5.

Among the clinical history studied, prolonged stay, infection associated with health care (HAI), previous antibiotic treatment, days of antibiotic use, simultaneous use of two or more antibiotics and coinfection behaved as risk factors with a significant difference ($p< 0.05$) (table 6).

On the analysis, was found that the proportion of exposed cases to a major hospital stay (≥6 días) was superior to the ones in controls (p =0.00), finding that a prolonged stay raise up to four times the risk to generate resistance compared to those with stays shorter to five days (OR = 4.75; IC 95%: 2.71 – 8.31), likewise, was signify (p =0.00) and 4 times bigger (OR = 4.46; IC 95%: 2.17 – 7.33) the risk to generate resistance in relation to a nosocomial infection compared to an infection acquired in the community.

In addition, it was found that receiving antibiotic treatment 48 hours previously raise up to 2 times the risk of bacterial resistance compared to those with no previous consumption (OR = 2.03; IC 95%: 1.14 – 3.63), instead, intake longer to 10 days on antibiotics use, such as the use of 2 or more, were statistically significant (p =0.00) y (p =0.06), respectively, raising the resistance risk (OR = 4.95; IC 95%: 3.05 – 8.05) y (OR = 1.88; IC 95%: 1.19 – 2.97). Finally, the presence of bacterial coinfection significantly raises the risk up to 10 times to present resistance, compared to those patients with only one isolated (OR = 10.28; IC 95%: 5.53 – 19.10). As to the variants of entrance motives, previous entrance, and entrance service, there were no significant distinctions (p >0.00) (table 6). On the multivariate analysis were found as risk factors independent to acquire bacterial resistance associated with health attention, days of antibiotics use, simultaneous use of 2 or more antibiotics and coinfection, as shown in table 7.

DISCUSSION

Bacterial resistance is a worldwide problem that requires vigilance and control to limit the damage. For such reason, results in heavy importance public health programs guided to specific actions, and for this, the study of the factors that generate resistance result necessary to direct those actions, therefore, the results of this study contribute to the construction and strengthening of the preventive measures onto bacterial resistance.

In the present study, important findings are that a prolonged stay, previous treatment, nosocomial infection, over 10 days of antibiotics use, coinfection and simultaneous use of 2 or more antibiotics were significant risk factors (p <.05) associated with multidrug-resistance, being the last four variants independent risk factors to resistance.

Within the risk factors related to bacterial resistance, was found that a prolonged stay of over 6 days rise the risk up to 4.7 times of generating bacterial resistance, due to the pharmacological exposition and the procedures that most patients are summited. On the other hand, previous exposure to antibiotics in a no over 48 hours lapse is one of the constants observed that concurs with the literature as a risk factor, however, other studies identify the consumption of antibiotics during a month,[9,10] especially when carbapenems, glycylcyclines, polymyxins, and fluoroquinolones are indicated,[11,12] which could lead to mistaken prescription or wrong diagnose coming from the doctor in charge, or well, wrong administration about the medication from the patient.

Infections associated with health attention, reported as significant due to the ease of transmission, have been reported with major resistance in patients exposed to hospital environments or health centers.[13] Likewise, 65% of nosocomial infections were caused by resistant bacteria, despite other studies reporting minor numbers up to 47.5%.[14]

Prolonged use of antibiotics is also shown as a significant risk factor, it's influenced by an important quantity of elements, including the environmental context, the little knowledge of the evidence that backup shorter therapy courses, the influence on other clinics, and the habits' role and experience into the selected time on antibiotics use.[15] In the same sense, another study reports an increase in antibiotics consumption by up to 36%,[16] and in our country's institutions, it's reported an indiscriminate use where almost 100% of entrances receive antibiotics treatment, beta-lactams mostly.[17] Insomuch as the coinfection variant, due to possible mutation by a resistant bacteria that gives those resistant genes.

Simultaneous use of 2 or more antibiotics showed as a risk factor and likewise, on another study, more than half of hospitalized patients (51.5%) received at least a systemic antibiotic dose, 26.4% received 2, 1.6% received 3, and 0.1% received 4 antibiotics, which speaks, as Serra et al. mentions, no update to the practice guides as well as the non-adherence of many professionals to them, that indicate antibiotic therapy empirically or without knowledge of susceptibility profiles. Those variants that showed no significance (p >0.05) were entrance motives, previous entrance, and service entrance, despite a region's study showing the last two mentions as risk factors.[7]

Inasmuch as a resistant bacterium, most were Gram-negative bacilli (56%, 285 bacteria), the rest corresponding to gram-positive cocci (44%, 221 bacteria); gram-negative isolated most frequently were *Escherichia coli*, followed by *Pseudomonas aeruginosa* and lastly *Klebsiella pneumoniae*; within gram-positive were *Staphylococcus aureus*, followed by *Staphylococcus epidermidis* and lastly, *Enterococcus faecalis*; agreeing with previous reports on another region's study. [7]

In addition, within higher resistance bacteria indicated, agreeing with the priority WHO's list and what has already been reported from the region,[7,9] we find within gram-negatives to *Pseudomonas aeruginosa, Acinetobacter*

baumannii, and Enterobacteriaceae; and on gram-positives we find *Staphylococcus aureus, Staphylococcus epidermidis,* and *Enterococcus;* previously mentioned and according to literature, could be due the genetic plasticity and capacity to acquire and diffuse a wide repertoire of resistance determinants, just like selective pressure from the hospital environment. Alike, there are studies where *Acinetobacter baumannii* it's reported with the highest resistance levels,[18] reported in others at least one MDR pathogen in 31% of the patients, one XDR pathogen in 17%, and no PDR,[12] unlike our study, where major resistance rate was reported.

CONCLUSION

Data in the present study indicated that the resistance level is to worry about, due to the fact 68% of gram-negative bacteria and 38% of gram-positive bacteria showed MDR, XDR, or PDR, most frequently associated with resistance were: *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus;* however, the highest resistance levels were presented by: *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Enterobacter cloacae.* Alike, within the total isolated bacteria, 23.5% (119 bacteria), belong to priority groups according to the WHO, and 97.5% (116 bacteria) are a critical priority, mostly *Pseudomonas aeruginosa* resistant to carbapenems, 1.6% (2 bacteria) are high priority, corresponding to *Enterococcus faecium* and *Staphylococcus aureus* both penicillin-resistant and 0.9% (1 bacteria) is a medium priority, corresponding to *Streptococcus pneumoniae* penicillin-resistant. And the resistant bacteria mostly associated with IAAS correspond to *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Escherichia coli*. Among the services most affected by bacterial resistance, they correspond, in descending order to Internal Medicine, followed by Surgery, Pediatrics, NICU, ICU, Gynecology and Obstetrics, and finally Emergencies. And, finally, a prolonged stay, previous treatment, nosocomial infection, more than 10 days of antibiotic use, coinfection, and use of two or more antibiotics were the significant risk factors ($p < .05$) associated with multidrug-resistance, being the last four variables were independent risk factors for multidrug-resistance.

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Table I. Type of clinical samples, number of bacterial isolates and level of resistance

Muestra clínica	Samples	Isolated	Bacterial resistance			
			MDR	XDR	PDR	No MDR
Urine	113	121	50	11	9	51
Exudate from Wound/Eschar	71	95	34	15	11	35
Blood culture or Catheter	96	148	63	15	10	60
Expectoration or Bronchial Secretion	86	96	20	11	10	55
Others	41	46	11	2	5	28
Total	407	506	178	54	45	229

MDR: Multidrug-resistance; XDR: Extensively drug-resistant; PDR: Pandrug-resistance.

Table II. Classification of isolated bacteria according to Gram staining and most frequent species

Clasification	n (%)	Main representatives (descending order)
Gram negative	285 (56)	*E. coli, P. aeruginosa, K. pneumoniae*
Gram positive	221 (44)	*S. aureus, S. epidermidis, E. faecalis*
Total	506 (100)	

Table III. Distribution of the isolates by species and level of multiresistance

Species	Gram Stain	Frequency	Bacterial resistance			
			MDR	XDR	PDR	No MDR
Escherichia coli	-	80	49	4	0	27
Pseudomonas aeruginosa	-	60	5	17	23	15
Staphylococcus aureus	+	48	12	0	0	36
Staphylococcus epidermidis	+	47	30	0	0	17
Klebsiella pneumoniae	-	40	14	7	0	19

Acinetobacter baumannii	-	38	3	20	10	5
Enterococcus faecalis	+	23	4	0	0	19
Enterobacter cloacae	-	22	6	1	8	7
Streptococcus alfa hemolitico	+	18	3	0	0	15
Staphylococcus haemolyticus	+	13	12	0	0	1
Staphylococcus hominis	+	12	7	0	0	5
Enterococcus faecium	+	9	1	1	0	7
Proteus mirabilis	-	7	4	0	0	3
Streptococcus agalactiae	+	7	0	0	0	7
Klebsiella oxytoca	-	6	2	0	0	4
Staphylococcus capitis	+	4	3	0	0	1
Streptococcus mitis	+	4	1	0	0	3
Enterobacter aerogenes	-	4	3	0	0	1
Rothia mucilaginosa	+	3	0	0	0	3
Streptococcus anginosus	+	3	1	0	0	2
Streptococcus pyogenes	+	3	1	0	0	2
Stenotrophomonas maltophilia	-	3	1	0	0	2
Streptococcus salivarius	+	2	0	0	0	2
Streptococcus bovis	+	2	0	0	0	2
Citrobacter freundii	-	2	1	0	0	1
Citrobacter youngae	-	2	1	0	1	0
Complejo Burkholderia cepacia	-	2	1	0	0	1
Corynebacterium urealyticum	+	2	0	0	2	0
Staphylococcus intermedius	+	2	1	0	0	1
Staphylococcus kloosii	+	2	1	0	0	1
Pantoea agglomerans	-	2	0	2	0	0
Morganella morganii	-	2	1	0	0	1
Klebsiella aerogenes	-	2	2	0	0	0
Enterococcus raffinosus	+	2	0	1	0	1
Acinetobacter species	-	2	0	1	0	1
Enterococcus casseliflavus	+	1	1	0	0	0
Aeromonas caviae	-	1	0	0	0	1
Arcanobacterium haemolyticum	+	1	0	0	0	1
Cedecea davisae	-	1	1	0	0	0
Acinetobacter lwoffii	-	1	1	0	0	0
Enterococcus hirae	+	1	0	0	0	1
Micrococcus lylae	+	1	0	0	0	1
Neisseria animaloris	-	1	0	0	0	1
Providencia alcalifaciens	-	1	1	0	0	0
Pseudomonas putida	-	1	0	0	0	1
Rothia dentocariosa	+	1	0	0	0	1
Salmonella species	-	1	0	0	0	1
Serratia plymuthica	-	1	1	0	0	0
Shigella boydii	-	1	1	0	0	0
Shigella flexneri	-	1	0	0	0	1

Staphylococcus auricularis	+	1	1	0	0	0
Delftia acidovorans	-	1	1	0	0	0
Staphylococcus carnosus	+	1	0	0	1	0
Staphylococcus simulans	+	1	0	0	0	1
Staphylococcus gallinarum	+	1	0	0	0	1
Streptococcus alactolyticus	+	1	0	0	0	1
Streptococcus porcinus	+	1	0	0	0	1
Streptococcus sanguinis	+	1	0	0	0	1
Streptococcus uberis	+	1	0	0	0	1
Staphylococcus pasteuri	+	1	1	0	0	0
Staphylococcus schleiferi	+	1	0	0	0	1

MDR: Multidrug-resistance; XDR: Extensively drug-resistant; PDR: Pandrug-resistance.

Table IV. Distribution of isolates by entry service and resistance level

Admission service	Isolated	Isolated MDR n (%)	Isolated XDR n (%)	Isolated PDR n (%)	Total MDR+XDR+PDR n (%)	Total No-MDR n (%)
Surgery	118	42 (36)	18 (15)	13 (11)	73 (62)	45 (38)
Internal Medicine	226	75 (33)	29 (13)	18 (8)	122 (54)	104 (46)
Gynecology	24	8 (33)	0	0	8 (33)	16 (67)
Pediatry	52	18 (35)	4 (8)	8 (15)	30 (58)	22 (42)
NICU	41	22 (54)	1 (2)	0	23 (56)	18 (44)
ICU	27	11 (41)	2 (7)	6 (22)	19 (70)	8 (30)
Emergency	18	3 (17)	0	0	3 (17)	15 (83)

MDR: Multidrug-resistance; XDR: Extensively drug-resistant; PDR: Pandrug-resistance; NICU: Neonatal Intensive; ICU: Intensive Care Unit.

Table V. Sociodemographic characteristics of the study population

Variant	Control Group n=154 $\bar{x}$ ± SD (%)	Study Group n=154 $\bar{x}$ ± SD (%)	*p*
Age	43 ± 24	41 ± 25	0.35
Gender			
Masculine	81 (53)	91 (59)	0.25
Femenine	73 (47)	63 (41)	
Scholarship			
Middle shcool or before	117 (76)	119 (77)	0.36
Highshcool or later	12 (8)	17 (11)	
Unknown	25 (16)	18 (12)	
Occupation			
employed	80 (52)	81 (52)	0.32
unemployed	53 (34)	58 (38)	
unknown	21 (14)	15 (10)	
Residence area			0.41
Rural	43 (28)	33 (21)	

Urban	107 (69)	117 (76)	
unknown	4 (3)	4 (3)	
Entrance Motive			
Non-infectious cause	109 (71)	123 (80)	0.85
infectious cause	45 (29)	31 (20)	
Entrance service			
Urgency	14 (9)	3 (2)	
Surgery	32 (21)	37 (24)	
Internal medicine	74 (48)	72 (47)	
Gynecology and Obstetrics	11 (7)	8 (5)	0.1
Pediatrics	10 (6)	12 (8)	
NICU	9 (6)	14 (9)	
ICU	4 (3)	8 (5)	
Comorbidity			
No	74 (48)	82 (53)	
Yes	79 (51)	70 (46)	0.33
Unknown	1 (1)	2 (1)	

NICU: neonatal intensive care unit; ICU: intensive care unit

Table VI. Bivariate analysis of clinical factors

Variable		Grupo Cases		Controls		X^2	p	OR	IC 95%	
		n	%	n	%				Min	Max
Hospital stay (days)	**≤ 5 days**	21	6.8	66	21.4	32.43	**0**	4.75	2.71	8.31
	≥6 days	133	43.2	88	28.6					
Reason admission	**No infectious**	123	39.9	109	35.4	3.42	0.064	0.61	0.361	1.03
	infectious	31	10.1	45	14.6					
Previous admission	**NO**	105	34.1	110	35.7	0.386	0.535	1.16	0.17	1.89
	YES	49	15.9	44	14.3					
HAIs	**NO**	34	11	86	27.9	36.91	**0**	4.46	2.17	7.33
	YES	120	39	68	22.1					
Previous antibiotic use	**NO**	115	37.3	132	42.9	5.9	**0.015**	2.03	1.14	3.63
	YES	39	12.7	22	7.1					
Admission service	**Emergency**	3	1	14	4.5	10.58	0.102	NA	_	_
	Surgery	37	12	32	10.4					
	Internal Medicine	72	23.4	74	24					
	Gynecology	8	2.6	11	3.6					
	Pediatry	12	3.9	10	3.2					
	NICU	14	4.5	9	2.9					
	ICU	8	2.6	4	1.3					
Period of Antibiotic use (days)	**≤ 10 days**	44	14.4	103	33.7	44.1	**0**	4.95	3.05	8.05
	> 10 days	108	35.3	51	16.7					
Simultaneous >2 antibiotic prescription	**NO**	60	19.6	85	69	7.58	**0.006**	1.88	1.19	2.97
	YES	92	30.1	27.8	22.5					
Coinfection	**NO**	73	23.7	139	45.1	65.92	**0**	10.28	5.53	19.1
	YES	81	26.3	15	4.9					

HAIs: Health-care associated infections; NICU: Neonatal Intensive; ICU: Intensive Care Unit.

Table VII. Significant multivariate model variables

Variable		Crude OR	IC 95% Min	IC 95% Max	Adjusted OR	IC 95% Min	IC 95% Max
HAIs	**SI**	4.46	2.17	7.33	1.49	1.08	2.06
	NO	1	-	-	1	-	-
Period of Antibiotic use (days)	**> 10 días**	4.95	3.05	8.05	1.72	1.26	2.35
	≤ 10 días	1	-	-	1	-	-
Simultaneous >2 antibiotic prescription	**SI**	1.88	1.19	2.97	0.72	0.56	0.93
	NO	1	-	-	1	-	-
Coinfection	**SI**	10.28	5.53	19.1	1.82	1.46	2.27
	NO	1	-	-	1	-	-

HAIs: Health-care associated infections

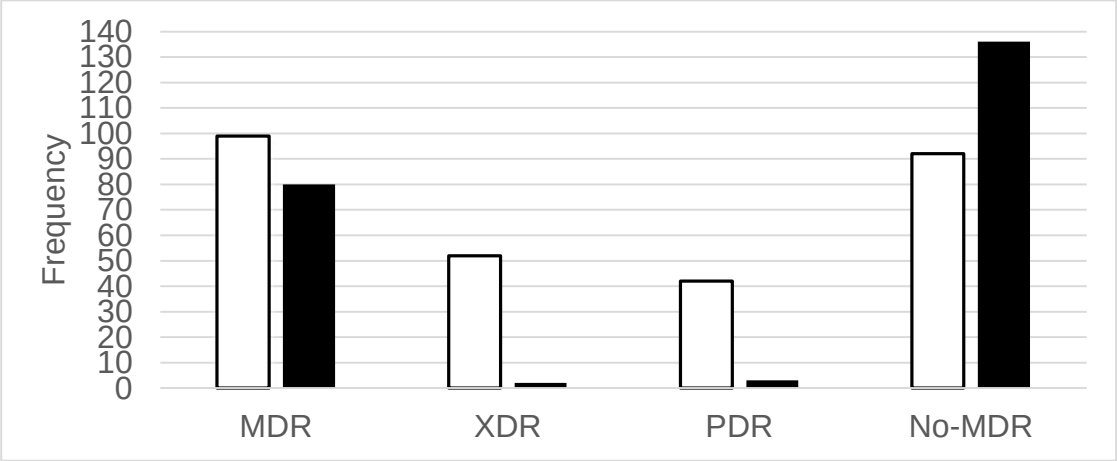

Figure 1. Distribution of isolates by level of multiresistance and staining. On white, gram-negative isolates; in black, isolated gram-positive. MDR: Multidrug-resistance; XDR: Extensively drug-resistant; PDR: Pandrug-resistance.

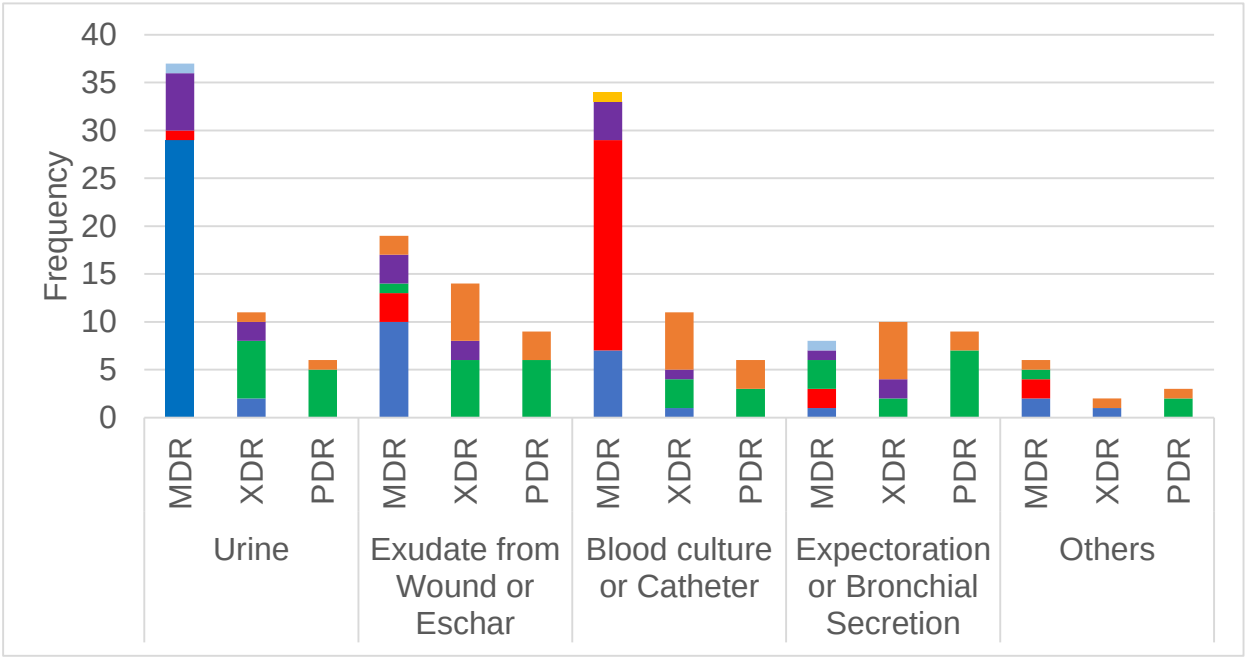

Figure 2. Most frequent resistant microorganisms and distribution according to sample origin: Escherichia coli (dark blue), Klebsiella pneumoniae (purple), Pseudomonas aeruginosa (green), Staphylococcus epidermidis (red), Acinetobacter baumannii (orange), Klebsiella aerogenes (light blue) and Burkholderia cepacia Complex (yellow). MDR: Multidrug-resistance; XDR: Extensively drug-resistant; PDR: Pandrug-resistance.