Antibiogram Profile of Antibacterial Multidrug Resistance in Democratic Republic of Congo: Situation in Bukavu City Hospitals

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Abstract

Background

Bacterial strains carrying multidrug resistance traits are gaining ground worldwide, especially in countries with limited resources. This study aimed to evaluate the spreading of multidrug-resistant bacteria strains in Bukavu city hospitals in the Democratic Republic of Congo.

Methods

We analyzed 758 antibiogram data recorded in files of patients consulted between January 2016 and December 2017 at three reference hospitals selected as sentinel sites, namely the Panzi General Reference Hospital (HGP), BIO -PHARM hospital (HBP), and Saint Luc Clinic (CSL).

Results

Of 758 isolates tested, the laboratories identified 12 bacterial strains in 712 isolates, of which 223(29.42%) presented MDR profile, including Escherichia coli (11.48%), Klebsiella pneumonia (6.07%), Enterobacter (5.8%), Staphylococcus aureus and coagulase-negative staphylococci (1.58%), Proteus mirabilis (1.85%), Salmonella enterica (1.19%), Pseudomonas aeruginosa (0.53%), Streptococcus pneumonia (0.4%)), Citrobacter (0.13%), Neisseria gonorrhea (0.13%), Enterococcus faecalis (0.13%) and Morganella morganii (0.13%). Infected patients were significantly adults (73.1% vs. 21.5%) compared to children and mainly women (63.7% vs. 30.9%; p = 0.001).

Conclusion

The observed expansion requires that hospital therapeutic committees set up an effective clinical management system and define the right combinations of antibiotics.

Background

By definition, Multidrug-Resistant (MDR) microbes are species non-sensitive to at least one agent in three or more antimicrobial categories [1]. Extended Drug-Resistant (XDR) strains resist at least one agent in all but two or fewer antimicrobial groups (bacterial isolates remain susceptible to only one or two classes. PanDrug-Resistant (PDR) strains are resistant to all agents from all categories of antimicrobials [1, 2]. As pointed out by the World Organization for Animal Health (WOAH), the Food and Agriculture Organization of the United Nations (FAO), and the World Health Organization (WHO), MDR microorganisms have dangerously reached high levels in all parts of the world, especially in low-income regions [3–6]. The pathogens responsible for tuberculosis (TB), malaria, sexually transmitted infections (STI), typhoid fever, bacterial dysentery, and pneumonia now exhibit MDR characteristics. Up to 17% of TB cases are MDR, and XDR of TB is increasingly observed worldwide [7].

The hospital is the primary source of MDR infections caused by *Staphylococcus aureus (SA)*, *Enterococcus faecium (EF)*, *Escherichia coli(EC)*, *Klebsiella pneumoniae(KP)*, Enterobacter spp. (EB), Citrobacter spp.(CB), *Pseudomonas aeruginosa(PA)*, and *Acinetobacter calcoaceticus(AC)* [8]. Up to 10% of hospitalized patients contract nosocomial infections [9], but the community-based transmission is also dangerously gaining ground. The death rate associated with diseases caused by bacteria resistant to antibiotics is often higher than that of susceptible bacteria [7, 10]. Resistance often leads to treatment failure and thus increases mortality from infections. When an infection can no longer respond to

treatment with a first-line antibiotic, more expensive drugs should be used. Collaterally, prolonging illness and treatment increases health care costs, as well as the financial burden on families and society [7, 11]. Many factors triggering microbial resistance are known, mainly the misuse or irrational use of antibiotics. In 20 to 50% of cases, their use in humans is unnecessary, and in animals, it is questionable in 40 to 80% cases [12].

The increasing proportion of poor-quality generic drugs is a growing concern in the sub-Saharan Africa region [12–14]. There are multiple drawbacks to using poor-quality antimicrobial drugs; that lead to microbial resistance, treatment failure, exacerbation of the disease, and increased death rates. The WHO and the US Centers for Disease Control and Prevention (CDCP) have recognized the importance of studying the factors of emergence and risk of resistance and the need to establish control [3, 8, 15]. The MDR scoreboard itself in the Democratic Republic of Congo (DRC) is not clearly defined. Epidemiological investigations are essential to monitoring the spread of MDR as in other countries with limited resources [16–18]. This study aimed to profile the spread of MDR bacterial infections in Bukavu, a town in eastern DRC.

Methods

Study design and data collection

The study was a retrospective cross-sectional analysis of the antibiogram data recorded in the files of patients consulted between January 2016 and December 2017. Three reference hospitals were selected as sentinel sites, namely the Panzi General Reference Hospital (HGP), BIO -PHARM hospital (HBP), and Saint Luc Clinic (CSL). Laboratories performed antimicrobial sensitivity tests on blood, urine, cerebrospinal fluid, and other samples, according to standard recommendations [19–21]. The susceptibility outcome was considered sensitive or resistant based on the inhibition diameter and according to data published in the 2017 CA-SFM recommendations.

Ethical considerations

All methods were carried out in accordance with relevant guidelines and regulations. All experimental protocols were approved by the research committee of the Faculty of Medicine (UOB). The clinical directors of the study hospitals allowed the collection of data. As retrospective study, informed consent was waived by institutional ethics review board of the Official University of Bukavu. We assured for the confidentiality of individual patient information.

Data analysis

The SPSSv20 statistical software and Windows Excel 10 served to run descriptive statistics with a statistically significant difference set at $p < 0.05$; 95%, regarding the demographics of patients with MDR, the frequency of MDR strains in each hospital, and each biological sample.

Results

Identification and Prevalence of MDR strains

Table 1 shows the total number (N) of each strain identified, the prevalence (%) of MDR and NMDR strains by column and row, as well as the ratio of MDR/NMDR. Of 758 isolates examined, laboratory technicians identified 12 bacteria present in 712 (93.93%) samples and did not identify the strains in 46 (6.07%) samples. Of those identified, 535 (70.58%) were NMDR, and 223 (29.42%) MDR. The column % shows that the most prevalent were *EC* (49.34%), *KP* (11.87%), EB (11.61%), and *SA*(11.61%). Individual MDR frequencies were *EC* (11.48%), *KP*(6.07%), EB(5.8 %), *SA*(1.58%), *PM* (1.85%), *S*(1.19%), *PA*(0.53%), *SP* (0.40 %), CB(0.13%), *NG* (0.13%), *EF* (0.13%) and *MM*(0.13%). By row, out of 374 *EC* isolates, there were 287 (76.74%) NMDR and 87 (23.26%) MDR, resulting in an MDR / NMDR ratio = 0.303. All 46 unidentified isolates were NMDR.

Table 1
Identity and Frequency of MDR and non-MDR strains

Strains name	Total	MDR	NMDR	Total	MDR	NMDR	MDR	NMDR	
	N	N	N	C%	C%	C%	R%	R%	Ratio
Escherichia coli (EC)	374	87	287	49.34	11.48	37.86	23.26	76.74	0.303
Klebsiella pneumoniae (KP)	90	46	44	11.87	6.07	5.80	51.11	48.89	1.045
Enterobacter spp (EB)	88	44	44	11.61	5.80	5.80	50.00	50.00	1.000
Staphylococcus aureus (SA)	88	12	76	11.61	1.58	10.03	13.64	86.36	0.158
Proteus mirabilis (PM)	28	14	14	3.69	1.85	1.85	50.00	50.00	1.000
Salmonella enterica (SE)	21	9	12	2.77	1.19	1.58	42.86	57.14	0.750
Pseudomonas aeruginosa (PA)	12	4	8	1.58	0.53	1.06	33.33	66.67	0.500
Streptococcus pyogenes (SP)	7	3	4	0.92	0.40	0.53	42.86	57.14	0.750
Citrobacter (CB)	1	1	0	0.13	0.13	0	100	0	-
Enterococcus faecalis (EF)	1	1	0	0.13	0.13	0	100	0	-
Morganella morganii (MM)	1	1	0	0.13	0.13	0	100	0	-
Neisseria gonorrhea (NG)	1	1	0	0.13	0.13	0	100	0	-
Strains unidentified	46	0	46	6.07	0.00	6.07	0.00	100	0.00
Total isolates	758	223	535	100	29.42	70.58	29.42	70.58	0.417
C% (column percentage); R%(row percentage)									

Frequency of MDR strains disaggregated by age, gender, hospital, specimens

Figure 1 shows that most infected patients were adults (73.1%) compared to children (21.5%, p = 0.036). EC, KP, EB, SA, PM, and SE are found in both age groups, while PA, SP, CB, EF, NG, and MM not found in paediatric patients. Likewise, most women (63.7%) were infected compared to men (30.9%; p = 0.001). PA has been found much more in men than in women; CB, EF, and MM in males only. The only case of NG was from a woman. In total, 53.8% of the 223 MDR strains came from the HGP hospital, 30.9% from the HBP hospital, and 15.2% from CSL (p = 0.001). EC, KP, and EB strains were isolated from all three hospitals; the other strains occurred in only one or two hospitals. The majority of biological samples tested were urinary tract infections (61.8%) followed by skin pus (23.8%), ear pus, vaginal secretion, stool, sputum, blood, and cerebrospinal fluid. EC was found in UT (80.4%), skin pus (8%), vagina (10.3%); KP in UT (56.5%) and skin pus (41.1%); EB in UT (47.7%), skin pus (20.5%), vagina (2.3%), stool (22.7%), blood (2.3%), cephalospinal fluid (2.3%); SA in UT (50%), skin pus (33.3%, ear pus (16.7%); PM in UT (35.7%), skin pus (50%, blood (7.1%) ; SE in UT (55.5%), skin pus (33.3%), ear pus (11.1%); BP in UT (25%), skin pus (50%), ear pus (25%) ; SP in UT (33.3%), skin pus (66.7%); CB in spindle (100%); EF in UT (100%); NG in UT (100%); MM in skin pus (100 %).

Susceptibility of MDR isolates to antibiotics used in hospitals

Table 2 shows the number of each strain exposed to a given antibiotic and, in parentheses, the percentage of susceptible strains.

For example, to ciprofloxacin, only 25% of 76 EC isolates, 12.8% of 39 KP isolates, 17.5% of 40 EB isolates, 40% of 10 SA isolates, 0% 4 PA isolates, and 0% of 1 MM isolates were susceptible. Against meropenem, 40.8% of the 49 EC strains tested were sensitive. For EC strains, we found 25% ciprofloxacin-sensitive, 27.3% moxifloxacin-sensitive, 9.3% clavulanic amoxicillin-sensitive, 0% ampicillin sensitive, 40.8% meropenem-sensitive, 60% gentamicin-sensitive, 26.5% cotrimoxazole-sensitive, and 27.8% chloramphenicol-sensitive. Likewise, 21.2% of EB were meropenem-sensitive, 80% of SA were chloramphenicol sensitive, and 40% sensitive to ciprofloxacin. Meanwhile, 33% of SP were susceptible to ciprofloxacin, and 66.7% susceptible to meropenem. Almost all MDR bacterial strains were resistant to ampicillin.

Table 2
Number of each strain and percentage (%) of sensitive isolates to each antibiotic

ABT categories	EC	KP	EB	SA	PM	SE	PA	SP	EF	MN	NG
Ciprofloxacin	76 (25.0)	39 (12.8)	40 (17.5)	10 (40.0)	14 (22.4)	7 (42.9)	4 (0)	3 (33.3)	1 (0)	1 (0)	1 (0)
Norfloxacin	8 (12.5)	4 (0)	3 (0)	2 (0)	1 (0)	2 (0)	1 (0)	1 (0)		1 (0)	
Moxifloxacin	11 (27.3)	15 (0)	6 (0)			1 (0)					1 (0)
Nalidixic acid	10 (20.0)	2 (0)	4 (0)		1 (0)	2 (0)					
Cotrimoxazole	68 (26.5)	33 (0)	33 (18.2)	4 (0)	12 (0)	8 (0)	2 (0)	2 (50.0)	1 (100)	1 (0)	1 (0)
Amoxi-Clav	54 (9.3)	36 (0)	34 (9.8)	5 (0)	11 (0)	4 (0)		3 (0)	1 (0)	1 (0)	
Ampicillin	15 (0)	28 (0)	15 (0)	3 (0)	10 (0)	1 (0)	2 (0)		1 (0)	1 (0)	
Oxacillin	6 (0)	8 (0)	4 (0)	2 (0)	2 (0)	2 (0)	1 (0)				
Ceftriaxone	69 (4.3)	44 (6.8)	36 (0)	11 (18.2)	13 (0)	7 (14.3)	4 (0)	3 (0)		1 (0)	
Cefuroxime	2 (0)	1 (0)	3 (0)								
Meropenem	49 (40.8)	44 (4.5)	33 (21.2)	8 (25)	14 (7.1)	8 (25)	2 (0)	3 (66.7)	1 (100)	1 (0)	
Imipenem			1 (100)								
Azythromycin	71 (22.6)	40 (7.5)	39 (7.9)	8 (0)	12 (0)	6 (0)	3 (0)	2 (0)	1 (0)	1 (0)	1 (0)
Erythromycin	9 (0)		8 (0)	1 (0)							
Amikacin	7 (0)	1 (0)	5 (0)	2 (0)	1 (0)	1 (0)		1 (0)	1 (100)		
Gentamicin	5 (60)		2 (0)			1 (0)		2 (0)			

ABT categories	EC	KP	EB	SA	PM	SE	PA	SP	EF	MN	NG
Kanamycin			1 (100)								
Chloramphenicol	18 (27.8)	33 (6.1)	18 (0)	5 (80)	9 (11.1)	5 (40)	3 (0)	1 (0)			
Clindamycin	18 (5.6)			1 (0)	1 (0)		2 (0)	2 (0)			
Tetracycline	1 (0)		1 (0)	1 (0)						1 (100)	
Doxycycline	24 (25)		10 (30)		1 (0)		1 (100)				1 (100)

Discussion

In 2014, the WHO [22] had expressed the need to establish a global surveillance system for antimicrobial resistance, then launched in October 2015, the Global Antimicrobial Surveillance System (GLASS), in close collaboration with various existing networks based on experience from other WHO surveillance programs. This study aimed to contribute to such a need. The results identified 12 bacterial strains were in the samples taken from 758 cultures, mainly the EC strain. The profiles found here are comparable to those reported in other studies in Africa, the USA, and Europe [24], as illustrated below. Some isolates might even be XDR bacteria, but we did not separate them because the data did not come from a controlled study. The GLASS report [22] revealed that the most common MDR bacteria were *Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus, and Streptococcus pneumoniae, followed by Salmonella spp*. The 29.4% median rate of MDR strains found in Bukavu ranges between 23% in the USA and 37% in India. In the USA, a study [24] conducted in community hospitals revealed 23% of MDR pathogens, of which the three most common were *SA*(28%), *EC*(24%), and coagulase-negative *staphylococci* (10%); the infecting organism varied according to the place of acquisition. In Rwanda, the prevalence of MDR strains was 28% based on three primary data [26]. Studies in India found 37.1% MDR bacteria, 13.8% XDR and 0% PDR [2, 25]. Despite the differences in the prevalence levels reported worldwide, the results support the alert on the increase in MDR bacteria around the world.

Aggregation of results by the hospital showed that more cases were from GHP (53.8%), followed by HBP (30.9%) and CSL (15.2%). The significant difference ($p = 0.001$) is only related to the size of each hospital. The profile also indicated that most isolates were from sexually transmitted UTIs (61.8%) followed by skin infections (23.8%). The majority of people carrying MDR strains were adults (60%), as expected since children are less prone to UTIs. The high percentage of women (51%) is due to anatomical causes (proximity to the vaginal and anal openings), poor hygiene habits, sexual intercourse, and pregnancy [17, 23].

The susceptibility profiles of the strains varied according to the classes of antibiotics. Regarding resistance to the beta-lactam category, the case of ampicillin and amoxicillin is striking. The test shows that these drugs are less effective against almost all strains. Many bacteria are also resistant to cephalosporins in this study. However, our previous research had shown that they are currently still widely prescribed and also used as self-medication in Bukavu [17, 18]. A review article [16] reports that MDR (penicillin + two other classes) is 25% in Africa, 20% in Latin America, 12% in Eastern Europe, 18% in Western Europe, and 26 % in the USA. Data from bacterial resistance surveillance networks show that the distribution of 3rd generation cephalosporin-resistant Enterobacteriaceae species has increased significantly [22, 27].

According to the authors, this resistance mainly concerns the production of extended-spectrum beta-lactamase (ESBL) and, to a lesser extent, plasma cephalosporinases (AmpC). For instance, the resistance of KP to third-generation cephalosporin is critical on a large scale in all WHO regions of the Americas, the Western Pacific, the Eastern Mediterranean, and the European Region [22]. Community-based infection with resistant E.coli producing extended-spectrum beta-lactamases is ubiquitous in Asia, the Middle East, South America, and parts of Europe [28].

Regarding aminoglycosides (AGs), gentamicin was more effective against EC (60%), resistant to *PA, KP*, and *Salmonella*. However, it is used mainly in combination with amoxicillin and azithromycin [18]. In the study by Bala et al. [29], no MDR isolate of gentamicin appeared. These in vitro results suggest that gentamicin may be an effective treatment option for MDR strains. In Bukavu hospitals, gentamicin is used mainly in combination with amoxicillin and azithromycin [18]. Parenteral administration of AGs, which limits their use as self-medication, partly explains their preserved efficacy. By far, the most common mechanism of resistance to AGs is the inactivation of these antibiotics by enzymes modifying their structure [30, 31].

This study showed high resistance of many infections to second-generation quinolones. Only 25% of the 76 EC strains were susceptible to ciprofloxacin, which backs what some studies reported in Asia and Africa [16, 22, 32–34]. EC ST131 is a clone of MDR disseminated worldwide that presents resistance to fluoroquinolones in addition to the production of ESBL CTX-M. EC ST131 strains tend to induce pyogenic liver abscesses and sometimes metastatic infections, including meningitis. The median resistance of SE Typhi to nalidixic acid is between 15.4–43.2% for pathogens isolated from patients with severe illness [28, 35–37].

Finally, the percentage of strains susceptible to meropenem was 41% for EC, 66.7% for SP, and less than 25% for the others, consistent with other studies. However, most clinicians consider carbapenems to be the class of choice for severe infections caused by ESBL-producing Enterobacteriaceae [34, 35]. Carbapenems-resistance of PA is the most typical and frequent example of resistance induced by developing cell membrane impermeability [38]. Furthermore, the enzymatic inactivation of carbapenems is the most common resistance mechanism in A. Baumannii [32]. Carbapenem-resistant Enterobacteriaceae (CRE) represents an immediate threat to public health that requires urgent and aggressive action. Community-wide infections are likely to lead to a dramatic increase in the practical use of carbapenems [39, 40]. A review article reported that the median prevalence of resistance to chloramphenicol in Enterobacteriaceae, isolated from patients with febrile illness, ranged from 31.0–94.2%.

Conclusion

The findings confirm the ongoing elevated prevalence of multidrug-resistant bacteria in Bukavu, not withdrawing that the rates found can even be underestimated. In most cases worldwide, the risk factors for antimicrobial resistance are insufficient infection control in hospitals, inadequate public health systems for antimicrobial stewardship, inadequate knowledge of prescribers and users, advertising, and pharmaceutical companies' impact. The observed expansion requires that hospital therapeutic committees set up effective control and clinical management systems and define the right combinations of antibiotics.

Abbreviations

AG: Aminoglycosides

CB: *Citrobacter*

CDCP: Centers for Disease Control and Prevention

CRE: Carbapenem-Resistant Enterobacteriaceae

CSL: Saint Luc Clinic

DRC: Democratic Republic of Congo

EB: *Enterobacter spp*

EB RC3G: Enterobacteriaceae resistant cephalosporin 3rd generation -

EC: *Escherichia coli*

EF: *Enterococcus faecalis*

ESBLE: Extended-spectrum beta-lactamase-producing Enterobacteriaceae

FAO: Food and Agriculture Organization of the United Nations

GLASS: Global Antimicrobial Surveillance System

HBP: BIO-PHARM hospital

HGP: Hospital General de Panzi

KP: *Klebsiella pneumoniae*

MDR: MultiDrug Resistant

MM: *Morganella morganii*

NG: *Neisseria gonorrhea*

NMDR : Non-MultiDrug Resistant

PA : *Pseudomonas aeruginosa*

PDR : PanDrug-Resistant

PM : *Proteus mirabilis*

SA : *Staphylococcus aureus*

SE: *Salmonella enterica*

SP: *Streptococcus pyogenes*

STI: Sexually transmitted infections

TB: Tuberculosis

WHO: World Health Organization

WOAH: World Organization for Animal Health

XDR: Extended Drug-Resistant

Declarations

Ethics and consent to participate

All methods were carried out in accordance with relevant guidelines and regulations. All experimental protocols were approved by the research committee of the Faculty of Medicine (UOB). As retrospective study, informed consent was waived by institutional ethics review board of the Official University of Bukavu.

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest/Competing interests

The authors declare that they have no competing interests

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Authors' contributions

C.A.I and P.B.M. designed the protocol, collected data, and did the first analysis. F.M.K. and P.W. did the literature search and wrote the first draft. J.N.K validated the protocol, revised data analysis, and wrote the final draft. All authors reviewed the manuscript.

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Figures

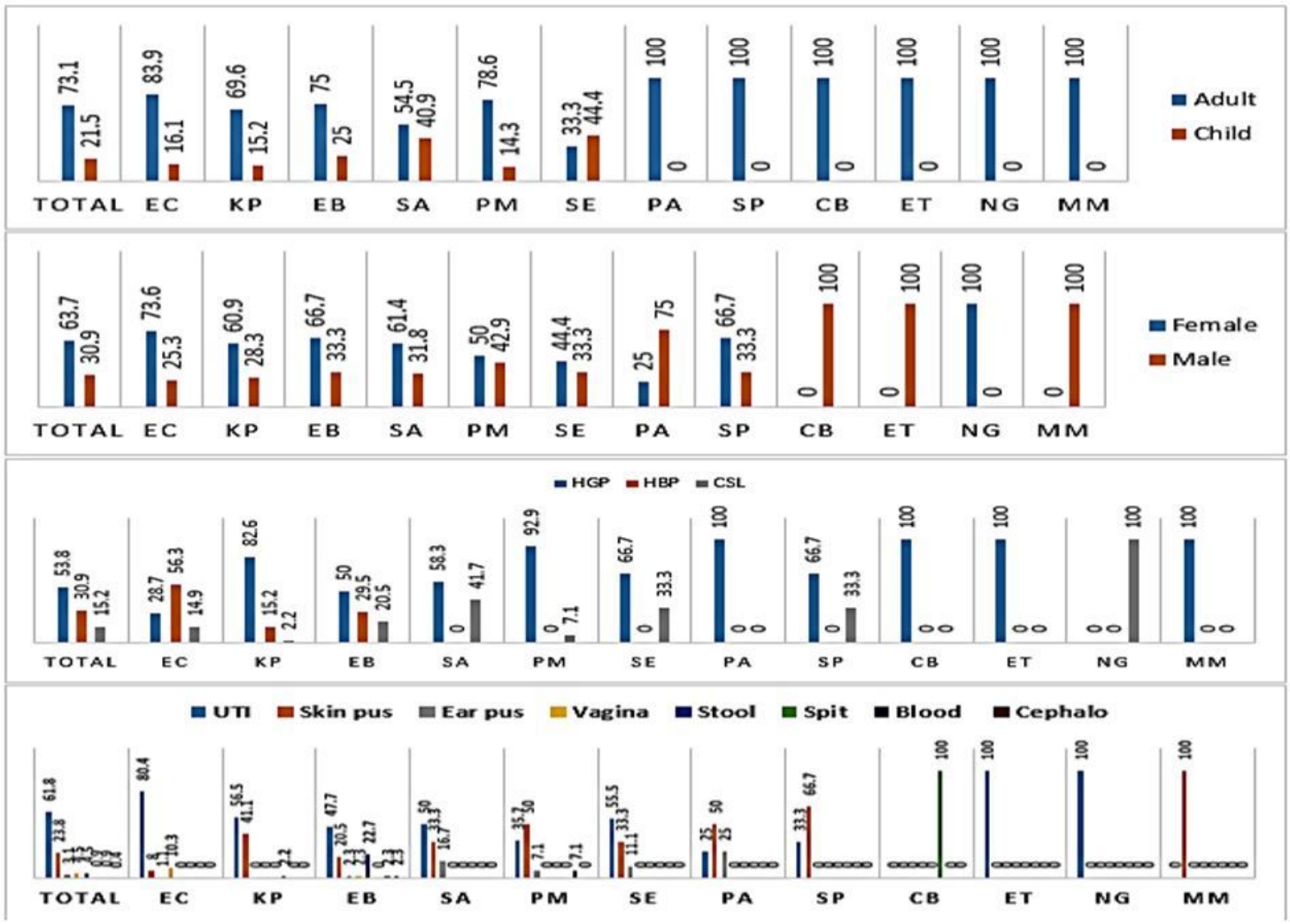

Figure 1

Frequency of MDR strains disaggregated by age, gender, hospital, specimens