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Journal of Infection 82 (2021) e8–e10

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Letter to the Editor

High rates of antimicrobial resistance among clinical isolates from microbiology laboratories in Syria

Dear Editor

We read with interest this recently published study in the Journal by Kwok et al. describing antimicrobial resistance (AMR).[1] Protracted conflicts have triggered large waves of internal displacement and cross-national forced displacement of millions of people across the Middle East and North Africa region, stretching already overburdened healthcare systems across the region.[2] An important public health challenge facing such contexts is AMR where the melee of conflict, overuse of antibiotics, lack of antimicrobial stewardship, weak laboratory infrastructure and insufficient quality and quantity of relevant human resources provide particular drivers for AMR.[3] Nosocomial and community transmission is exacerbated by poor infection control practices and inadequate shelter or sanitation leading to increases in AMR which increases the economic burden on patients and the health system.[4,5] This is becoming increasingly pertinent during the COVID-19 pandemic where antimicrobials are overused alongside a weakened antimicrobial stewardship program.[6] Data in such conflict affected countries is limited with little reliable data available for Syria.[7]

The few published studies are limited by the small number of samples or patients, lack of generalizability, and mostly originated from the major cities, particularly Damascus and Aleppo.[7] Here we report data from 5 public hospitals and 4 private laboratories in 4 major cities across Syria including Damascus, Homs, Latakia, and Tartous. Minimum inhibitory concentrations (MICs) for 1463 out of 3577 isolates (41%) were provided. For the rest, only disc diffusion data was reported with results as sensitive, intermediate, or resistant. The results were obtained after requests were sent to the laboratories by one of the authors. A survey in which available equipment, protocols and training was performed with the participating laboratories. Reports were retrieved for a variety of clinical samples including blood, sputum, urine, and wounds. All samples were collected between June 2016 and March 2018. Methods used by the laboratories included a description of the morphological characteristics of the colonies, biochemical tests and API tests (BioMérieux, France) to determine the genus and/or species of the isolates. Results of antibiotic susceptibility tests were collected for up to 100 isolates of each bacterium in each location. For antibiotic susceptibility testing, 7 labs used the agar disk diffusion method while the remaining 2 labs used the VITEK® 2 method (BioMérieux, France). Susceptibility reports were provided in paper format. Diameters of inhibition zones and MIC values were extracted to Excel™ sheets, and assigned R, I or S where *R*=resistant, *I*=intermediate and *S*=susceptible, following the Clinical and Laboratory Standards Institute (CLSI) guidelines.[8] An antibiogram was assigned to each clinical isolate, and the number/percentage of susceptible isolates of each bacterium was calculated against each antibiotic. Rates of susceptibility were then calculated and compared per facility, city, or species/genus. Multi-drug resistance (MDR) bacteria were defined as microorganisms that are resistant to one or more agents in at least three separate classes.

Data for 3577 bacterial isolates were provided. The susceptibilities and resistance patterns are detailed in Table 1. A notable finding from this study is the absence of standard operating procedures and guidelines among laboratories; this was noted from discussions with the microbiologists as well as the array of antibiotic discs used and reported for isolates. It is notable that antibiotic discs were used for bacterial isolates even when the bacteria are known to be intrinsically resistant, when no CLSI MIC break point exists or when the antibiotic tested is not used in clinical practice to treat the infection. Some of these discrepancies are underlined in the table. A key example are the antibiotic sensitivities performed for *Pseudomonas* spp. where co-amoxiclav and cefixime are tested. On direct questioning, microbiologists reported a locally devised criteria for interpreting the results e.g. a zone of >21 mm as suggestive of *Pseudomonas* being sensitive to co-amoxiclav.

For Gram-negatives (excluding *Acinetobacter,* which is intrinsically resistant to most antibiotics tested), high proportions of resistance to co-amoxiclav are reported with a range of 75–89% for *Klebsiella* spp., *Proteus* spp., *E. coli and Enterobacter* spp. For ciprofloxacin, the range is 43–57%; for amikacin, it is 12–50% and for meropenem, it is 8–45%. The resistance patterns for the *Pseudomonas* isolates are concerning with resistance of 43% and over reported for antibiotics that should be effective (piperacillin-tazobactam, meropenem, ciprofloxacin, and amikacin). For carbapenem resistance (suggested here by meropenem resistance,) 20% of *E. coli* and *Proteus* isolates and 45% of *Pseudomonas* isolates were resistant.

For *Acinetobacter*, 90% of isolates were reported as resistant to meropenem and 85% were resistant to amikacin which is very concerning. *Acinetobacter* is a bacterium that has increasingly been seen in clinical settings. It has intrinsic resistance to a number of commonly used antibiotics, and multi- or pan-resistant strains have been known to cause infection among those injured during conflict (so called “Iraqibacter”)[9] or nosocomial transmission, particularly in intensive care units. As such, this is of particular concern in Syria where protracted conflict and humanitarian crisis continue. Verbal communication to ZAK reported that two patients died in one center during the summer of 2017, both harbouring pan-drug resistant isolates of *Acinetobacter baumannii* (Personal communication).

Resistance to tigecycline among most Gram negatives bacteria was high with 64% of *Acinetobacter*, 9% of *Klebsiella*, 29% of *Proteus* were reported to be resistant. However, 67% of *Pseudomonas aeruginosa* was surprisingly sensitive, emphasizing the inaccuracy of the laboratory operation; *E. coli* resistance was low at 1.7%. For col-

https://doi.org/10.1016/j.jinf.2020.09.026

Table 1
Antimicrobial resistance rates of 10 bacterial species/genera against 11 selected antimicrobial agents.

Bacterium[a]		Antimicrobial agent [a,b]										
		AMC	AMX	CFM	CPM	PTZ	MER	AZM	CIP	AMK	TIG	COL
Staphylococcus	T	296	95	142	256	141	108	158	228	149	132	12
aureus	R	176	61	138	146	33	43	119	160	85	9	11
(GPC)	%	**59.5**	**64.2**	**97.2**	**57.0**	**23.4**	**39.8**	**75.3**	**70.2**	**57.0**	**6.8**	**91.7**
Staphylococcus	T	124	53	54	186	113	68	91	65	19	96	2
epidermidis	R	15	13	50	44	9	9	42	7	2	4	2
(GPC)	%	**12.1**	**24.5**	**92.6**	**23.7**	**8.0**	**13.2**	**46.2**	**10.8**	**10.5**	**4.2**	**100**
Streptococcus	T	122	5	98	113	21	30	33	89	62	16	–
pyogenes	R	32	5	88	31	6	15	22	59	58	2	–
(GPC)	%	**26.2**	**100**	**89.8**	**27.4**	**28.6**	**50.0**	**66.7**	**66.3**	**93.5**	**12.5**	**–**
***Enterococcus* spp.**	T	64	–	–	64	56	60	59	79	–	10	–
(GPC)	R	22	–	–	32	9	9	44	46	–	0	–
	%	**34.4**	**–**	**–**	**50.0**	**16.1**	**15.0**	**74.6**	**58.2**	**–**	**0**	**–**
***Klebsiella* spp.**	T	408	56	149	456	274	247	281	329	437	88	54
(GNR)	R	352	56	143	300	102	58	205	175	112	8	5
	%	**86.3**	**0**	**96.0**	**65.8**	**37.2**	**23.5**	**73.0**	**53.2**	**25.6**	**9.1**	**9.3**
***Proteus* spp.**	T	195	65	112	202	103	113	100	119	212	47	52
(GNR)	R	159	50	76	95	29	22	98	52	74	14	16
	%	**81.5**	**76.9**	**67.9**	**47.0**	**28.2**	**19.5**	**98.0**	**43.7**	**34.9**	**29.8**	**30.8**
***Acinetobacter* spp.**	T	216	13	37	190	170	135	132	154	175	108	173
(GNR)	R	213	13	34	185	158	122	124	151	149	69	2
	%	**98.6**	**0**	**91.9**	**97.4**	**92.9**	**90.4**	**93.9**	**98.1**	**85.1**	**63.9**	**1.2**
***Pseudomonas* spp.**	T	311	47	133	353	214	227	217	306	363	74	153
(GNR)	R	277	43	125	209	92	104	162	174	184	24	7
	%	**89.1**	**91.5**	**94.0**	**59.2**	**43.0**	**45.8**	**74.7**	**56.9**	**50.7**	**32.4**	**4.6**
Escherichia coli	T	885	39	144	924	638	724	693	845	916	178	61
(GNR)	R	693	37	122	521	138	147	520	480	110	3	5
	%	**78.3**	**94.9**	**84.7**	**56.4**	**21.6**	**20.3**	**75.0**	**56.8**	**12.0**	**1.7**	**8.2**
***Enterobacter* spp.**	T	259	17	119	293	115	170	150	238	307	38	–
(GNR)	R	195	16	112	166	12	14	93	116	129	0	–
	%	**75.3**	**94.1**	**94.1**	**56.7**	**10.4**	**8.2**	**62.0**	**48.7**	**42.0**	**0**	**–**

[a] AMC, amoxicillin-clavulanic acid; CFM, cefixime; CPM, cefepime; PTZ, piperacillin-tazobactam; MER, meropenem; AZM, azithromycin; CIP, ciprofloxacin; AMK, amikacin; TIG, tigecycline; COL, colistin. T, total; R, resistant. GPC, Gram-positive coccus. GNR – Gram-negative rod.
[b] Results were interpreted based on the Clinical and Laboratory Standards Institute (CLSI) criteria. Inappropriately selected antimicrobial agents, to which intrinsic resistant could exist, or which would not be used clinically were underlined.

istin, resistance is reported at 1.2% for *Acinetobacter*, 8.2% for *E. coli*, 9.3% for *Klebsiella* spp. and 30.8% for *Proteus* spp.. If these results are accurate, they represent high rates of resistance to this antibiotic, considered as "last resort" option in many cases for treatment of extremely drug resistant (XDR) pathogens. Though these results need to be treated with caution given inconsistencies with reporting, at face value, they indicate high rates of AMR.

In 2015, the Global Antimicrobial Surveillance System (GLASS) was launched by WHO to improve understanding of AMR internationally.[3,10] However, without addressing the factors which hamper accurate reporting of resistance patterns, particularly in conflict affected settings, we will be unable to define the true extent of AMR or address its causes in such contexts.[10]

Author contributions

ZAK and AY conceptualized the study with input from AA, RAN, Ash, Asa, EA and wrote the first draft. NK, SK, WE, AA contributed heavily to editing, rewriting and analysis.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Acknowledgments

None. The authors declare no source of funding.

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