Microbiology and Pathology Antibiotic Resistance in Uropathogenic Citrobacter Spp. Isolated from Internally Displaced Persons with Urinary Tract Infections in Internally Displaced Camps, Maiduguri

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Abstract

Background: We sought to investigate the health challenges attributed to urinary tract infections (UTI) amongst internally displaced persons (IDPs) in north-eastern Nigeria.Methods: Urine specimens were collected, micro-biologically processed and subjected to antimicrobial susceptibility testing using standard agar disc diffusion techniques in accordance with standard protocols.Results: Citrobacter spp. accounted for 1407 (30.01

Index terms— citrobacter, uropathogenic, antimicrobial susceptibility, internally displaced persons, multi-drug resistance, urinary tract infections.

1 Introduction

nternally displaced persons (IDPs) are 'persons or groups of people who have been compelled to flee or leave their homes or places of customary residence, in particular as a result of, or in order to avoid the effects I of armed conflicts, situations of generalised violence, violations of human rights or natural or man-made disasters, and who have not crossed an internationally recognised state border [1]. Controversially, IDPs are often referred to as refugees, even though they do not fall within the legal definitions of being called refugee because, they are distinct from refugees who are displaced outside their national borders [2,3].

Estimates from the Internal Displacement Monitoring Centre (IDMC) indicate that the number of people displaced annually by conflict and violence has increased globally since 2003 [4]. A massive 40.3 million of them were newly uprooted during 2016 equalling to 15,000 people displaced every day in African countries alone [4, **??**,6, **??**,8]. By the end of 2017, a recordbreaking 65.6 million people had become displaced within their own country as a result of violence **??**5].

Three quarters of these IDPs reside in ten countries of the world, and five of these are located in Sub Saharan Africa. The total number of people displaced by conflict in the region is almost 12 million [4,6].The IDMC's Global Overview [6] reported that the majority of the increase in new displacement during 2015 was the result of protracted crises in the Democratic Republic of the Congo, Iraq, Nigeria, South Sudan and Syria. In total, these five countries accounted for 60 per cent of new displacement worldwide [6].

In Central Africa, conflict and violence have resulted in over a million displacements of people in the Democratic Republic of Congo [4]. Other African countries which have had large numbers of IDPs in the past decade are Somalia, Uganda, Kenya and Sudan [9].

In Nigeria, the insurgent activities of Jam?'at Ahl as-Sunnah lid-Da'wah wa'l-Jih?d (Islamic State's West Africa Province) commonly called Boko Haram (BH) in the past decade have forced more than 2,152,000 people to flee their homes with 1,434,142 of these coming from Borno State [10]. This has resulted in an unprecedented humanitarian crisis in the North eastern part of the country and the Lake Chad region [4]. Inter communal

clashes resulting from ethno religious disputes, between Fulani herdsmen militia and farmers have also resulted in over 700,000 people being displaced from the Middle Belt region of Nigeria [4].

Internal displacement has significant effects on the health and well-being of the affected populations. These impacts could be categorised as directly due to violence and injury or indirectly due to increased rates of communicable diseases and malnutrition [11,12,13,14]. According to Owaje et al. [15] there areseveral risk factors, working in synergy during displacement which promote communicable diseases. These factors include the massive movement of populations and resettlement in temporary locations, overcrowding, economic, environmental degradation, poverty, inadequate availability of potable water, poor sanitation and bad waste management [11]. These conditions are further complicated by the absence of shelter, food shortages and poor access to healthcare [16]. In Sub-Saharan Africa, the combined effects of these factors depend on the location and increased risk of diseases such as acute respiratory infections [17], diarrhoeal diseases [18] and scabies [19].

Diarrhoeal and Urinary tract diseases are major causes of morbidity and mortality among IDPs and mainly result from substandard or inadequate sanitation facilities, poor hygiene and poor hand washing practices due to scarcity of soap and water [16].

Urinary Tract Infection (UTI) continues to be one of the most important causes of morbidity and mortality. Hitherto, UTIs caused by Citrobacter species have been described in 5 to 12% of bacterial urine isolates in adults [20,21].The genus Citrobacter is a distinct group of aerobic, Gram negative bacilli from the Enterobacteriaceae family, widely distributed in water, soil, food and intestinal tract of humans and animals. We report here the emergence of Citrobacter as a significant uropathogen among IDPs living in IDP camps in Maiduguri, Nigeria, and their susceptibilities to antimicrobial agents in order to generate data that will improve the efficacy of the treatment of this infection.

2 II.

3 Materials and Methods

The study was conducted between February 2017 through January 2018 and the studied population was composed of 5000 IDP patients seeking medical attention at out-patient IDP-clinics in Maiduguri (Muna Garage, NEMA mobile Clinics, UNICEF Clinic, Jidari, ALIMA Clinics, Arabic Teachers College, Teachers Village, NYSC Camp, Gubio) metropolis. The benchmarks for patient inclusion were -patients who presented with UTI symptoms: like burning during micturition, fever, pyuria, frequency of urine, dysuria, haematuria, flank pain, suprapubic discomfort, and whose urine specimens showed significant bacterial growth (?10 5 CFU/mL) associated with a white blood cell count of >10 4 /mL as outlined by Metri and Jyothi [22].

4 a) Specimen Collection

Informed verbal consent was obtained from all patients prior to specimen collection. Afterward, they were educatedon the clean-catch midstream urine techniques as documented by Collee et al. [23] and Ochada et al. [24]to collect urine specimens of at least 20mL into a sterile Universal container (Sterling, UK). For female patients, after proper positioning of the thigh, they were instructed to spread the labia and clean the area with sterile swabs, then pass a small amount of urine into the toilet, and finally urinate into the container. For male patients, after hand washing, a clean-catch midstream urine sample was collected after cleaning of the glans with sterile swabs. The specimens were labelled appropriately, transported to the laboratory, and stored at 4 o C for further analyses.

5 b) Specimen

Processing, Identification and Maintenance

In the laboratory, a calibrated loop method was used for the isolation of bacterial pathogens from urinary specimens. A sterile 4.0 mm platinum wired calibrated loop was used to deliver 0.001mL of urine. Concurrently, a loopful of urine sample was plated on Cystine-Lactose-Electrolyte Deficient (CLED) agar, Mannitol Salt (MSA) agar, MacConkey agar, and blood agar medium (Biotech Laboratories Ltd. UK). The inoculated plates were incubated aerobically at 37°C for 24 h and in cases where no growth was observed for 48 h. The number of isolated bacterial colonies was multiplied by 1000 for the estimation of bacterial load/mL of the urine sample. By the description of Prakash and Saxena [25], a urine specimen was considered positive for UTI if an organism was cultured at a concentration of ?10 5 cfu/mL or when an organism was cultured at a concentration of 10 4 cfu/mL and >5 pus cells per highpower field, epithelial cells, casts, and crystals were observed on microscopic examination. Identification of bacterial isolates to species level was done on the basis of their cultural characteristics as illustrated by Murray et al. [26] and standard biochemical characteristics was conducted on API 20E (Biomerieux, France). Confirmation of isolates as Citrobacter spp., was done using Polymerase Chain Reaction (PCR) as described by Thepa and Tribuddharat [27]. Identified and pure isolates were cryopreserved at -84°C.

6 c) Antibiotic Susceptibility Testing

The antimicrobial susceptibility pattern of all the isolates were tested by employing the modified single disc diffusion technique described by the Clinical and Laboratory Standards Institute (CLSI, 2017) [28]. The

antibiotics tested were Amikacin (10?g), Amoxicillin (25?g), Amoxicillin/clavulanic acid (30?g), Ceftriaxone (30?g), Cephalexin (30?g), Chloramphenicol (30?g), Ciprofloxacin (5?g), Co-trimoxazole (25?g), Erythromycin (15?g), Gentamycin (10?g), Levofloxacin (5?g), Nalidixic acid (30?g), Nitrofurantoin (300?g), Norfloxacin (5?g), Ofloxacin (5?g), Perloxacin (5?g), Streptomycin (10?g) and Tetracycline (30?g), all obtained from Oxoid (England). Breakpoints and interpretation for susceptibility/resistance was based on CLSI [28] criteria. Standard strains of E. coli ATCC25922, and S. aureus ATCC25923 were used routinely in this study as control organisms. We defined any isolate as multidrug resistant (MDR) strain if it shows resistance against three or more different antibiotics (29).

Resistance against different antibiotics appears on the same bacterial strains more often than expected.

7 d) Statistical Analysis

Statistical analysis was done using SPSS (version 20) to determine frequency distribution, mean, harmonic mean, standard deviation, analysis of variance (ANOVA), Duncan Multiple Range and Pearson correlation coefficient.

8 i. Ethics

Ethical approval was secured from Research Ethics Committee of the University of Maiduguri Teaching Hospital. Permission from Camp Clinical Directors was also obtained.

9 III.

10 Results

In order to categorise symptomatic urinary tract infections among the IDPs, 5000 mid-stream urine specimens were collected, processed and the results analysed. Of the 5000 urine specimens collected 4300 (86.00%) were found to be positive for significant bacteriuria while 700 (14.00%) yielded no growth. Among these 4300 culture positive specimens, 4688 (i.e. 1.09 isolates per sample) uropathogenic bacteria isolates were obtained, of which 4110 had a single pathogen and 578 had two types of bacteria isolates. The age of our patients ranged from 1 to 72 years, with a mean of 34.2 $\pm$ 12.6 years and a median of 37 years. UTI was significantly more prevalent among the females (?? value = 0.002) than the males with 3474 (80.79%) significant specimens obtained from females while 826 (19.21%) were from the males, thus making male: female ratio of 1:4.2.

As presented in Figure **??**, overall, Gramnegative bacteria accounted for 83.8% of the isolated uropathogens, while Gram positive bacteria accounted for 16.2%. Citrobacter species accounting for 1407 (30.01%) of all the isolates were found to be second most common uropathogens among the IDPs following Escherichia coli with 1896 (40.44%) while Enterobacter aerogenes (presently known as Klebsiella aerogenes) was the least isolated bacteria with 57 (1.22%).

Table1 shows that the number of uropathogenic Citrobacter isolated from females were significantly higher than those from their male counterparts ($p<0.05$) with 1182 (84.0%) from the females while 225 (16.0%) were from the male.

Figure **??** shows Age-wise distribution of uropathogenic Citrobacter spp. isolated. As shown in all age groups, the isolation of Citrobacter species from the urine of the subjects increased with age and picked in the 31 to 40 years age group and then declining to its lowest level in the 51 to 60 years age group before rising again.

Figure 3, depicts the in vitro susceptibility patterns of the isolated Citrobacter spp. to eighteen different antimicrobial agents. As illustrated, all the uropathogenic Citrobacter isolates were resistant to Amoxicillin, Cephalexin, Co-trimoxazole, and Tetracycline. While, more than 50% of the isolates showed resistance to Amoxicillin/clavulanic acid (98%), Ceftriaxone (90%), Erythromycin (85%), and Ciprofloxacin (56%). In descending order, resistance was shown to Chloramphenicol and Levofloxacin (46%) each, Pefloxacin (44%), Norfloxacin and Ofloxacin (43%) each, Streptomycin (32%), Gentamicin and Nalidixic acid (10%) each, Nitrofurantoin (6%) while none of the isolates showed resistance to Amikacin (0%).

Table 2 shows the frequency of Citrobacter spp., isolates and their antibiotic resistance patterns. The result showed that Citrobacter freundii (850 isolates, 60.4%) was the most predominant among the uropathogenic Citrobacter species encountered in this study. This was followed by C. koseri (421 isolates, 29.9%), while C. amalonaticus and C. intermedius accounted for 68 (4.85%) isolates each.Additionally, all the isolated Citrobacter were multidrug resistant (i.e. showed resistance to at least three classes of the tested antimicrobial agents).

11 IV.

12 Discussion

In spite of the multitudinous health difficulties confronted by the IDPs, there is limited documentation of these health challenges. Emphasis has been bestowed more on their physical and mental health challenges [30,31,32] which for example includes sexual assaults and substance abuse [33,34]. However, little or no reports are available about their urogenital challenges, hence the significance of this present study. We investigated the prevalence and contribution of UTIs, particularly those attributable to uropathogenic Citrobacter among these susceptible groups of individuals. From this study, the prevalence of UTI among the IDPs presenting with urinary symptoms is

86.0%, while the prevalence rate accountable to uropathogenic Citrobacter is 30.01%. With regards to prevalence of uropathogens among IDPs, there is no baseline data for reference. Nevertheless, this high rate of UTI prevalence observed is consistent with previous report of 75.0% and 80.0% recorded in the same Maiduguri area amongst patients seeking medical attention by Kachalla et al. [35] and Abdu et al. [36] respectively. This high isolation rate had been attributed to various reasons such as the differences in specimens, specimen collection and processing methods [37]. Furthermore, this high prevalence rates could be due to environmental factors in the IDP-camps including poor waste disposal and environmental sanitation, overcrowding, inadequate access to water supply and healthcare services as identified by Lam et al. [38] In humans, the emergence of Citrobacter in a wide spectrum of infections such as in the urinary tract, respiratory tract, wounds, bone, peritoneum, endocardium, meninges and blood stream is on the increase [39,40,41,42]. Among these various sites of infection, the urinary tract is regarded as the most common [43,44], with isolation rate ranging from 5 to 44% [44,45,46,47]. This is in comparison with 30.01% observed in this study. Citrobacter freundii (60.4%) was found to be the most prevalent among the uropathogenic Citrobacter species. While Citrobacter koseri constitute 29.9%, Citrobacter amalonaticus and Citrobacter intermedius constituted 4.85% of the isolates each. However, the frequency of Citrobacter in urine specimens varies from one study to the other [37,45,47,48]. In the present study, women have higher rate of uropathogenic Citrobacter than men (Table 1), because anatomically, in females, the urethra has been known to be shorter and closer to the anus [49]. Other investigators have also reported similar findings to ours [37,50,51]. Furthermore, the high prevalence of uropathogenic Citrobacter among these female groups aside from sexual activities, may be related to the study participants whose immune system might have been impaired. Nonetheless, study conducted in India has shown sharp contrast to our findings where the condition was more prevalent in males when compared to females counterparts [22].

Globally, there is an increasing incidence of resistance among uropathogens to older antimicrobial agents and also to the newer and supposedly more potent antimicrobial agents [52]. The in vitro antibiotic susceptibility profile of the uropathogenic Citrobacter species isolated in this study showed a discouraging pattern with multidrug resistance being prominent among the organisms against which the drugs were tested. Majority of the isolates in the current study were found to be resistant to Amoxicillin, Amoxicillin/ clavulanic acid, Ceftriaxone, Cephalexin, Ciprofloxacin, Co-trimoxazole, Erythromycin, and Tetracycline [Figure 3]. This has important implications as most patients in our locality receive these drugs, or a combination of these drugs as empirical therapy or as definitive treatment.

As revealed by the present study none of the isolates was resistant to Amikacin, while the values of 10% and 32% of the uropathogenic Citrobacter isolates were resistant to Gentamicin and Streptomycin respectively. Therefore the aminoglycosides should be considered as being the most effective antimicrobial drugs of choice for treating uropathogenic Citrobacter infections and should be administered while awaiting the culture result. This outcome is similar to previous studies [36,53,54,55,56]. Earlier, Abdu and Lamikanra [57] suggested that what was responsible for the high susceptibility recorded to the aminoglycosides and one of such explanations was the fact that aminoglycosides are rarely abused as they are administered parenterally, a dosage form which is far less liable to self-medication than the orally administered antibiotics in this locality, furthermore, the cost of Amikacin is about $70 per vial, taking it far beyond the reach of the vast majority of people in a locality where people are considered poor. Despite the impressive efficacy associated with the aminoglycosides, many studies have documented a contrary result with higher resistance to these agents among uropathogenic Citrobacter [22,44,45,58]. Apart from their innate ability to transfer their resistance to aminoglycosides, one of the reasons suggested for the low efficacy of aminoglycosides in those studies was that they are frequently prescribed for treatment of infections [44].

With the increasing incidence of drug resistant organisms seen presently, there is need to evaluate the activity of Nitrofurantoin even though it is a drug such extensively drug-resistant strains. Yet, as revealed, Nitrofurantoin is the second most efficacious antimicrobial agent to the isolated uropathogenic Citrobacter. The maximum resistance percent value was found as 6% (94.0% susceptible), 42 isolates each for C. freundii and C. koseri (Table 2). Since good in vitro activity was shown by Nitrofurantoin it may be considered as first line oral therapy for IDPs patients with UTI. There is very limited data on Nitrofurantoin activity against Citrobacter isolates. Nevertheless, the few available reports were found to be similar to the present findings [53,59]. Various reports have also corroborated our findings with Nitrofurantoin susceptibility among uropathogenic Escherichia coli [60,61,62,63]. Besides its multiple mechanisms of action that have enabled it to retain potent activity against pathogens [60,64], other possible explanations that might have allowed Nitrofurantoin to still show good in vitro efficacy against uropathogenic Citrobacter in this study might be attributed to its unpleasant side effects such as, gastrointestinal discomfort, pulmonary, liver, and nerve toxicity [65,66] that discourage its abuse leading from extensive self-medication. However, in contrast to the efficacious outcome of Nitrofurantoin reported in this study, a significant increase in resistance of uropathogenic Citrobacter and uropathogenic Escherichia coli to Nitrofurantoin have been reported [67,68,69,70].

In this study, the overall susceptibility of the uropathogenic Citrobacter isolated from the IDPs for the fluoroquinolones group was worrisome. Surprisingly, apart from the Nalidixic acid that the isolates showed least resistance to (10%), resistance to other groups were significantly high. As revealed by the study, Ciprofloxacin resistance was found to be most frequently encountered with 56%, this is followed by Levofloxacin with 46%. Perfloxacin was next with 44%, while the value obtained for both Norfloxacin and Ofloxacin was 43%. This

pattern of resistance is in agreement with the results of previous studies [22,37,45,71], an outcome suggesting that the fluoroquinolones have limited usefulness in the management of uropathogenic Citrobacter within the studied environment. This is unexpected considering that the fluoroquinolone group of antimicrobial agents are employed as empirical therapy or as definitive treatment for UTI and were incorporated into the therapeutic management of infectious agents only recently [57]. Furthermore, the ability of these organisms to spread easily from person to person with consequential remedial complications having recognised them as efficacious anti-infective drugs only a few years ago [72]. This outcome thus calls for urgent and drastic regulatory measures in order to combat this situation, for failure to do so, we may be trending towards a postantibiotic era which calls for a great deal of research into the development of new antibiotics. Studies have also shown that mutations in gyrA and parC genes are the most common mechanism involved in high-level quinolone resistance, in addition to the spread of plasmid-mediated quinolone resistance genes and efflux-pump mutants [73].

In spite of the fact that Chloramphenicol is strictly regulated and it is not commonly prescribed due to its adverse effect (aplastic anaemia), moderate rates of resistance observed in the present study (46%) may be due to the fact that Chloramphenicol is widely used in our study environment with other broad spectrum antibiotics in the treatment of life threatening infections. The result obtained in this study is in agreement with a study in Ethiopia which documented Chloramphenicol resistant strains of Citrobacter spp. from UTI [37,48]. Nevertheless, it is not in agreement with the study of Liu et al. (2017) who reported a high susceptibility rate of Chloramphenicol (87%) in China [56].

In the current study, all the uropathogenic Citrobacter isolates were resistant to Co-trimoxazole and Tetracycline, while 85% were resistant to Erythromycin. These findings authenticate the figures from previous studies [37,71]. However, unlike in these previous studies, these isolates showed highest rates of resistance to Co-trimoxazole, Erythromycin and Tetracycline. Highest resistance (100%) against 18%; 26%; and 32% reported for Co-trimoxazole by Metri et al. [45], Liu et al. [56] and Mishra et al. [53] respectively. For Erythromycin the high resistance rate of 85% was reported against 3.28% Azithromycin by Liu et al [56].

The percent resistance values of the ?-lactam group were similar (Table 2). Among the ? -lactam antibiotics, Amoxicillin and Cephalexin showed the highest percent (100%) resistant isolates; the resistance pattern slightly decreased in the following order: Amoxyclav (98%) and Ceftriaxone (90%). As illustrated, there is no significance difference between the patterns of resistance shown by the uropathogenic Citrobacter to Amoxy-clav and Ceftriaxone. For Amoxy-clav: Ceftriaxone, 100%:100% of C. freundii isolates had the highest percentage of resistance, while the values of resistance for C. koseri, C. amalonaticus and C. intermedius were 100%:95%; 79.4%:11.8%; and 79.4%:11.8% respectively.

This increased resistant level may be ascribed to the easy access to these drugs in our study environment. Furthermore, these drugs are purchased directly over-the-counter from pharmacies and other unauthorised sources without a doctor's prescription and are commonly used for a broad spectrum of infections. With this pattern of resistance, it is recommended that most ?-lactams antibiotics should not be used as first line agents in the blind treatment of UTIs. This is more so, as ascribed by Paramythiotou and Routsi, [74] infections caused by resistant pathogens are associated with higher rates of morbidity and mortality than infections caused by susceptible pathogens.

Multiple antibiotic resistance (MAR) index reveals (table not shown) that all of the isolates were resistant to at least three antibiotic groups This highlighted the fact that, most of the antibiotics tested in this study have lost their potency in respect of the organisms against which they are deployed. This could be linked to several factors including: possession of multiple resistance genes in the bacterial genome that enable them to transfer resistances to virtually all the antibiotics, source of the isolates, its ability to evade antibiotic effects and variation in antibiotic concentration. Many studies have identified bacterial source as an important determinant of MAR especially due to Citrobacter spp. when it occurred in an infection. This emergence has coincided with previous findings that documented Citrobacter spp. is often resistant to multiple classes of antibiotics, suggesting that both clinical and environmental strains may be a reservoir of antimicrobial resistance determinants [39,56,75,76,77,78]. Many factors contribute to the emergence of MAR in Citrobacter among which over prescribing of antibiotics by clinicians, over-usage and incomplete course of antibiotics by patients, availability of the antibiotics could not be ignored in regions like ours. Additionally, environmental and personal hygiene can also contribute to the spread of resistant species among people especially in clinical settings. Mass media campaigns, regular training, and reformation of drug policies would to a significant extent alleviate the increased spread of MAR isolates among the populace. The findings have revealed that there is a crucial necessity for persistent monitoring of susceptibility of pathogens in different populations to commonly used anti-microbial agents. The data obtained from this study may be used to determine trends in antimicrobial susceptibilities, to formulate local antibiotic policies and overall to assist clinicians in the rational choice of antibiotic therapy to prevent misuse, or overuse, of antibiotics.

V.

13 Conclusion

In conclusion, the study highlights the emergence of Citrobacter spp., a rare bacterium as the second most common urinary pathogen, which is multidrug resistant among the IDPs. UTI particularly those associated by Multidrug resistant organisms (e.g. Citrobacter spp.) should be incorporated as one of the innumerable health challenges

encountered by Internal Displacement and remain a pressing issue. A great deal therefore remains to be done to address IDPs prevention and control to decrease UTI especially those associated with Citrobacter morbidity and mortality. This protection and assistance needs to continuously evaluating susceptibility pattern of uropathogens to traditional as well as new antimicrobials in well-defined populations and limiting the inappropriate and injudicious use of antibiotics so as to prevent further emergence of drug resistance, to find enduring solutions to their plight and to prevent further displacement from taking place. However, this requires intervention of different agencies, government and nongovernmental bodies.

1

Age (Years)	Male	Female	Total (%)
0 -10	25	81	106(7.5)
11 -20	20	121	141(10)
21-30	30	303	333(23.7)
31 -40	50	428	478(34)
41 -50	35	134	169(12)
51 -60	20	14	34(2.4)
61 -70	30	39	69(4.9)
>70	15	62	77(5.5)
Total	225	1822	1407(100)

Figure 1: Table 1 :

2

Antibiotic	Amikacin	Augmentin	Gentamicin	Septrin	Amoxicillin	Ampicillin	Cefuroxime/clavulanic acid	Ceftriaxone	Ciprofloxacin	Cotrimoxazole	Nalidixic acid	Levofloxacin	Norfloxacin	Ofloxacin	Pefloxacin	Mecillinam
Citrobacter Isolates	TOTAL (421)	0	141(10)	150(32)	1407(100)	1379(98)	1266(90)	1407(100)	788(56)	141(10)	647(46)	605(43)	605(43)	619(44)	1	
	C. intermedius (68)	0	7.4	14.7	100.0	79.4	11.8	100.0	20.6	7.4	10.1	11.8	11.8	20.6	3	
	C. koseri	0	8.3	23.8	100.0	100.0	95.0	100.0	33.3	8.3	47.5	47.3	47.3	47.5	7	
	C. amalonaticus (68)	0	7.4	14.7	100.0	79.4	11.8	100.0	20,6	7.4	19.1	11.8	11.8	20.6	3	
	C. freundii (850)	0	11.3	38.8	100.0	100.0	100.0	100.0	72.9	11.3	49.5	45.9	45.9	46.0	1	

Figure 2: Table 2 :

.1 Acknowledgments

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.2 Conflicts of Interest

None.

.3 Author's Contributions

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