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Original Research Article

Management of Typhoid Fever at a University Hospital in Sub-Saharan Africa: Challenges and Prospects

Godwin Terver Jombo[1], Emmanuel Msugh Mbaawuaga[2], Usman Ahmed[1], Paul Ogor Abba[3], James Orduen Tsor[4]

[1]Department of Medical Microbiology and Parasitology, College of Health Sciences, Benue State University Makurdi, Nigeria
[2]Department of Biological Science, Faculty of Science, Benue State University, Makurdi Nigeria
[3]Department of Medical Microbiology, Benue State University Teaching Hospital, Makurdi, Nigeria
[4]Department of Physics, Faculty of Science, Benue State University, Makurdi Nigeria.

Corresponding Author: Godwin Terver Jombo

ABSTRACT

Correct diagnosis of typhoid fever using clinical signs and symptoms alone is usually difficult in most Nigerian health settings especially where laboratories are also ill equipped. Tying clinical features of typhoid fever with laboratory findings becomes necessary for quick reference by health facilities with poor laboratory settings. This study was therefore set up to ascertain the association between clinical presentations of suspected typhoid fever patients and probable corresponding laboratory diagnosis of typhoid fever among them. Three hundred and eighty-nine patients with clinical diagnosis of typhoid fever attending Benue State University Teaching Hospital (BSUTH) Makurdi between November 2016 and April 2017 were consecutively recruited into the study. Structured close-ended questionnaires were administered to the respondents on their socio-demographic parameters, and on symptoms and signs of typhoid fever. Blood and stool samples were collected from each subject where Widal test was carried out on the blood samples and stool samples were cultured. Results were analysed using Excel and Epi-Info. Of the 389 subjects 35.0% (136/389) had titres ≥80 while 65.0% (253/389) had titres ≤40. Among the males 39.5% (94/238) had Salmonella antibody agglutination titres ≥80 while 27.8% (42/151) of the females had titres of ≥80. There was significant gender difference (P< 0.05) with male preponderance and a mildly strong age correlation (R= 0.44). The most prevalent clinical features recorded were Fever 77.9% (n=303), Headache 63.0% (n=245), Weakness 50.9% (n=198) and Abdominal pain 24.7% (n=96). Stool cultures yielded four species of *Salmonella enterica serovar typhi* and one *Salmonella enterica serovar paratyphi* with a weak positive predictive value of 13.7%. The most active antimicrobials were ofloxacin, amoxiclav and ceftriaxone (100% active each) while co-trimoxazole, amoxicillin, erythromycin, and tetracycline were 100% resistant. Widal agglutination test should not be considered first line test for typhoid fever and a more reliable serological test is needed. It may however be used in conjunction with prevailing clinical features and culture procedures while ofloxacin, amoxiclav and ceftriaxone should be considered drugs of choice. We should also sustain sensitivity testing against the highly resistant drugs as part of monitoring and surveillance.

Key Words: Agglutination test, Diagnosis, Salmonella, Typhoid fever

INTRODUCTION

It is estimated that there are at least 21 million cases of typhoid fever with an estimated 600,000 deaths every year across the globe and Nigeria records a conservative yearly prevalence of at least 4.5 million

cases. [1-4] Clinical diagnosis of typhoid fever is very common in Nigeria's primary and secondary healthcare centres among patients presenting with mostly fever, headache and other constitutional symptoms. In some instances in unconventional health settings manned by unqualified health personnel, patients take pleasure in being told that they have typhoid fever! [5-7] In well established health settings in Nigeria including the teaching hospitals and other parts of Africa, clinicians often commence treatment against typhoid fever based on clinical findings and then possibly the widal agglutination test results. [8-11]

Findings from a study on 840 apparently healthy individuals in Abeokuta showed that 92.6% (426/460) and 92.4% (351/380) of the females and males respectively tested positive for typhoid using widal agglutination test. In another study in Jos on 300 febrile patients admitted to hospital showed that 5.6% (n=9) had positive widal agglutination tests. And in Maiduguri, the incidence of suspected typhoid was found to be 30.5 per 1000 admissions with a male: female ratio of 3: 2. It was found to be commoner among the 5-9 years age group. [12-14]

Considering the serious and life threatening complications arising from invasive Salmonella infections, prompt and efficient management of the disease, correct interpretation of early signs and symptoms of the disease in the locality becomes necessary. [15-18] This study was set up to associate the clinical symptoms and signs of patients suspected to have typhoid with the laboratory findings principally the widal agglutination test and stool culture. This information will be useful to health personnel compelled by personnel, infrastructural and logistic constraints to make clinical diagnosis of typhoid fever for its early and efficient management. This indeed formed the basis for this study.

MATERIALS AND METHODS

Study Setting

The study was carried out at the Benue State University Teaching Hospital (BSUTH) over a six months period (November 2016-April 2017). Patients attending the hospital over this period who had fever (Axillary temperatures of $\geq 37.5^{O}C$) and with clinical diagnosis of typhoid fever were recruited into this study. Participation was voluntary and consents of subjects were duly obtained. Well structured questionnaires covering relevant socio-demographic and medical information such as presenting symptoms and signs, and history of recent antibiotics intake were obtained. The control group which was gender and age matched was obtained from people who visited the Microbiology laboratory who had no fever such as IT students and patient's relations. Blood and Stool samples were then collected from each consented subject and analysed accordingly. Data obtained was analysed using simple descriptive methods and SPSS 16 version Statistical software. Chi square, Regression, Correlation coefficient, and Analysis of variance (ANOVA) were appropriately used to calculate comparisons and associations. Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for widal test was calculated. P values less or equal to 0.05 were considered significant. Ethical approval for the study was obtained from the Ethics review board of the BSUTH.

Collection and Processing of Blood Samples

About three to five millimetres of blood were collected from superficial veins using sterile disposable needles and syringes into plain test tubes. These were transported to the serology laboratory and Widal test carried out on the respective sera using tube agglutination test in line with standard laboratory procedures. The cut off points for somatic (O) and flagellar (H) antigens were 1:≥80 and 1: ≥160 respectively. [19-21]

Collection of stool specimens

Fresh stool specimens were collected into clean, dry, leak - proof, chemical-free and screw-crap universal containers. The

samples were transported in dry containers to the Medical Microbiology Laboratory of the Benue State University Teaching Hospital, where they were processed with minimum delay.

Stool culture

Approximately 1 gram of well-mixed faeces was inoculated into deoxycholate citrate agar (DCA) and incubated overnight at 37^{o}C.

Non-lactose fermenting colonies on DCA were sub-cultured on to nutrient agar overnight at 37^{o}C for purity. Pure cultures were incubated into Kligler Iron Agar (KIA) and urea agar slopes.

Test for Identification of Isolates

All isolates were identified based on their motility, morphology, biochemical and serological reactions.

Motility Test

Pure cultures from nutrient agar plates were sub-cultured in peptone waster and incubated at 37^{o}C for 6 hours. A ring of plasticine was made on a clean, grease-free slide. A drop of the well-mixed culture was placed on a clean cover-slip. The circular area of plasticine on the slide was inverted and super-imposed over the drop of culture on the cover-slip. Quickly, the arrangement was inverted, with the cover-slip facing upwards. Thus, the culture hanged down in the centre of the ring of plasticine.

The preparation was examined with x10 objective lens with reduced illumination. True motility was indicated by the tumbling movement of bacteria from one spot to another. This was clearly differentiated from the Brownian movement of water molecules.

Urease Test

This test was carried out to rule out *Proteus Species* which hydrolyze urea to yield ammonia and carbon-dioxide. The presence of ammonia renders the medium alkaline and the indicator (Phonol red) changes colour to a reddish-pink.

The urease broth (OXOID) in test tubes was inoculated by shaking few colonies from pure cultures of the test organism on nutrient agar into the urea broth. All tubes were incubated at 37^{o}C for 6 hours.

Controls: Positive: *Proteus vulgaris*
Negative: *Escherichia coli*

Serological Typing

A thick saline suspension of an overnight agar culture of the isolate was made on one end of a clean, grease-free slide. Using a flame-sterilized wire-loop, a drop of the bacterial suspension was mixed with a drop of O and H antisera.

A negative control was run by mixing a drop of the bacterial suspension with a drop of sterile normal saline at the other end of the same slide. The preparations were tilted on the slide several times and the result was read within 60 seconds.

A positive result was indicated by agglutination. Isolates were confirmed as *Salmonella typhi* by their agglutination with specific antisera, in conjunction with biochemical reactions on Kligler Iron Agar (KIA). [22,23]

Test on KIA

A pure culture of the test organism on nutrient agar was inoculated on to KIA slope by using a straight wire to stab the broth and streak the slope. The tubes were plugged with sterile cotton wool and incubated at 37^{o}C overnight.

Specific Identification of Bacterial Isolates

Bacterial cultures were identified as *Salmonella typhi* if they showed the following biochemical characteristics:

Lactose	----------	Negative
Mannitol	----------	Positive
Glucose	----------	Negative
Oxidase	----------	Negative
Motility	----------	Positive
Urease	----------	Negative
Growth on KIA--- Slope :		(red-pink-alkaline)
	------Butt:	(Yellow-acid reaction)
	----------	Gas production (nil)
	----------	Hydrogen Sulphide production (weak)

Antibiotic Sensitivity Testing

Preparation of inoculums

Pure cultures of *Salmonella typhi* were picked with flame-sterilized wire loop and inoculated into 10 millilitres of peptone water in Mcartney bottles. The peptone water cultures were incubated at 37^{o}C for 4 hours. The turbidity of the growth was compared with that of a 0.5 Barium Sulphate turbidity standard corresponding to that of a previously prepared inoculum which yielded a dense but no-confluent growth on a sensitivity agar plate. Each inoculum was diluted to match the standard and used in flooding a sensitivity test plate.

Method of Antibiotic Sensitivity Test.

The modified Kirby-Bauer's disc diffusion technique was used to determine the antibiotic sensitivity of each isolate. Commercial standardized single discs of Chloramphenicol, Cotrimoxazole, Amoxicillin, Erythromycin Ciprofloxacin, Ofloxacin, Amoxiclav, Ceftriaxone, Gentamicin, and Tetracycline were placed on the surface of the sensitivity agar plates previously flooded with a broth culture of the test organism. All the plates were incubated overnight at 37^{o}C. [24,25]

A strain of *Escherichia coli* isolated in the laboratory was used as the control. Both test and control plates were incubated in the same atmosphere and temperature. [24]

Interpretation of Zones of Inhibition

An insolate was regarded as sensitive to a certain drug if the diameter of the zone of inhibition around the disc is greater than or equal to that of the control organism (18mm) and resistant if the zone diameter is less than 18mm. [25,26]

RESULTS

Of the 389 patients suspected patients to have typhoid fever, 61.2% (n=238) were males and 38.8% (n=151) females; the age range was four and 72 years with a median age of 56 and bi-modal ages of 41 and 52 years. The overall widal antibody agglutination titre pattern among the respondents showed that 35.0% (136/389) had titres ≥80 while 65.0% (253/389) had titres ≤40. Among the males 39.5% (94/238) had Salmonella antibody agglutination titres ≥80 while 27.8% (42/151) of the females had titres of ≥80.

Age and gender distribution of widal agglutination test titres among the respondents showed that 26.4% (n=10), 31.3% (n=22), 56.4% (n=31) and 41.7% (n=15) of the males aged 11-20, 21-30, 31-40, and 41-50 years respectively had titres ≥80. Similarly, males 51-60, 61-70 and those above years and respectively 34.3% (n=12), 30.0% (n=3), and 35.3% (n=1). Among the females: 20.0% (n=1), 11.8% (n=2), 28.9% (n=11), and 34.5% (n=10) of those aged ≤10, 11-20, 21-30, and 31-40 years respectively had widal agglutination test titres ≥80. Also females aged 41-50 and 51-60 years had 38.7% (n=12) and 25.0% (n=6) titres ≥80 respectively. Zero percent antibody titres were recorded among the 61-70 and >70 years group each. There was significant gender difference with more positive agglutination titres among the females compared to the males ($P < 0.05$). Also the rate of titres of ≥80 generally increased with increasing age with a positive correlation (R= 0.44) (Table 1).

The clinical features recorded among the suspected typhoid patients include: Fever 77.9% (n=303), Headache 63.0% (n=245), Weakness 50.9% (n=198), Abdominal pain 24.7% (n=96), Constipation 26.5% (n=103), Confusion 19.8% (n=77), Diarrhoea 16.2% (n=63), Bitterness in the mouth 17.5% (n=68), Internal heat 22.9% (n=89) and Joint pains 28.0% (n=109). (Figure 1).

Stool cultures grew four *Salmonella enterica serovar typhi* and one *Salmonella enterica serovar paratyphi* (Five species). Analysis of patterns of Widal agglutination tests and stool cultures showed that of the 136 subjects with agglutinations titres of ≥80 four (3.0%) had positive stool cultures while among the 253 subjects with titres of ≤40, one stool sample grew Salmonella (0.4%). This shows a weak positive predictive value of 13.7% (Figure 2).

Antimicrobial susceptibility profiles of the Salmonella isolates showed that: none (100%) of the isolates were susceptible to co-trimoxazole, amoxicillin, erythromycin, and tetracycline. On the other hand all the isolates (100%) were susceptible to ofloxacin, amoxiclav and ceftriaxone. Chloramphenicol, ciprofloxacin and gentamicin were 80% (n=4), 20% (n=1), and 40% (n=2) resistant respectively. (Table 2).

Table 1. Age and gender distribution of Widal Agglutination test titres among suspected typhoid fever patients attending Benue State University Teaching Hospital, Makurdi Nigeria (N=389).

Age		Male			Female		
Intervals	Numbers	Widal Result	Number (%)	Numbers	Widal Result	Number (%)	Total (%)
≤10	2	≤40 ≥80	2 (100) 0 (0.0)	5	≤40 ≥80	4 (80.0) 1 (20.0)	7(1.8)
11-20	38	≤40 ≥80	28 (73.6) 10 (26.4)	17	≤40 ≥80	15 (88.2) 2 (11.8)	55(14.1)
21-30	59	≤40 ≥80	37 (62.7) 22 (31.3)	38	≤40 ≥80	27 (71.1) 11 (28.9)	97(24.9)
31-40	55	≤40 ≥80	24 (43.6) 31 (56.4)	29	≤40 ≥80	19 (65.5) 10 (34.5)	84(21.6)
41-50	36	≤40 ≥80	21 (58.3) 15 (41.7)	31	≤40 ≥80	19 (61.3) 12 (38.7)	67(17.2)
51-60	35	≤40 ≥80	23 (65.7) 12 (34.3)	24	≤40 ≥80	18 (75.0) 6 (25.0)	59(15.2)
61-70	10	≤40 ≥80	7 (70.0) 3 (30.0)	7	≤40 ≥80	7 (100) 0 (0.0)	17(4.4)
>70	3	≤40 ≥80	2 (66.7) 1 (35.3)	0	≤40 ≥80	0 (0.0) 0 (0.0)	3(0.8)
Total	238 (61.2)			151 (38.8)			389 (100)

1. Gender Difference: P< 0.05
2. Age Correlation: Positive age correlation R= 0.44

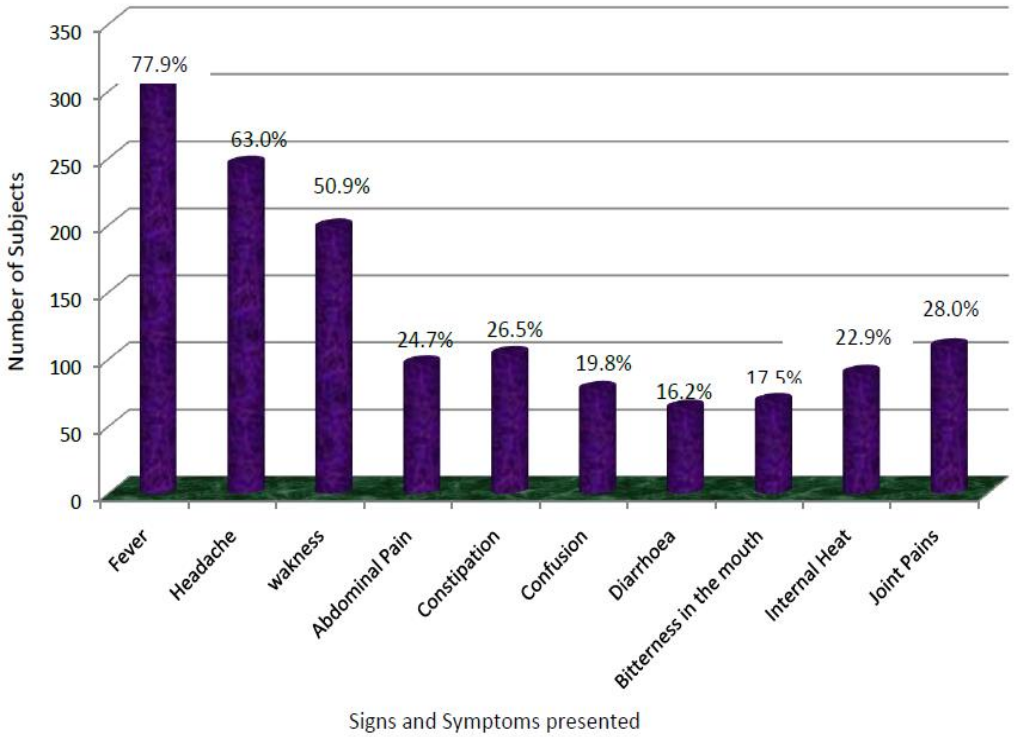
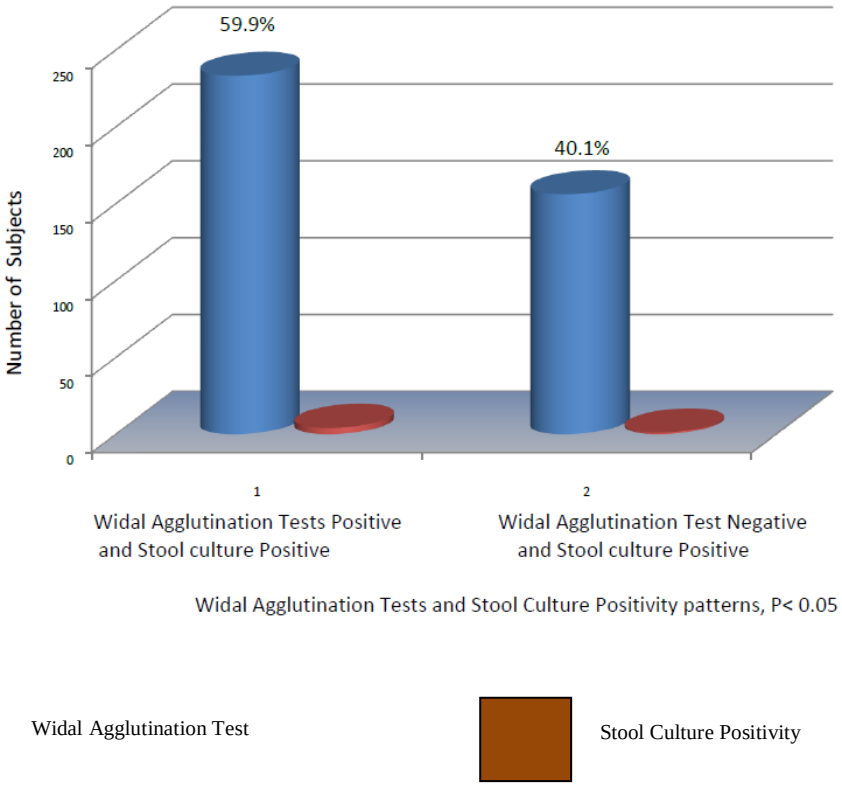


Figure 1. Symptoms and signs presented by subjects with suspected typhoid fever at Benue State University Teaching Hospital, Makurdi Nigeria (N=389)



Sensitivity (O =73.8%, H = 25.3%); Specificity (O = 77.1%, H = 79.8%); Positive Predictive Value PPV (O = 13.7%, H = 5.0), and Negative Predictive Value NPV (O = 99.4%, H = 96.9%)

Table 2. Antimicrobial Susceptibility profiles of *Salmonella species* isolated among Typhoid fever patients at Benue State University Teaching Hospital Makurdi, Nigeria (n=5).

Antimicrobial	Resistant (%)	Mildly Sensitive (%)	Moderately Sensitive (%)	Highly Sensitive (%)	Total (%)
Chloramphenicol,	4 (80.0)	1 (20.0)	0 (0.0)	0 (0.0)	5 (100)
Co-trimoxazole,	5 (100)	0 (0.0)	0 (0.0)	0 (0.0)	5 (100)
Amoxicillin,	5 (100)	0 (0.0)	0 (0.0)	0 (0.0)	5 (100)
Erythromycin	5 (100)	0 (0.0)	0 (0.0)	0 (0.0)	5 (100)
Ciprofloxacin,	1 (20.0)	2 (40.0)	0 (0.0)	2 (40.0)	5 (100)
Ofloxacin,	0 (0.0)	0 (0.0)	1 (20.0)	4 (80.0)	5 (100)
Amoxicillin + Clavulanic acid (Amoxiclav)	0 (0.0)	0 (0.0)	3 (60.0)	2 (40.0)	5 (100)
Ceftriaxone,	0 (0.0)	1 (20.0)	1 (20.0)	3 (60.0)	5 (100)
Gentamicin,	2 (40.0)	1 (20.0)	2 (40.0)	0 (0.0)	5 (100)
Tetracycline	5 (100)	0 (0.0)	0 (0.0)	0 (0.0)	5 (100)

DISCUSSION

Findings from the present study show that 39.5% of the males and 27.8% of the females respectively had widal agglutination titres of ≥ 80 with a significant male preponderance and an overall significant titre of 35.0%. Four stool samples cultured Salmonella species among the 136 with significant titres while one stool was positive for those with titres ≤40 with a significant positive correlation.

Being a hospital based study with sample sampling method dependent on the mode of presentations at the hospital, the male preponderance may be associated with the mode of presentations at the facility. Also the rate of exposure to sources of infection among males due to their probable increased activity could be a contributory factor. A similar hospital based multicentre study in Akure similarly recorded male preponderance over females. The findings

of Zailani in Ile-Ife where there was no associated age and gender difference further stresses the varying socio-demographic patterns of the disease. [27,28]

The finding of 35% widal agglutination titre of ≥80 among the 389 suspected typhoid patients and the concurrent four positive stool cultures among them shows how limited this serological test is in establishing diagnosis of typhoid fever. Although with one positive Salmonella stool culture among the 253 subjects with titres ≤40 it shows that widal agglutination test has a weak positive predictive value but with a strong negative predictive value (>96%). In our community just like in most rural and urban settings across the country, several infections and infestations are capable of masking typhoid fever disease with false positive results. Widal test should therefore not be solely relied upon to establish diagnosis of typhoid as this is prone to errors of misdiagnosis as several studies have alluded to this fact. [29-32]

The clinical symptoms presented by the respondents in which fever 77.9%, headache 63.0%, weakness 50.9%, joint pains 28.0% and constipation 26.5% were the highest signs and symptoms. While these are not different from clinical presentations of several febrile diseases around us, they serve a guide. The fact that there was no significant difference in the preponderance of these features among those with agglutination titres ≥80 as compared to those with lower titres stresses the difficulty in establishing clinical diagnosis of the disease. [33-35]

The continuous testing of antimicrobials known to be inactive against Salmonella in our communities such as tetracycline, co-trimoxazole, amoxicillin, erythromycin and chloramphenicol which were highly inactive in the present study is expected. This is part of monitoring and surveillance concerning those antimicrobials to ascertain at which point Salmonella may have lost resistance to them. The higher susceptibility of Salmonella spp, of above 60% to tetracycline, ampicillin, chloramphenicol and co-trimoxazole in studies in north-central and north-eastern Nigeria further stresses the need for the potential usefulness of these drugs in the future treatment of enteric fevers. This is with most regard to the affordability and availability of them. The high sensitivity recorded by ofloxacin, amoxiclav, ceftriaxone and ciprofloxacin is in line with the current susceptibility profiles of Salmonella species across the country and most parts of sub-Saharan Africa. [7,36-39]

This study was limited by the fact that Selenite F enrichment medium was not used to culture stool samples which would have yielded higher stool culture results. The findings however give a fair picture of the position of widal agglutination test in the diagnosis of typhoid fever.

In conclusion, this study has shown that among patients presenting at BSUTH suspected of typhoid fever, there is male preponderance with no significant difference in the clinical picture of those with high and low agglutination titre. Also widal agglutination test is shown to have a weak positive predictive value with a strong negative predictive value and should be used with extreme caution and research into tests with higher positive predictive values should continue. In addition ofloxacin, amoxiclav, ceftriaxone and ciprofloxacin should be used for therapy where susceptibility results are readily unavailable.

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