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ORIGINAL RESEARCH article

Effect of antimicrobial susceptibility testing on treating Libyan outpatients with a suspected bacterial infection

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Abstract: Clinical microbiology serves as a partner to clinicians in the diagnosis and treatment of infectious diseases. Antibiotics are prescribed empirically before the availability of antimicrobial susceptibility testing data, especially when the patient's medical status could deteriorate by suspending the treatment. To investigate the impact of antimicrobial susceptibility testing on the management of outpatients with suspected bacterial infection in Libyan patients, a cross-sectional prospective study concluded on microbial microdroplet culture by including outpatients with suspected bacterial infection, who have done antimicrobial susceptibility testing. Thus, 53 Libyan patients with urinary tract infections and 14 Libyan patients with skin infections were included in this study. Before the availability of antimicrobial susceptibility testing data, 25 patients were appropriately treated while 42 patients were inappropriately treated. After the availability of antimicrobial susceptibility testing data, the number of appropriately treated patients increased to 57 patients. Thus, antimicrobial susceptibility testing improved the management of 41 patients by discontinuing an unnecessary antibiotic in four patients, starting necessary antibiotic therapy in 18 patients, and changing to more appropriate antibiotic in 19 patients. However, the antimicrobial susceptibility testing has no impact on the management of 24 patients and has led to the worsening of the management of two patients. The effect of antimicrobial susceptibility testing of antibiotic de-escalation was assessed in 35 patients; however, antibiotic de-escalation occurred in six patients. Thus, data of antimicrobial susceptibility testing has improved the management of Libyan outpatients with bacterial infection but their role in antibiotic de-escalation was slight.

Introduction

Antimicrobial susceptibility testing (AST) is the gold standard for diagnosing bacterial infectious diseases. However, in most cases, treatment with antibiotics is started empirically without the availability of AST. This is especially true in the case of severely ill patients when delayed treatment is harmful to the patients. Oppositely, antibiotic therapy may be withheld until the availability of AST data if the patient is not seriously ill, or in

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situations where minimum exposure to drugs is advisable such as in the case of pregnant women [1, 2]. However, because of its unmistakable role in properly selecting antibiotics, AST is an important component of properly managing infection [3, 4]. Microbiological culture and sensitivity testing and AST can serve three important functions that will ultimately improve the management of infectious disease and limit the development and spread of bacterial resistance. Firstly, microbiological culture and sensitivity testing will verify the presence of infectious agents, consequently, proper action can be taken. Secondly, AST will determine the sensitivity pattern of the isolated pathogen, allowing the selection of the most appropriate antibiotics. Thirdly, AST will enable the de-escalation of broad-spectrum antibiotics [5-8]. Antibiotic de-escalation is a strategy adopted by the antibiotic stewardship program (ASP) to limit the use of broad-spectrum antibiotics to decrease the spread of bacterial resistance [9-11]. To achieve the full purpose of AST, it is recommended for microbiology laboratories to follow the selective reporting approach. Selective reporting consists of performing AST by usual practice, but the results are reported to prescribe selective antibiotics recommended as first-line agents [12, 13]. The selective reporting approach has successfully increased the susceptibility of some gram-negative bacteria to ciprofloxacin by limiting its reporting in the AST report [14].

Similarly, the use of cephalexin was increased and the use of co-amoxiclav was decreased in the treatment of urinary tract infections (UTI) by applying the AST with selective reporting [15]. Although, the role of AST in the management of antibiotic therapy appears clear, its wide application may be limited because of its cost, and time-consuming. For these reasons, many physicians prefer the initiation and continue the treatment with a broad-spectrum antibiotic. Also, there have been some data reported no significant role for AST in the selection of antibiotics [16, 17]. The purpose of the current study was the assess the impact of AST on the management of patients with suspected bacterial infections presented to the outpatient clinics in Libya.

Materials and methods

Study design, data collection, inclusion criteria and exclusion criteria: This was a cross-sectional study conducted at outpatient clinics in MMC, Misrata, Libya. Patients who came to visit the outpatient clinics at MMC during the data collection period were eligible for inclusion in the study if they had a presumptive diagnosis of infectious disease. Patients were excluded from the study if the treating physician did not request a microbiological C/S test, even with the expectation of bacterial infection, and prescription of antibiotics. Data were collected for four months from April 2023 to September 2023. Data were collected from the patient's medical record, by interviewing the treating physician and interviewing the patients. Data collection form was prepared to record the following information; age, gender, co-morbidity, expected diagnosis and site of infection, empiric antibiotic therapy, result of C/S test and AST, and antibiotic prescribed after obtaining the AST report. Permission to conduct the study was obtained from the Faculty of Pharmacy, Misrata University (Feb. 2023).

Definition of variables: Appropriateness of antibiotic selection was judged according to the AST report, and the expected microbiological coverage.

Patients were flagged as appropriately treated if:

- Their C/S test showed no significant pathogenic bacterial growth, and they were not given an antibiotic.
- They were given an antibiotic(s) and their C/S test revealed pathogenic bacteria, that are sensitive to the prescribed antibiotic(s).
- Their C/S test revealed pathogenic bacteria and the prescribed antibiotic was not included in the AST but it is expected to be effective against the isolated bacteria.

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Patients were flagged as inappropriately treated if:

- They had received empiric antibiotic therapy while the C/S test showed no significant pathogenic bacterial growth, (unnecessary empiric antibiotics).
- They were given an antibiotic and their AST result revealed pathogenic bacteria, that is either immediately sensitive or resistant to the prescribed antibiotics, (incorrect treatment).
- Their AST result revealed pathogenic bacteria and the prescribed antibiotic was not included in the AST, and it is not expected to be effective against the isolated pathogen, (poor bacteria coverage).
- Their C/S test revealed pathogenic bacterial growth, and no antibiotic was prescribed, (delayed treatment).

Effect of AST on de-escalation of antibiotics: For evaluation of the de-escalation process, the antibiotics used were classified into four ranks based on previous data [18, 19] as shown in **Table 1**.

Table 1: Ranking of antibiotics

Rank	Beta lactam antibiotics	Non beta lactam antibiotics
1	Penicillin G, Phenoxymethyl Penicillin, Cloxacillin, Ampicillin, Amoxicillin	Trimethoprim, Nitrofurantoin
2	Amoxicillin-clavulanate, 1st and 2nd generation cephalosporins	Cotrimoxazole, Tetracycline, Oxytetracycline,
3	Third-generation cephalosporin (non-antipseudomonal), Ureido/carboxy-penicillins	Doxycycline, Macrolides
4	Piperacillin + Tazobactam, Ticarcillin + Clavulanic Acid, 4th cephalosporin, Antipseudomonal 3rd generation cephalosporins	Fluoroquinolones, Aminoglycosides IV vancomycin
5	Ertapenem, Imipenem, Doripenem, Meropenem	Tigecycline, Linezolid, Daptomycin, Colistin

Statistical analysis: Data were analyzed by IBM SPSS statistical version 25. A p-value of less than 0.05 was considered as significant. Qualitative data was expressed as mean±SD or median with interquartile range (IQR) depending on the normality of their distribution. Categorical variables were presented as frequency and percentage. Most of the variables were categorical, therefore, the association between these variables was assessed by cross-tabulation analysis with the Chi-square test.

Results

In this study, 67 Libyan patients were included with a presumptive diagnosis of infectious disease. The patients' ages ranged from six months to 75 years with a median of 49 years (range: 22-57 years). Half of the patients were of male gender. Most of the patients were suffering from UTI (n=53, 79.0%), and the rest were having skin or wound infections (n=14, 21.0%). In **Figure**, 67 samples were sent for culture and sensitivity tests (C/S), and five samples did not yield significant bacterial growth (7.5%). Different bacteria were isolated from the other samples (n=62, 92.5%).

Regarding antibiotics used for empiric therapy and after the availability of AST data, before the availability of AST, 35 patients out of the 53 patients with UTI (66.0%), and 12 patients out of the 14 patients with wound infectious (85.7%) had received empiric antibiotic therapy. For patients with UTI, the most frequently prescribed empiric antibiotics were doxycycline (28.6%), levofloxacin (20.0%), and ciprofloxacin (13.4%). However, for patients with skin infections, three antibiotics were used for empiric therapy amoxicillin-clavulanate (50.0%), ciprofloxacin (25.0%), and ceftriaxone (25.0%). After the availability of AST data, the number of patients without

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antibiotics decreased from 20 patients (29.9%) to five patients (7.5%). After the availability of AST reports, 49 patients with UTI, were on antibiotics. The most commonly used antibiotics for UTI after the availability of AST reports were ciprofloxacin (20.4%), amoxicillin-clavulanate (14.3%), doxycycline (12.2%), nitrofurantoin (12.2%), and cefuroxime (10.2%). Other less commonly used antibiotics for UTI after the availability of AST reports were ceftriaxone (6.1%), cefixime (6.1%), co-trimoxazole, levofloxacin (6.1%), meropenem (4.0%) and azithromycin (2.0%). On the other hand, all the patients with skin or wound infections received antibiotics after the availability of AST reports. The most prescribed antibiotics were ceftriaxone (28.6%), ciprofloxacin (21.4%), and amoxicillin-clavulanate (14.3%). Other less commonly prescribed antibiotics were meropenem, vancomycin, nitrofurantoin, doxycycline, and piperacillin/tazobactam. Each of these antibiotics was prescribed to one patient.

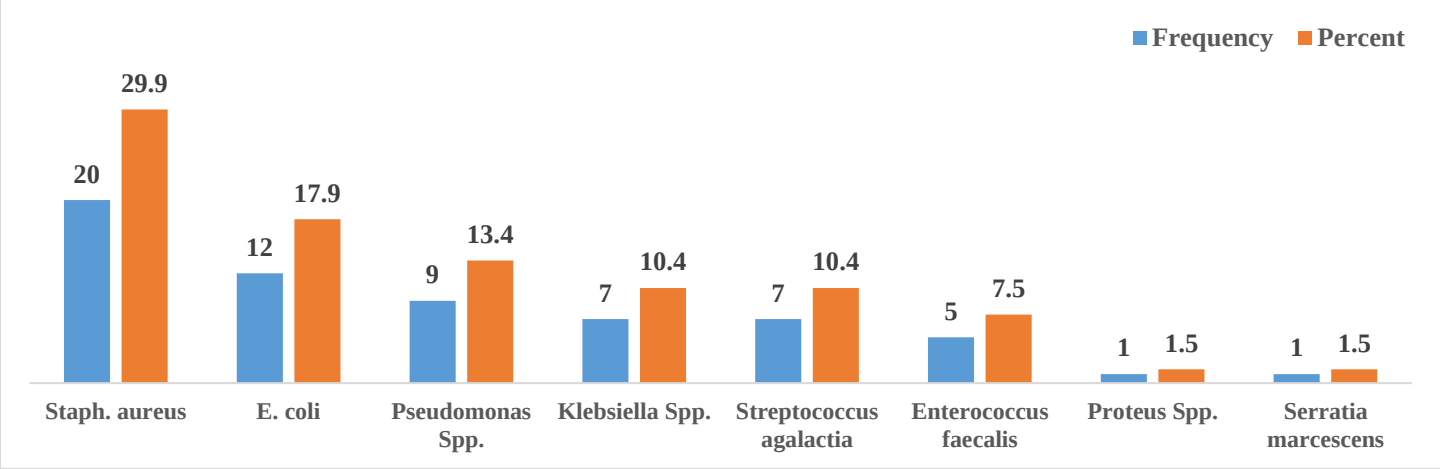

Figure 1: Distribution of isolated bacteria

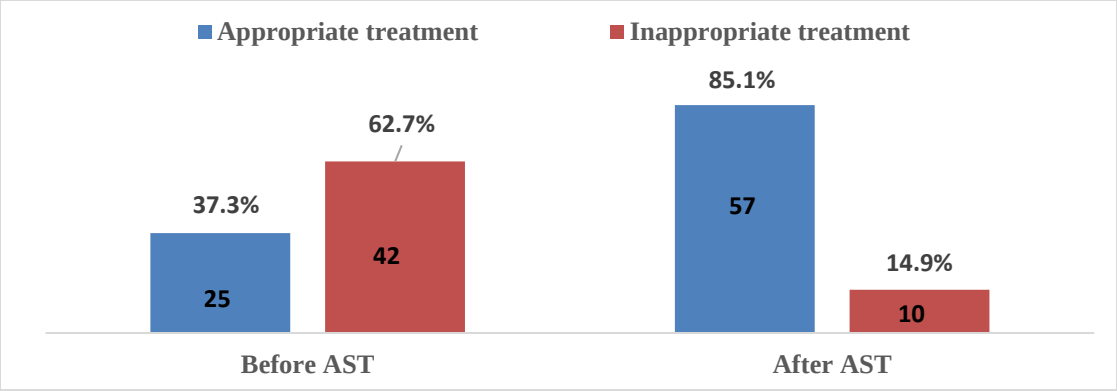

Figure 2: Appropriateness of antibiotics before and after the availability of antimicrobial susceptibility testing

Regarding the appropriateness of empiric antibiotic therapy, before the availability of AST results, 37.3% of the patients were considered appropriately treated, and the other patients were considered inappropriately treated (62.7%). However, after the availability of AST data, the frequency of appropriately treated patients increased to 85.1% of patients and the frequency of inappropriately treated patients decreased to 14.9% (**Figure 2)**. The difference in the percentage of patients who were treated properly before and after the availability of AST data was significant by using the Chi-square test (p=0.038). **Figures 3** and **4** show the details of the patients with appropriate and inappropriate treatment before and after the availability of AST.

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Thus, in **Figure 3**, before the availability of AST data, 14 patients had received antibiotics to which the isolated bacteria were proven to be sensitive by AST. This frequency increased to 40 patients after the availability of AST data. The patients who were prescribed antibiotics with anticipated good bacterial coverage increased from 10 patients before AST to 13 patients after the availability of AST. Among the patients with no significant bacteria growth, one patient was not given empiric antibiotics; however, antibiotic therapy was discontinued in the other three patients after the availability of AST, to raise this number to four patients. The number of patients who were prescribed antibiotics with poor bacterial coverage decreased from 12 before AST to seven after the availability of AST data. The number of patients who prescribed antibiotics to which the isolated bacteria were resistant was decreased from seven before AST to two patients after the availability of AST. The number of patients with delayed treatment decreased from 19 to nil after the availability of AST data. Finally, the number of patients with unnecessary antibiotics decreased from four before AST to one patient after AST.

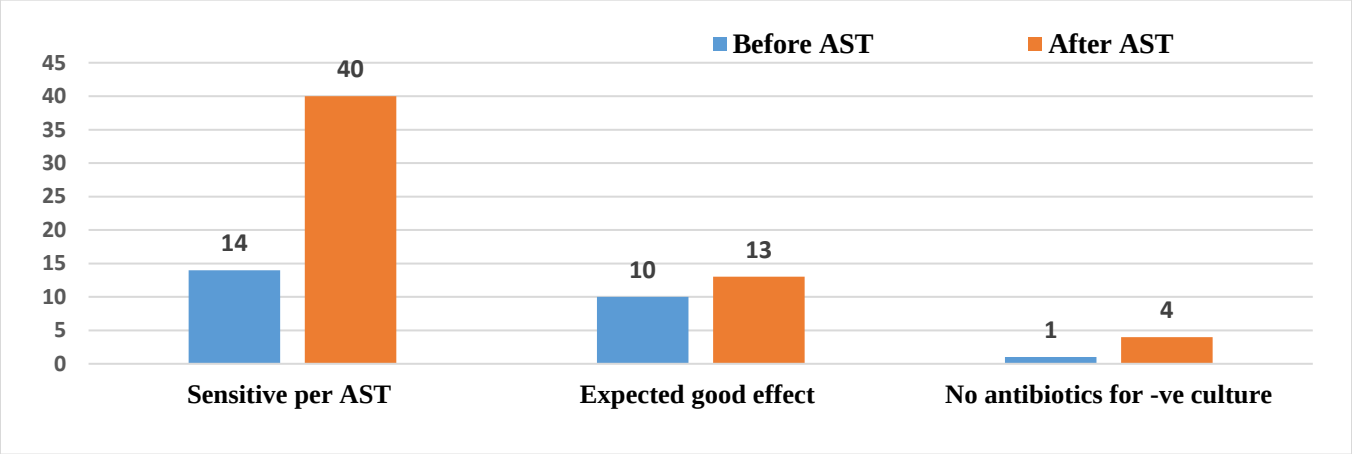

Figure 3: Patients with appropriate treatment before and after the availability of antimicrobial susceptibility testing

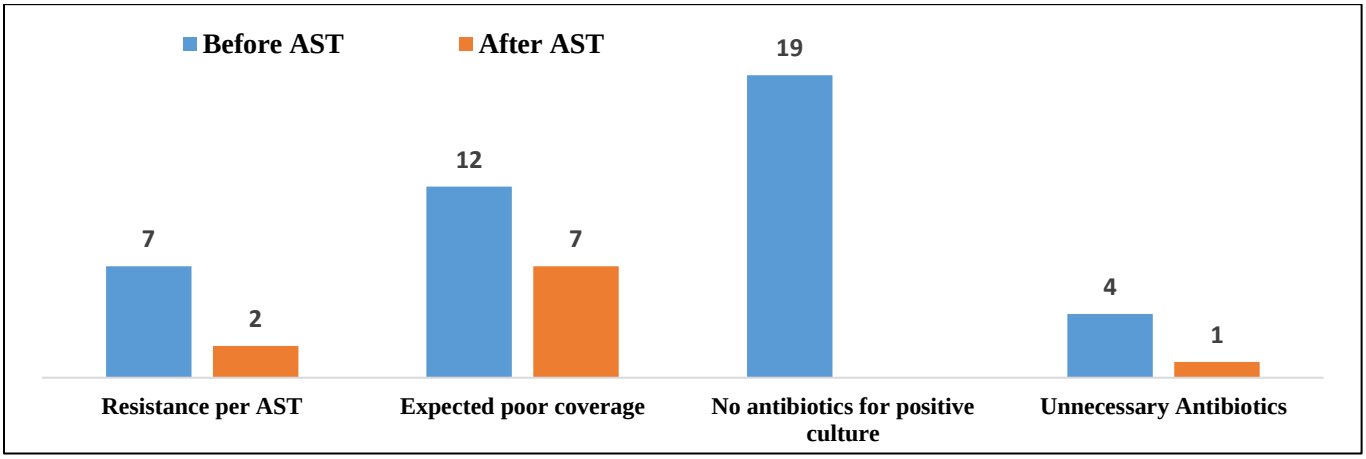

Figure 4: Patients with inappropriate treatment before and after the availability of antimicrobial susceptibility testing

In **Figure 5**, about the impact of AST on prescribing and selection of antibiotics, after the availability of AST data, the antibiotic treatment was continued as before the availability of AST data for 36.0% of patients. However, for these patients, 16 patients were considered appropriately treated. On the other hand, the availability of AST data has led to changing the antibiotic regimen for 64.0% of patients. Nevertheless, in two out of these 43 patients, the action taken after the availability of AST was inappropriate. One was prescribed an unnecessary antibiotic

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after the AST data. The other patient was started with antibiotics with poor bacterial coverage against the isolated bacteria. This patient had an *S. aureus* infection and was prescribed cefixime, which was not included in the AST and was considered inappropriate because of the expected high resistance rate among *S. aureus* against cefixime. The availability of AST data improved the management of 41 patients (**Figure 5**). 18 patients were started with proper antibiotic therapy as their microbiological culture and sensitivity tests revealed pathogenic bacteria required antibiotic treatment; 19 patients were changed to other antibiotics with better antibacterial effect on the isolated bacteria, and four patients were discontinued unnecessary antibiotic therapy as their C/S test revealed no pathogenic bacteria growth.

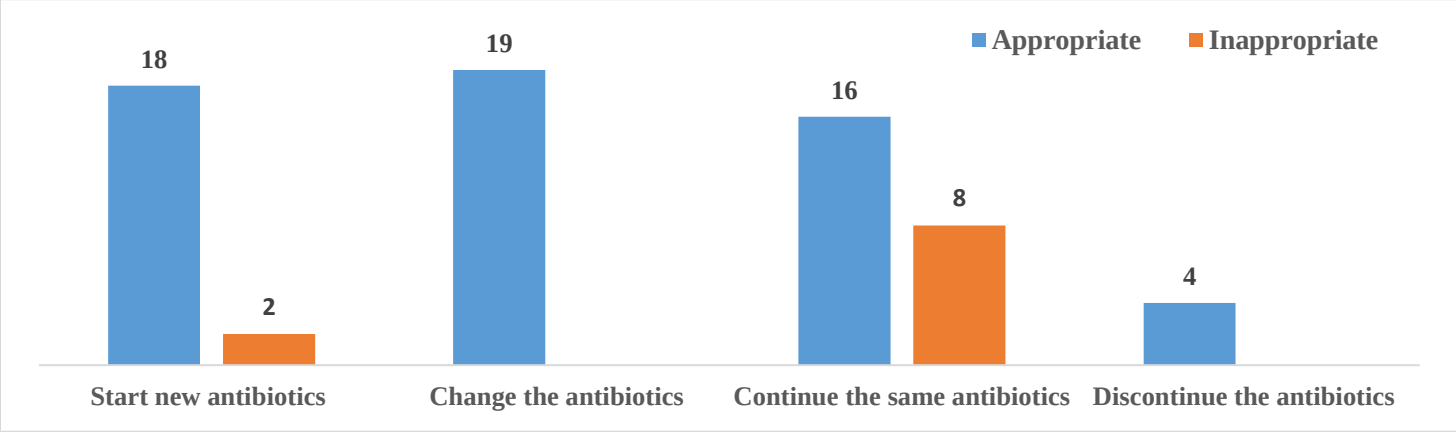

Figure 5: Changing antibiotic regimen after the availability of antimicrobial susceptibility testing

Regarding the impact of AST on the de-escalation of antibiotics, an assessment of antibiotic de-escalation was attempted in 35 patients, who had received appropriate antibiotics before and after the availability of AST data. Antibiotic de-escalation occurred in six of the 35 patients (17.2%). On the other hand, 10 patients had their antibiotics escalated after the availability of AST. In 19 of the 35 patients (54.3%), the antibiotic given after the AST belongs to the same rank as the antibiotic given before the AST. This because, after the availability of AST, many of these patients were continued with the same antibiotic given before the AST. The possibility of further de-escalation was assessed by looking for a lower-rank antibiotic that was reported as sensitive in the AST report. The outcome of further de-escalation is given in **Table 2**. According to the data of AST, further de-escalation was possible in 17 patients of the 29 patients in whom antibiotic de-escalation did not occur (48.5%).

Table 2: Possibility of further de-escalation based on antimicrobial susceptibility testing

Further de-escalation	De-escalation	Same rank	Escalation	Total
Possible n (%)	00 (0.0%)	10/19 (52.6%)	07/10 (70%)	17/29 (58.6%)
Not possible n (%)	06	09/19 (47.4%)	03/10 (30%)	12/29 (41.4%)

Discussion

In most instances, antibiotics are prescribed empirically before the availability of AST data, especially when the patient's medical status could deteriorate by suspending the treatment. In such cases, the anticipation of the pathogenic bacteria and its susceptibility to antibiotics is key to the proper selection of empiric antibiotics.

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However, performing the AST before the initiation of empiric therapy is a good strategy to confirm the presence of bacterial infection and to change the antibiotic to a more appropriate one. In this study, the appropriateness of empiric antibiotic treatment and the impact of AST on the management of patients with UTI and patients with wound infection who were treated as outpatients in MMC were assessed. Before the availability of AST, the empiric antibiotic treatment was assigned as inappropriate in 62.7% of patients and as appropriate in 37.3% of patients. Among the patients with inappropriate initial treatment, about half of the patients did not receive empiric antibiotics whereas their microbiological culture and sensitivity tests later indicated a bacterial infection; therefore, these patients were considered as having delayed treatment, which could worsen their medical condition and lead to more complication and development of bacteria resistance [20]. The number of patients with delayed therapy in our study was higher than what was reported in China and Jordan [21, 22]. After the availability of AST, the patients with delayed treatment were completely reduced to nil since all the patients with positive cultures received antibiotics for the treatment of their bacterial infection. In a study conducted on UTI patients, the availability of AST reduced the number of patients with delayed treatment to about 50.0% [23]. The remaining patients received empiric antibiotics, but they were assigned as inappropriately treated as the following: In four patients the empiric antibiotics were unnecessary since the microbiological culture and sensitivity test did not yield significant bacterial growth. The availability of AST improved the management of these patients by discontinuing unnecessary antibiotics. In seven patients the AST indicated the isolated bacteria were resistant to the prescribed antibiotics. AST has improved the antibiotic therapy for five of those patients by changing their antibiotics to other antibiotics to which the isolated were sensitive. However, the other patients continued their previous empiric antibiotic, so the AST had no impact on these patients. For the assessment of the appropriateness of antibiotics in such patients we have adapted a previous method [22]. This method depends on the available pharmacological data on whether the prescribed antibiotic would have good bacterial coverage against the isolated bacterial strains or not. Based on this criterion, we assigned those patients as inappropriately treated. Examples of such cases are patients with *Pseudomonas aeruginosa* who had received either amoxicillin-clavulanate, ceftriaxone, cefixime, or doxycycline which are known to be ineffective against *Pseudomonas aeruginosa* [24]. In some patients, the culture and sensitivity test revealed the presence of *Streptococcus agalactiae*, and these patients were treated empirically with doxycycline, which has poor bacteria coverage against these bacteria [25]. AST had no impact on the treatment of these patients since they were continued on the same antibiotic after the availability of AST. On the other hand, AST have improved the management of some patients since they were changed to sensitive antibiotics (50.0%) or, changed to another antibiotic not included in the AST but with potential good bacterial coverage (50.0%).

Among the patients assigned as appropriately treated, about 50.0% of patients had received empiric antibiotics to which the isolated bacteria were proven to be sensitive by the AST, and the other 40.0% of patients were prescribed antibiotics that were not included in the AST. Nevertheless, the selection of antibiotics for those patients was considered appropriate, since all the prescribed antibiotics are expected to have good antibacterial effects on the isolated bacteria. Thus, some patients with *E. coli* were prescribed either ceftriaxone, cefixime, or levofloxacin. Any of these antibiotics are expected to have a good antibacterial effect on *E. coli*. Although these patients were assigned to have appropriate empiric antibiotic treatment, the availability of AST has further improved the management of the patients as they were changed to new antibiotics to which the isolated bacteria were proven to be sensitive by AST. However, for the remaining patients, the empiric antibiotics were not changed after AST. The last patient in this group had a negative C/S test and was not given an empiric antibiotic therefore; it was assigned as appropriately treated before the availability of the AST result. Unfortunately, this patient was

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prescribed ciprofloxacin after the result of the C/S test revealed no bacterial growth, therefore this patient was assigned as inappropriately treated and the AST was considered as having a worsening impact on the treatment of this patient. However, this patient may have worsened clinical conditions, and the treated physician may consider this case as symptomatic bacteriuria, in which an antibiotic is recommended even when the C/S is negative [26]. Because empiric antibiotic treatment is usually initiated with broad-spectrum antibiotics, to provide good bacterial coverage to a wide range of expected bacteria. Directing antibiotic therapy against the causative organism or what is known as antibiotic de-escalation is a critical role of AST to prevent the development of bacterial resistance and to limit the irrational use of broad-spectrum antibiotics. Antibiotic de-escalation is a well-known strategy for the appropriate use of antibiotic agents, and one of the components of antibiotic stewardship programs [27]. In our study, antibiotic de-escalation occurred in 17.0% of patients. Several reasons could prevent antibiotic de-escalation, such as the adverse effects of antibiotics, the availability of suitable dosage forms [28-30], and most importantly, the inclusion of narrow-spectrum antibiotics among the AST. Selective reporting is an important and effective strategy to improve antibiotic de-escalation. This strategy depends on performing the AST as usual but includes specific antibiotics in the reports. A previous study found that the chances of prescribing an antibiotic increased almost three-fold when the isolated bacteria was reported as susceptible to that antibiotic [31]. A previous study found an increase in prescribing cephalexin for the treatment of UTI (20.0%) and a decrease in prescribing co-amoxiclav (8.0%) when antibiotic susceptibility reporting was reporting cephalexin instead of co-amoxiclav [32]. Likewise, using selective susceptibility reporting reduced the utilization of ciprofloxacin by about 50.0% in the treatment of infection caused by *Enterobacteriaceae.* Following this intervention, the susceptibility of *E. coli* to ciprofloxacin was increased significantly [33].

Conclusion: This study shows a high impact of antimicrobial susceptibility testing in the management of Libyan patients with expected bacterial infection, especially for patients who were not prescribed empiric antibiotics or who have been prescribed unnecessary antibiotics.

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