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Prospective Audit of Empirical Antibiotic Therapy for Septic Patients

Yonit Wiener-Well MD[1], Mustafa Hadeedi MD[2], Yuval Schwartz MD[1,2], Amos M. Yinnon MD[1,2] and Gabriel Munter MD[2]

[1]Infectious Disease Unit and [2]Division of Internal Medicine, Shaare Zedek Medical Center, affiliated with the Hebrew University Hadassah Medical School, Jerusalem, Israel

ABSTRACT **Background:** Antibiotic stewardship programs are necessary to test the appropriateness of local guidelines for empirical antibiotic treatment by audits.

Objectives: To assess whether compliance to local guidelines achieved a higher rate of appropriate antibiotic treatment and reduced morbidity and mortality, and whether infectious disease counseling improved the rate of appropriate treatment.

Methods: Our cohort comprised 294 patients with proven bacteremia. Data were retrieved from medical records including diagnosis, empiric antibiotic treatment, and outcomes.

Results: The empirical treatment was consistent with bacterial susceptibility in 227 patients (77%), and matched in 64% of the time to the first line, and another 24% to the second line of institutional guidelines. A strong correlation was found between appropriate empiric treatment according to bacterial susceptibility and reduced mortality (odds ratio [OR] 0.403, *P* = 0.007). A similar correlation was found with the choice of appropriate antibiotics according to local guidelines (OR 0.392, *P* = 0.005). Infectious disease consultation was related to an increase in the rate of appropriateness of treatment according to guidelines (85% vs.76%, *P* = 0.005). A tendency to increased appropriateness was related to microbial susceptibility (87% vs. 74%, *P* = 0.07).

Conclusions: In this study, initiation of appropria te empiric antibiotic therapy, according to the hospital's guidelines, was found associated with reduced mortality in patients with bacteremia.

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KEY WORDS: antibiotic stewardship, audit, appropriate empirical antimicrobial treatment, bacteremia, infectious disease consultation

The increased rate of sepsis is thought to be a consequence of advanced age, immuno-suppression, and increased frequency of multi-drug resistance infection [1-3]. Sepsis is one of the main causes of death among hospitalized patients [4] and septic shock is associated with an estimated in-hospital fatality rate of 30–40% [5-8]. Sepsis due to nosocomial pathogens carries a higher mortality rate than sepsis due to community-acquired pathogens [9,10].

When patients present with a clinical syndrome of sepsis, intravenous antibiotic therapy should be initiated immediately following appropriate cultures, since early initiation of antibiotic therapy correlates with lower mortality [11,12]. Studies have shown that early administration of appropriate empiric antibiotic therapy (i.e., antibiotic treatment before the results of cultures are available) for a patient suspected of harboring bacteremia has a positive impact on outcome [13,14]. In one report, early use of adequate antibiotic therapy for bacteremic patients was associated with a 50% reduction in mortality compared to bacteremic patients when infecting organisms were resistant to initial antibiotics [13]. A prospective cohort study of 2124 patients, conducted in Israel, demonstrated that inappropriate antibiotic selection was surprisingly common (32%). Mortality was markedly increased in these patients compared to those who had received appropriate antibiotics (34% vs. 18%) [15].The choice of antibiotics can be complex and should consider the patient's history (e.g., prior antimicrobial treatment), co-morbidities, clinical context (e.g., community or hospital-acquired), Gram stain data, and local resistance patterns. Treating sepsis with adequate empirical antibiotics requires a balance between the disadvantages associated with the use of broad-spectrum antimicrobials (cost, side-effects, and impact on future resistance) and the increased chance of matching the in vitro susceptibility of the pathogen. Hospital guidelines can assist physicians in selecting appropriate empirical treatments, taking into account local specific considerations [16-18]. These guidelines should be assessed periodically and amended if necessary, as part of the overall antimicrobial stewardship program.

In this study, the adequacy of empirical antibiotic treatment for septic hospitalized patients was assessed. Our aims were to determine the rate of appropriate empiric antibiotic treatment provided and to evaluate whether patients who receive empirical treatment according to the hospital's guidelines receive appropriate treatment at a higher rate than patients who received antibiotic treatment without compliance to the guidelines. A second aim was to examine whether there is a correlation between appropriate empirical treatment and morbidity and mortality, and whether infectious disease counseling improves the rate of appropriate empirical treatment.

PATIENTS AND METHODS

STUDY SITE

Shaare Zedek Medical Center is a 1000-bed, tertiary center affiliated with the Faculty of Medicine at the Hebrew University of Jerusalem. The microbiology laboratory receives about 30,000 blood culture sets annually, of which about 8% are positive (40% are considered as contaminated and therefore the remainders are considered true positive cultures). This accumulates for a total of approximately 1800 true positive cultures annually. In 1994, the infectious disease unit issued local guidelines for antibiotic therapy, using local data of bacterial resistance and international recommendations. These guidelines are revised every few years and are distributed to all physicians working in the hospital.

This retrospective, observational study included all consecutive patients hospitalized and treated for positive blood cultures, during 5 months (September 2017 to January 2018). Data were retrieved from patient electronic medical records.

The data included demographic, clinical and laboratory data, and follow-up clinical information. The Charlson Comorbidity Index [19] was determined for each patient as a scoring system for chronic diseases.

All patients older than 18 years of age with true positive blood cultures, acquired in the community, nursing homes, or Shaare Zedek Medical Center were included in the study.

PATIENT EXCLUSION CRITERIA

- Patients not hospitalized, or discharged during the first 72 hours after culture collection
- Patients whose blood cultures were considered as contaminated. For this study we defined contaminants as alpha-hemolytic streptococci, *Micrococcus*, coagulase negative staphylococci, *Bacillus*, and diphtheroids, unless two different sets grew the same organism and there was clinical relevance
- Patients who died within 48 hours after initiation of antibiotic therapy

Patients were included only once, unless different organisms were isolated, in a clinically different episode of sepsis.

Empiric antibiotic treatment (before culture results were received) was defined as appropriate if the organism (subsequently isolated) turned out to be susceptible, according to the microbiology laboratory report or to the empirically prescribed antimicrobial. The microbiology laboratory usually published bacterial identification and susceptibility patterns within 2–3 days from the day the culture was obtained.

Appropriate adherence to hospital guidelines was defined as compliance to the preferred antibiotics (first-line) suggested for the presumed diagnosis. Second-line therapy is the alternative antibiotic regimen suggested in cases of abnormal renal function, hypersensitivity, or other patient-related considerations.

Our primary endpoint was the percent of appropriate empirical antibiotic treatment, 7-day survival, and in-hospital survival. Our secondary endpoint was time until defervescence, time until normalization of peripheral leucocyte count (between 4000 and 10,000/μl), and duration of admission.

We compared patients who were treated according to hospital guidelines to patients who were treated not according to the guidelines, and patients who received infectious disease consultation at the time of selecting empiric antibiotics to patients who did not receive. Infectious disease consultation was given prior to antibiotic selection, by specialists or fellows, and was documented in the medical files.

STATISTICAL ANALYSIS

Odds ratios (OR) and 95% confidence intervals (95%CI) were calculated for dependency between qualitative variables followed by a significance test (Chi-square test for independency or Fisher's exact test). Comparison of qualitative variables was performed using Student's *t*-test. Stepwise regression was performed to detect variables significantly related to mortality. *P* values < 0.05 were considered significant. Statistical analyses were performed using the IBM Statistical Package for the Social Sciences statistics software, version 20 (SPSS, IBM Corp, Armonk, NY, USA).The study was approved by the local institutional review board.

RESULTS

A total of 294 consecutive bacteremic patients were included in this study. Another 357 positive blood cultures were considered contaminated and excluded from the study.

The main demographic and clinical data of the patients are shown in Table 1. The mean age of the patients was 70 ± 17 years, and 54 (18%) lived in nursi ng homes. The infection was community acquired in 206 patients (70%). The main source of infection according to the presumed diagnosis at the time of prescribing empiric antibiotics, was urinary tract in 88 patients (30%), respiratory tract in 64 (22%), and abdominal in 36 (12%). After determining the definitive diagnoses, urinary tract remained the main source of infection, respiratory tract infection was the source in only 13%, and abdominal source was found in 16%.

The most frequent empirical antibiotics used were cephalosporins (52% of all antibiotic courses), followed by penicillins (22%), and vancomycin (21%). The mean duration of empirical antibiotics was 2 ± 0.85 days. When use of empirical antibiotics was determined, an infectious disease consultation was obtained in 56 patients (19%). A change in treatment (adjusting, escalating, or de-escalating), following received culture results, was made in 225 patients (78%). In the definitive treatment, there was an increase in use of carbapenems from 5% to 16% and a decrease in the use of vancomycin to 9%. Empirical treatment was appropriate according to susceptibility of bacteria in 219 patients (77%).

The mean time for normalization of temperature was 2.4 ± 2.1 days and for normalization of peripheral white blood count 4.5 ± 5.2 days. Of the patients, 24 (8%) died during the first week after bacteremia and 58 (20%) during hospitalization. The univariate analysis revealed a strong inverse correlation be-

Table 1. Demographic and clinical characteristics of patients with proven sepsis (N=294)

Characteristic	Mean ± SD or N (%)
Age (years)	70 ± 17
Gender Male Female	 145 (49) 149 (51)
Residence Home Nursing home/other institution	 240 (82) 54 (18)
Charlson Comorbidity Index	5 ± 3
Interval between admission and bacteremia (days) Mean Median (range), no of patients (%) ≤ 2 days	7 ± 17 1 (0–129), 206 (70%)
Creatinine clearance by Crockroft Gault (ml/min)	59 ± 49
Initial diagnosis Urinary tract infection Respiratory tract infection Intra-abdominal infection Skin and soft tissue infection Central line infection Neutropenic fever Endocarditis Central nervous system infection Sepsis of unknown origin	 88 (30) 64 (22) 36 (12) 25 (9) 24 (8) 15 (5) 4 (1) 2 (0.7) 49 (17)
Procedure/surgery*	57 (19)
Infectious disease consultation during the time of selecting empirical antibiotics	56 (19)
Duration of empirical treatment (days)	2 ± 0.85
Change in treatment following culture results	225 (77)
Appropriate empirical treatment: Appropriate to microbial susceptibility Appropriate to first line regimen Appropriate to second line regimen Appropriate for final diagnosis**	 226 (77) 182 (64) 83 (24) 180 (64)
Appropriateness of definitive treatment	290 (99)
Isolated organisms and resistant mechanisms	
Enterobacteriaceae Amp-C beta-lactamases ESBL CPE	193 (58.6) 13 (4) 61 (21) 1 (0.3)
Streptococci***	54 (16.4)
Staphylococcus aureus	33 (10)
MRSA	14 (5)
Pseudomonas	17 (5.2)
Anaerobes	12 (3.6)
Miscellaneous	20 (5.2)
Days until normalization of temperature	2.4 ± 2.1
Days until normalization of peripheral WBC	4.5 ± 5.2
Mortality during the first week after bacteremia	24 (8)
Mortality during hospitalization	58 (20)
Length of hospitalization (days)	21.6 ± 25.5

*Procedure or surgery performed during the hospitalization and related to the infection

**The diagnosis of the infection, in retrospect

***Streptococci: Enterococci 24 (7.3%), *Streptococcus pneumoniae* 14 (4.8%), beta-hemolytic streptococci 8 (2.4%), and other clinically relevant streptococci 8 (2.4%)

CPE = carbapenemase producing Enterobacteriaceae, ESBL = extended spectrum beta-lactamase, MRSA = methicillin resistant *Staphylococcus aureus*, SD = standard deviation WBC = white blood cells

tween appropriate empirical treatment, according to microbial susceptibility and mortality (OR 0.405, 95%CI 0.214–0.758, $P = 0.007$) [Table 2], and a similar inverse correlation was found between selecting appropriate antibiotics according to guidelines and mortality (first or second line of protocols) (OR 0.392, 95%CI 0.208–0.738, $P = 0.005$). Infectious disease consultation was associated with an increased rate of appropriateness of the treatment according to the first line of protocol (78% vs. 61%, $P = 0.031$) [Table 2].

The risk factors for mortality during the first week after bacteremia and during hospitalization are shown in Table 3. Appropriate empirical treatment according to bacterial susceptibility was found to be protective (OR 0.403, 95%CI 0.214–0.758, $P = 0.007$). Other factors were not found to predict statistically significant risk for mortality (including age, gender, creatinine clearance, neutrophil percentage at the day of bacteremia, peripheral white count at the day of bacteremia, resistance mechanisms, infectious disease consultation, change in treatment after culture results, appropriateness to first line of guidelines, and definitive treatment and appropriateness for final diagnosis).

In a multivariate regression stepwise analysis the factors found to be associated with reduced mortality [Table 4] were appropriate empirical treatment according to bacterial sensitivity (OR 0.408, 95%CI 0.191–0.870, $P = 0.020$), presence of fever (> 37°C) at the time of diagnosis of sepsis (OR 0.648, 95%CI 0.466–0.902, $P = 0.010$), and urinary tract infection (OR 0.204, 95%CI 0.074–0.562, $P = 0.002$).When tested alone, the relation between empirical antibiotic treatment according to first line of the protocols and mortality was significant (OR 0.844, 95%CI 0.458–1.554, $P = 0.031$); however, when analyzed in a multivariate model, the statistical difference was not significant, possibly because of the effect of more powerful parameters.

We examined the relationship between appropriateness of antibiotics and a composite endpoint of time until defervescence and time until normalization of peripheral leucocyte count. Appropriate empirical antibiotics according to first or second line of protocols was associated with faster resolution of the composite endpoint (4 vs. 6 days, $P = 0.03$), as well as appropriate empirical antibiotics according to patient diagnosis in retrospect (4 vs. 5 days, $P = 0.03$). The same tendency, with no significance, was found between infectious disease consultation and resolution of fever or leucocyte count. The duration of hospitalization was significantly shorter if an appropriate empirical antibiotic was used (20 vs. 27 days, $P = 0.021$), but longer where there was evidence for consultation (42 vs. 17 days, $P < 0.001$).

DISCUSSION

Sepsis is one of the main causes of death among hospitalized patients [4], and it is associated with high rates of in-hospital

Table 2. The univariate correlation between appropriateness of empiric antibiotic treatment, infectious disease consultation, and in-hospital mortality

Outcomes	With consultation N (%)	Without consultation N (%)	*P* value	Odds ratio for mortality (95%CI)	*P* value*
Appropriate according to microbial susceptibility	45 (87)	174 (74)	**0.007**	0.403 (0.214–0.758)	0.09
Appropriate according to first line regimen	40 (78)	142 (61)	0.698	0.844 (0.458–1.554)	**0.031**
Appropriate according to first or second line regimen	45 (85)	177 (76)	**0.005**	0.392 (0.208–0.738)	0.203

*Bold indicates significance

Table 3. Risk factors for in-hospital mortality, a univariate analysis

Characteristics	In-hospital mortality			
	Deceased mean ± SD or N (%)	Survived mean ± SD or N (%)	Odds ratio (95%CI)	*P* value*
Charlson Comorbidity Index	6 ± 2	5 ± 6		**0.001**
Interval between admission and bacteremia (days)	13 ± 23	6 ± 15		**0.013**
Temperature (°C)	37.9 ± 1	38.1 ± 1		**0.003**
Systolic blood pressure (mmHg)	97 ± 20	106 ± 25		**0.006**
Diastolic blood pressure (mmHg)	56 ± 13	61 ± 13		**0.003**
Duration of empirical treatment (days)	2.0 ± 1	2.1 ± 1		**0.021**
Procedure/surgery	1 (4.2)	52 (24.9)	0.076 (0.169 – 1.024)	0.076
Appropriate to bacterial susceptibility	16 (69.6)	154 (75.9)	0.403 (0.214 – 0.758)	**0.007**

Early infectious disease consultation and appropriateness of empiric treatment according to recommendations are not included in the table because they were not associated with statistically significant reduced mortality.
SD = standard deviation
*Bold indicates significance

Table 4. Factors affecting in-hospital mortality, a multivariate regression analysis

Variable	Odds ratio (95%CI)	*P* value*
Interval between admission and bacteremia (days)	1.008 (0.992 – 1.025)	0.324
Duration of empirical antibiotics (days)	0.693 (0.440 – 1.091)	0.113
Respiratory tract infection	3.031 (1.257 – 7.307)	0.14
Intra-abdominal infection	0.152 (0.032 – 0.712)	0.17
Skin and soft tissue infection	0.480 (0.151 – 1.529)	0.214
Urinary tract infection	0.204 (0.074 – 0.562)	**0.002**
Empirical treatment appropriate to bacteria sensitivity	0.408 (0.191 – 0.870)	**0.020**
Increase in temperature	0.648 (0.466 – 0.902)	**0.010**
Minimal systolic blood pressure	0.989 (0.968 – 1.011)	0.334
Minimal diastolic blood pressure	0.991 (0.953 – 1.030)	0.654

*Bold indicates significance

mortality [5-8]. Early initiation of empiric antibiotic therapy is associated with a beneficial impact and lower mortality [12-15]. Treating sepsis with adequate empirical antibiotic requires a balance between the advantages of broad spectrum treatment to increase matching of the causative pathogen's susceptibility and detriments associated with broad-spectrum antibiotic drug treatment, mainly emerging resistance and side effects. International and local guidelines can help the clinician to choose the adequate treatment.

In this study, all bacteremic patients during 5 consecutive months were included and the appropriateness of empirical antibiotic treatment was determined according to the local guidelines and the pathogen susceptibility.

RATE OF APPROPRIATENESS OF EMPIRICAL TREATMENT AND REDUCED MORTALITY

Among the 294 enrolled patients, empirical treatment was appropriate according to the susceptibility of bacteria in 226 patients (77%). A strong correlation was found between appropriate empirical treatment, according to bacterial susceptibility, and reduced mortality. Many studies have addressed the adequacy of empirical antibiotic treatment in relation to mortality. In a prospective cohort study of 2124 patients, the rate of appropriate empirical therapy was lower (68%) and mortality was markedly increased for patients who received inappropriate antibiotics compared to those who had received appropriate antibiotics (34% vs. 18%) [15]. Similar results were found in a study from Israel, which demonstrated the benefit of appropriate empirical antimicrobial treatment in patients with blood stream infection [20]. Antibiotic treatment that matched in vitro susceptibility of the pathogen, for 24–48 hours before results of cultures were available, was associated with significantly reduced fatality. A larger, multicenter trial (MONARCS trial) showed the same effect of adequate antibiotic therapy, with reduction of mortality from 42% to 33% ($P < 0.001$) [21].

APPROPRIATENESS ACCORDING TO THE GUIDELINES AND APPROPRIATENESS OF THE GUIDELINES

In 64% of the patients there was appropriateness of empirical treatment to local guidelines for first line recommendations, and another 24% of the patients appropriate according to the second line regimen accumulating to 88% of the patients receiving either the first or the second line of the recommended antibiotics. An inverse correlation was found between choosing appropriate antibiotics according to local guidelines and mortality. A prospective observational study which examined compliance to guidelines found that prescription of empirical antimicrobial therapy in agreement with practice guidelines made it possible to achieve a crude rate of 89% of adequate antimicrobial therapy. Inadequate antimicrobial therapy was associated with a 39% increase in mortality [22].

INFECTIOUS DISEASE CONSULTATION

The importance of infectious disease consultation was shown in a retrospective cohort that found reduction in all-cause mortality for multidrug-resistant organism infections [23]. Another large multicenter study, involving 847 patients, concluded that infectious diseases consultation was associated with improved adherence to quality measures, reduced in-hospital mortality, and earlier discharge in patients with *Staphylococcus aureus* bacteremia [24]. In our study, early infectious disease consultation reduced morbidity in all bacteremic patients. In addition, we found that prolonged hospitalization was associated with infectious disease consultation. This association may be as a result of selection bias, as it is plausible that consultation was requested by infection diseases specialists only in complex cases.

LIMITATIONS

We included only patients with positive blood cultures. This may cause a selection bias of certain patients, perhaps the most seriously ill. Therefore, the results may not be applicable for all septic patients. Moreover, our cohort is smaller than that presented in some previous studies, and was conducted in a single institution. However, the study's strengths derive from the vast, accurate data that were collected for all patients.

CONCLUSIONS

Administration of appropriate empirical antibiotics decreases the mortality in bacteremic patients, and the administration of antibiotics according to the hospital-specific infectious disease guidelines reduces the rate of inappropriateness of antibiotic treatment. Therefore, we conclude that our guidelines are appropriate. According to current antibiotic stewardship guidelines, each hospital needs to develop recommendations for empiric antibiotic treatment for commonly encountered infections, based on local isolates and susceptibility patterns, and subsequently conduct audits to verify their adequacy.

Correspondence

Dr. Y. Wiener-Well
Infectious Disease Unit, Shaare Zedek Medical Center, Jerusalem 91301, Israel
Phone: (972-2) 655-5147
Fax: (972-2) 666-6840
email: yonitw@szmc.org.il

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Capsule

The COVID-19 RNA-synthesizing machine

Many in the scientific community have mobilized to understand the virus that is causing the global coronavirus disease 2019 (COVID-19) pandemic. **Gao** et al. focused on a complex that plays a key role in the replication and transcription cycle of the virus. They used cryo-electron microscopy to determine a 2.9-angstrom-resolution structure of the RNA-dependent RNA polymerase nsp12, which catalyzes the synthesis of viral RNA, in complex with two cofactors, nsp7 and nsp8. nsp12 is a target for nucleotide analog antiviral inhibitors such as remdesivir, and the structure may provide a basis for designing new antiviral therapeutics.

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Eitan Israeli

Capsule

Containment works

National governments have taken different approaches in response to the coronavirus disease 2019 (COVID-19) pandemic, ranging from draconian quarantines to laissez-faire mitigation strategies. In data from China collected in February 2020, **Maier** and **Brockmann** noticed that, unexpectedly, the epidemic did not take off exponentially. Nonexponential spread occurs when the supply of susceptible individuals is depleted on a time scale comparable to the infectious period of the virus. The results of the authors' modeling approach indicate that the public response to the epidemic plus containment policies were becoming effective despite the initial increase in confirmed cases.

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Eitan Israeli