Adequacy of Early Empiric Antibiotic Treatment and Survival in Severe Sepsis: Experience from the MONARCS Trial

Rodger D. MacArthur,[1] Mark Miller,[2] Timothy Albertson,[3] Edward Panacek,[3] David Johnson,[4] Leah Teoh,[5] and William Barchuk[5]

[1]Wayne State University, Detroit, Michigan; [5]Abbott Laboratories, Parsippany, New Jersey; [3]University of California, Davis, Sacramento, California; and [2]McGill University, Montreal, and [4]Department of Medicine, Royal University Hospital, Saskatoon, Canada

As part of the Monoclonal Anti-TNF: A Randomized Controlled Sepsis (MONARCS) trial, which enrolled patients with suspected sepsis, we sought to determine whether adequate antibiotic therapy was associated with a decreased mortality rate. The study enrolled 2634 patients, 91% of whom received adequate antibiotic therapy. The mortality rate among patients given adequate antibiotic treatment was 33%, versus 43% among patients given inadequate treatment ($P < .001$). We conclude that adequate antibiotic therapy results in a significant decrease in the crude mortality rate among patients suspected of sepsis.

Sepsis is associated with an in-hospital mortality rate of 30%–40% [1, 2]. The influence of factors such as causative organism, portal of entry, age, or the occurrence of septic shock on the outcome of septicemia has been investigated [3–6]. Early empiric antibiotic treatment of patients suspected of having sepsis is standard practice. Though adequate antibiotic therapy has been shown to reduce mortality rates, this issue has not been studied in detail. By necessity, the association of early empiric antibiotic treatment with mortality in patients with sepsis must be investigated in an observational manner, because ethical considerations preclude a prospective randomized trial. Data from the Monoclonal Anti-TNF: A Randomized Controlled Sepsis (MONARCS) trial [7]—a double-blind, placebo-controlled trial designed to evaluate the safety and efficacy of afelimomab, an antitumor necrosis factor (TNF) $F(ab')_2$ antibody fragment—provided the opportunity to determine the relationship between mortality and the adequacy of early empiric antibiotic treatment.

In the present study, we analyzed a large group of septic patients for whom detailed data were collected. The aim of the study was to explore the overall association between increased mortality and inadequate empiric treatment.

Patients and trial procedures. The MONARCS trial was a multicenter, double-blind, placebo-controlled trial among patients with sepsis. The study included hospitalized adults >18 years old who met criteria for sepsis syndrome [8]. In addition, microbiologic or definitive clinical evidence of acute infection was required for study entry. Neutropenic patients were excluded from enrollment. Patients were randomly allocated to receive either afelimomab or a placebo. Case records for each patient were evaluated in a blinded fashion by a clinical evaluation committee (CEC), using prospectively defined criteria (figure 1). Members of the CEC were blinded to treatment assignment and outcome. There were 7 members of the CEC, of whom 2 were physicians trained in infectious diseases. These 2 physicians (RDM, MM) were primarily responsible for evaluating each case for adequacy of antibiotic therapy. Agreement was obtained by consensus opinion, primarily utilizing the algorithm shown in figure 1. Concordance scoring among evaluators was not performed. Each patient was classified according to primary site of infection, primary causative organism(s), and adequacy of antimicrobial therapy. Therapy was judged to be either adequate or inadequate on the basis of the in vitro susceptibility of an isolated organism and/or the initiation of antibiotic treatment between 24 h before and 72 h after study enrollment. In the absence of sensitivity data for particular organisms and antibiotics utilized, an organism was defined as sensitive if, at that particular institution, $\geqslant$80% of isolates of the relevant pathogen were sensitive to the antibiotic utilized. If data were not listed for the specific antibiotic used, the isolated organism was defined as sensitive if $\geqslant$80% of isolates at the particular institution were susceptible to comparable antibiotics. Organisms reported as intermediate in sensitivity to a particular antibiotic were classified as sensitive for this report. The primary study end point was the 28-day all-cause mortality rate.

Data analysis. The Jonckheere-Terpstra test was used to

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Reprints or correspondence to: Dr. Rodger D. MacArthur, Dept. of Medicine, Wayne State University, 4201 St. Antoine, UHC 7D Detroit, MI 48201 (rmacarthur@med.wayne.edu).

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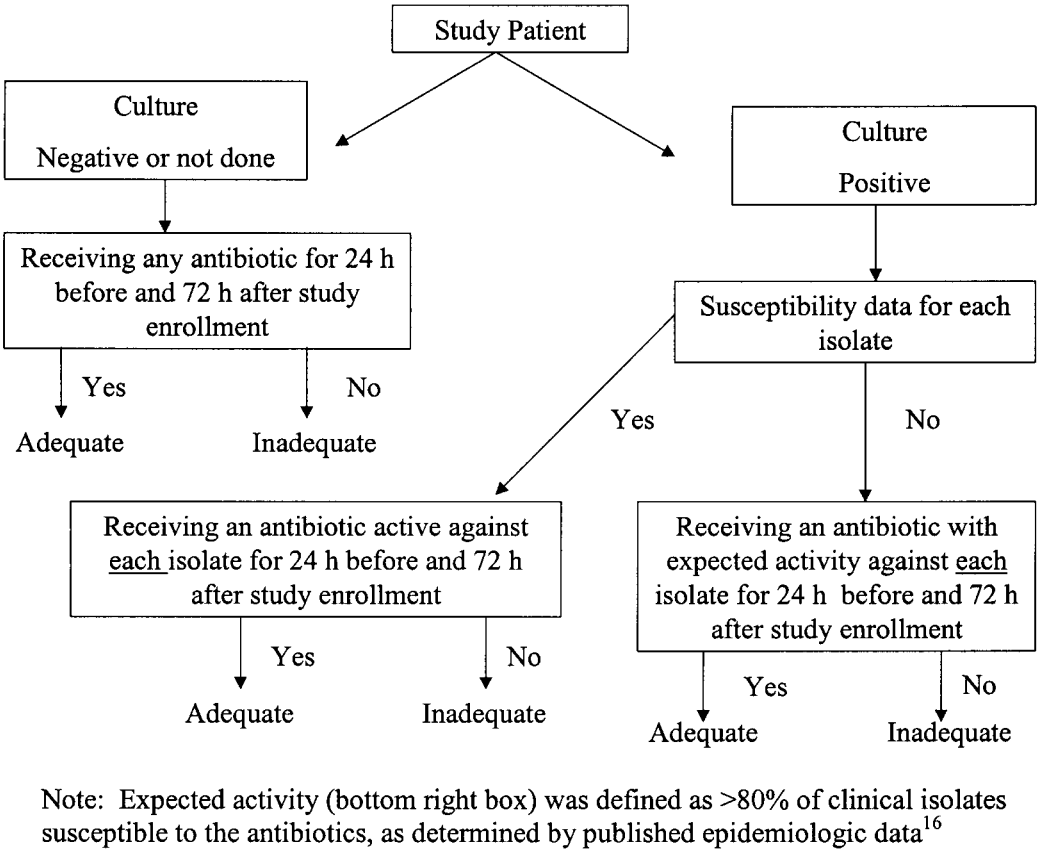

Figure 1. Algorithm for prospectively determining adequacy of antibiotic therapy. Antibiotics were considered to have expected activity if >80% of clinical isolates were susceptible to them, as determined by published epidemiologic data [16].

evaluate the association between the number of infecting organisms per patient and the adequacy of antibiotic treatment. The Cochran-Mantel-Haenszel test, stratified by treatment, was used to investigate the association between mortality and adequacy of antibiotic therapy for all 2634 patients enrolled.

Results. The MONARCS trial was conducted at 157 centers in North America. A total of 2634 patients were enrolled. Details on empiric antibiotic treatment and outcome were ultimately available for all patients. The baseline characteristics of patients who received adequate and inadequate empiric antibiotic therapy are summarized in table 1. Adequate antibiotic treatment was given to 2391 patients (91%). The group receiving adequate antibiotic therapy was slightly younger, but the 2 groups were well balanced for other demographic and baseline characteristics. The most common gram-positive organisms (i.e., those found in >5% of patients) were *Staphylococcus aureus* and *Streptococcus pneumoniae,* and the most common gram-negative organisms were *Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa.* In both groups, the most frequent sites of infection were the abdomen, lungs, and blood (i.e., primary bacteremia, in which the blood was the only site of infection identified).

Certain isolated organisms (table 1) were associated with inadequate antibiotic treatments more often than were other organisms. In particular, *S. aureus, P. aeruginosa,* and fungi were more likely to have been associated with inadequate antibiotic treatments, which most likely reflects the increase in resistance associated with these organisms in hospitalized patients. The site of infection did not appear to be associated with the adequacy of antibiotic treatment (table 1). However, higher numbers of infecting organisms per patient were significantly associated ($P < .01$) with inadequacy of antibiotic treatment (table 2).

The mortality rate on day 28 of the study for all randomized patients is summarized in table 3. The overall mortality rate was 34% (898 of 2634 patients). Mortality rates of 33% and 43% were observed among patients receiving adequate and inadequate antibiotic treatment, respectively, and an increased mortality rate was significantly associated with inadequacy of

Table 1. Baseline characteristics of 2634 patients with suspected sepsis, according to receipt of adequate or inadequate antibiotic treatment.

Variable	Patients with adequate treatment (n = 2391)	Patients with inadequate treatment (n = 243)	P[a]
Age in years, mean ± SD	59.2 (17.0)	61.5 (17.0)	.05
Sex, % men	59.7	64.2	.15
Clinical evaluation score, mean value			
APACHE II	24.8	25.5	.20
SAPS II	55.6	57.1	.15
MOD	7.5	7.5	.86
SOFA	9.4	9.6	.46
Septic shock	1564 (65.4)	150 (61.7)	.25
Pathogen isolated			<.01[b]
Gram-positive bacteria	690 (28.9)	81 (33.3)	
Staphylococcus aureus	338 (14.1)	47 (19.3)	
Streptococcus pneumoniae	205 (8.6)	17 (7.0)	
Gram-negative bacteria	674 (28.2)	59 (24.3)	
Escherichia coli	369 (15.4)	31 (12.8)	
Klebsiella pneumoniae	173 (7.2)	19 (7.8)	
Pseudomonas aeruginosa	116 (4.9)	25 (10.3)	
Mixed gram-positive and gram-negative bacteria	267 (11.2)	62 (25.5)	
Other[c]	45 (1.9)	15 (6.2)	
None	715 (29.9)	26 (10.7)	
Site of infection			.04
Abdomen	595 (24.9)	67 (27.6)	
Lung	619 (25.9)	66 (27.2)	
Blood[d]	568 (23.8)	68 (28.0)	
Other or none identified	609 (25.5)	42 (17.3)	
Positive blood culture result	935 (39.1)	105 (43.2)	.21

NOTE. Data are no. (%) of patients, unless otherwise indicated. MOD, multiple organ disfunction score; SAPS II, simplified acute physiology score II; SOFA, sequential organ failure assessment score.

[a] P value was calculated using analysis of variance and Pearson's χ^2 test.

[b] Gram-positive bacterial infection vs. gram-negative bacterial infection vs. mixed gram-positive and -negative bacterial infection vs. other pathogen vs. no pathogen identified.

[c] E.g., fungus.

[d] Primary bacteremia, in which blood was the only identified site of infection.

antibiotic support ($P < .001$). Among patients randomized to receive a placebo, those receiving adequate initial empiric antibiotic therapy had a 38% (OR: 1.38) greater chance of being alive on day 28 than did similarly treated patients who were given inadequate antibiotic therapy.

The 28-day mortality rate among patients receiving adequate or inadequate antibiotic treatment, stratified by demographic, clinical, and microbiologic variables, is detailed in table 3. With the exception of patients with sepsis that was classified as due to *P. aeruginosa* or "other" pathogen, or with sepsis for which no pathogen was isolated, the mortality rate was lower for patients who received adequate empiric antibiotics. Patients with sepsis due to gram-positive bacteria, patients with sepsis due to *E. coli*, and those with septic shock had the greatest benefit from adequate antibiotic treatment (on the basis of the δ for mortality rates between those receiving adequate versus those receiving inadequate antibiotic therapy), with absolute reductions in mortality rates ranging from 22% to 17%.

The mortality rate among patients with *P. aeruginosa* infections who were receiving inadequate antibiotic treatment was slightly lower than that among those given adequate antibiotic treatment, but the number of patients infected by these pathogens was low. The highest mortality rate associated with inadequate antibiotic treatment was observed among patients infected with *S. aureus*.

Discussion. In the MONARCS trial, 91% of enrolled patients received adequate antibiotic support, and the overall mortality rate was 34%, with rates of 33% and 43% for patients

Table 2. No. of infecting organisms per patient in 2634 patients with suspected sepsis, according to receipt of adequate or inadequate antibiotic treatment.

No. of organisms isolated	No. (%) of patients	
	With adequate treatment (n = 2391)	With inadequate treatment (n = 243)
0	715 (29.9)	26 (10.7)
1	1221 (51.1)	113 (46.5)
2	301 (12.6)	57 (23.5)
3	93 (3.9)	22 (9.1)
4	39 (1.6)	17 (7.0)
5	16 (0.7)	8 (3.3)
6	5 (0.2)	0 (0.0)
7	1 (<0.1)	0 (0.0)

receiving adequate and inadequate antibiotic treatment, respectively. Thus, a 10% decrease in the overall crude mortality rate was associated with adequate early empiric antibiotic treatment. With the exception of a small group of patients infected with *P. aeruginosa*, no subgroup had a prognosis so poor that adequate empiric antibiotic treatment was not beneficial. In fact, reductions in mortality rates were apparent even among patients with septic shock and positive blood culture results, clinical features associated with the highest in-hospital mortality rates [3, 6]. Several factors were associated with a greater likelihood of inadequate antibiotic treatment, including multiple infecting organisms per patient, fungal infection, and *P. aeruginosa* infection.

To the best of our knowledge, the MONARCS trial is the largest prospective, randomized sepsis study yet conducted, and

Table 3. Twenty-eight–day all-cause mortality rates among 2634 patients with suspected sepsis, according to receipt of adequate or inadequate antibiotic treatment.

Variable	Mortality rate, proportion (%) of patients	
	With adequate treatment (n = 2391)	With inadequate treatment (n = 243)
Overall mortality	793/2391 (33.2)	105/243 (43.2)
Treatment group		
Afelimomab	364/1174 (31.0)	57/131 (43.5)
Placebo	429/1217 (35.3)	48/112 (42.9)
Age in years		
<65	346/1328 (26.1)	42/118 (35.6)
⩾65	447/1063 (42.1)	62/124 (50.0)
Septic shock	541/1564 (34.6)	77/150 (51.3)
Pathogen isolated		
Gram-positive bacteria	242/690 (35.1)	46/81 (56.8)
Staphylococcus aureus	137/338 (40.5)	24/47 (51.1)
Streptococcus pneumoniae	65/205 (31.7)	7/17 (41.2)
Gram-negative bacteria	207/674 (30.7)	25/59 (42.4)
Escherichia coli	104/369 (28.2)	15/31 (48.4)
Klebsiella pneumoniae	51/173 (29.5)	8/19 (42.1)
Pseudomonas aeruginosa	45/116 (38.8)	9/25 (36.0)
Mixed gram-positive and gram-negative bacteria	77/267 (28.8)	22/62 (35.5)
Other[a]	23/45 (51.1)	6/15 (40.0)
None	244/715 (34.1)	6/26 (23.1)
Site of infection		
Abdomen	210/595 (35.3)	26/67 (38.8)
Lung	222/619 (35.9)	30/66 (45.5)
Blood[b]	204/568 (35.9)	33/68 (48.5)
Other or none identified	157/609 (25.8)	16/42 (38.1)
Positive blood culture results	321/935 (34.3)	48/105 (45.7)

NOTE. Data are no. of patients who died/no. of patients in group or subgroup (%).

[a] E.g., fungus.

[b] Primary bacteremia, in which blood was the only identified site of infection.

the detailed data collected on enrolled patients has provided the opportunity to investigate a number of treatment-related questions. Parallel comparison of the results of our study with the results reported by others must be interpreted with caution because of the heterogeneity of patients with sepsis, differences in definitions of adequate antibiotic treatment, and differences in standards of care. Nevertheless, our results are consistent with previous studies [9–13], in which the proportion of patients receiving adequate empiric antibiotic treatment ranged from 63% to 83%. Although our study found that 91% of persons enrolled were treated with adequate antibiotics, the increased rate relative to other studies may have been due to our definition of "adequate." In particular, patients for whom no organism was isolated were considered to have received adequate antibiotics if any antibiotic was given during the period between 24 h before and 72 h after study enrollment. In addition, it is likely that classification of organisms that were intermediate in sensitivity as being sensitive increased the number of persons classified as having received adequate antibiotics; the increased use of broader-spectrum antibiotics might also have this effect.

Leibovici et al. [14] found that the mortality rate among patients with bacteremia who experienced septic shock was 74.9% for those receiving adequate empiric antibiotic treatment and 84.7% for those receiving inadequate empiric antibiotic treatment. In a separate analysis, these same investigators [15] reported mortality rates for patients with septic bacteremia who did not necessarily experience septic shock: 20% for adequate versus 34% for inadequate antibiotic treatment. Behrendt et al. [11] found similar values, reporting a 15.8% mortality rate for patients with septic bacteremia who received adequate antibiotic treatment and 28.7% for those given inadequate antibiotic treatment. As was the case in the present study, in these analyses [11, 14, 15] there was a decrease of ~10% in the mortality rate among patients administered adequate antibiotic treatment compared with that among patients administered inadequate antibiotic treatment.

The main limitation on the present investigation is that it was observational and not randomized, and, thus, an unknown risk factor for mortality might have been unequally distributed among the 2 groups. On the other hand, the fact that detailed data were collected in real time for a large group of patients and the fact that the effect of adequate antibiotic treatment trended in one direction support the validity of our interpretation. The present report quantifies the benefit associated with adequate empiric antibiotic therapy. These data suggest that continuing efforts should be aimed at reducing the administration of inadequate empiric antimicrobial treatment to septic patients.

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