ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1992, p. 620–625
0066-4804/92/030620-06$02.00/0

Vol. 36, No. 3

Addition of Rifampin to Combination Antibiotic Therapy for *Pseudomonas aeruginosa* Bacteremia: Prospective Trial Using the Zelen Protocol

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Received 31 July 1991/Accepted 10 January 1992

A multicenter, prospective randomized trial was conducted to determine if the addition of rifampin to a combination therapy of an antipseudomonal beta-lactam agent and aminoglycoside improves the outcome of patients with *Pseudomonas aeruginosa* bacteremia. The Zelen protocol for randomized-consent design was used. Consent was sought only from patients randomized to the experimental therapy (rifampin+). If the experimental therapy was refused, the patient would then receive the standard combination therapy (control); however, when outcome was evaluated, all patients randomized to the rifampin+ group, including those that declined rifampin, were compared with the control group. One hundred twenty-one consecutive hospitalized patients with positive blood cultures for *P. aeruginosa* were enrolled. Entry was stratified for prior use of empiric antipseudomonal antibiotics, neutropenia, severity of illness, and presence of pneumonia. Fifty-eight patients were randomized to receive rifampin (600 mg orally every 8 h for the first 72 h and then every 12 h for a total of 10 days) plus a beta-lactam agent plus an aminoglycoside. Sixty-three received the standard therapy of a beta-lactam plus an aminoglycoside agent (control). Bacteriologic cure occurred significantly more frequently in patients randomized to the rifampin+ regimen. Breakthrough or relapsing bacteremias occurred in 2% of the three-drug (rifampin+) group, compared with 14% for the two-drug (standard therapy) group. Despite this favorable trend in bacteriological response, no significant differences in survival were seen for the two treatment groups. Rifamycin derivatives warrant further clinical study as antipseudomonal agents. The Zelen protocol appears well suited for comparative trials of antimicrobial agents.

Pseudomonas aeruginosa continues to be an important pathogen, especially among debilitated and immunocompromised individuals. Infections caused by *P. aeruginosa* are difficult to treat because of the organism's intrinsic resistance to many antibiotics and its propensity to develop resistance during therapy (10, 13–17). These properties have so limited the effectiveness of antibiotic monotherapy that combination antibiotic therapy has been advocated for serious *P. aeruginosa* infection (1, 11, 13, 19). Nevertheless, the mortality rates for bacteremia due to *P. aeruginosa* continue to be consistently higher than for other bacterial pathogens (1, 3, 5, 8).

In an exploration for more potent antipseudomonal combinations of antibiotics, rifampin was found to be synergistic in vitro with antipseudomonal penicillin and an aminoglycoside against *P. aeruginosa* (20, 22, 26). Compared with the double combination of an antipseudomonal beta-lactam agent and an aminoglycoside, a triple combination of rifampin, an antipseudomonal beta-lactam agent, and an aminoglycoside significantly improved survival in neutropenic mice infected with *P. aeruginosa* (9, 21, 25). Moreover, selected patients with *P. aeruginosa* sepsis who failed standard antipseudomonal combination therapy were successfully treated with the addition of rifampin (23). Therefore, in order to more clearly define the role of rifampin in the therapy of *P. aeruginosa* infections, we conducted a controlled, prospective, randomized trial of 121 patients with *P. aeruginosa* bacteremia, comparing rifampin in combination with antipseudomonal penicillin and an aminoglycoside with standard two-drug therapy.

MATERIALS AND METHODS

A multicenter, prospective, nonblinded randomized trial was conducted from 1985 to 1987. A total of 121 consecutive patients with *P. aeruginosa* bacteremia were enrolled from four medical centers: Presbyterian University Hospital, VA Medical Center, and Mercy Hospital (all in Pittsburgh, Pa.) and Bowman Gray School of Medicine of Wake Forest University (Winston-Salem, N.C.).

Study design. The randomized consent design described by Zelen was approved after considerable discussion by the Institutional Review Boards at all four participating institutions (24). Patients were assigned to either a three-drug-combination group (rifampin plus a beta-lactam and an aminoglycoside) or a two-drug-combination group (standard therapy of a beta-lactam and an aminoglycoside) (Fig. 1) by using a code generated by a random-numbers table.

Antibiotics were administered as follows: (i) rifampin, 600 mg orally every 8 h for at least 3 days and 600 mg every 12 h thereafter for 7 days; (ii) tobramycin, 1.7 mg/kg of body weight every 8 h (dosage adjusted for renal dysfunction); (iii) piperacillin, 4 to 5 g every 4 h (dosage adjusted for renal dysfunction). Other antipseudomonal beta-lactams or ami-

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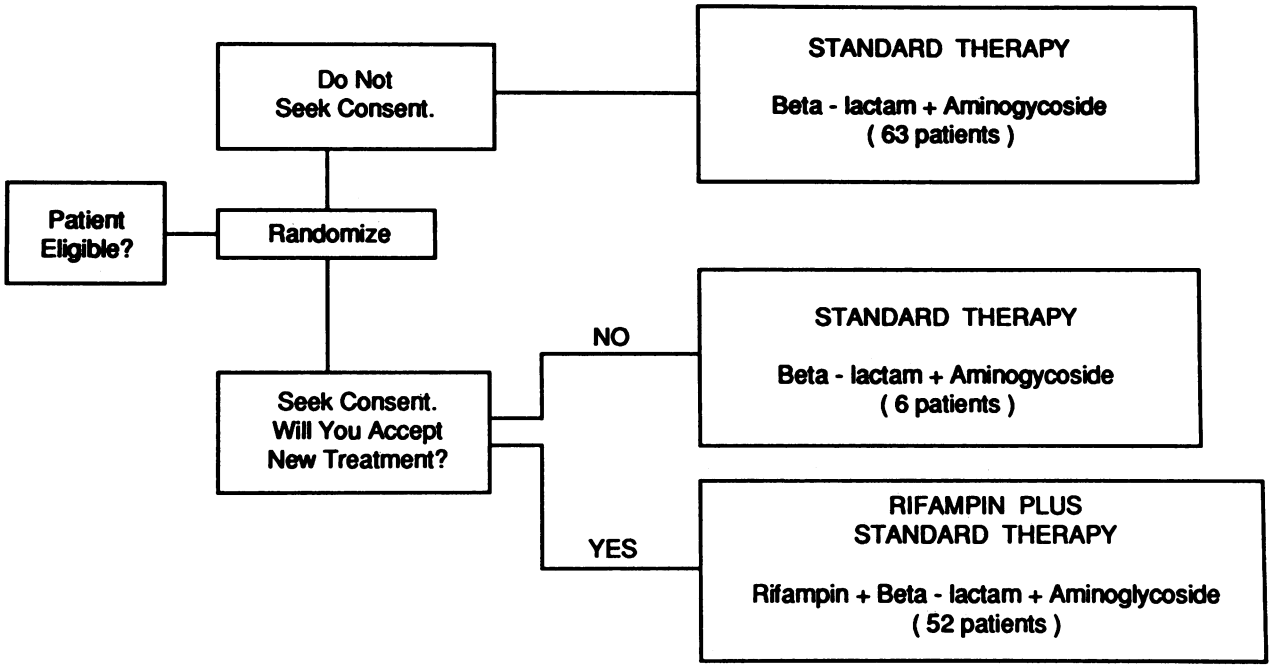

FIG. 1. Schematic allocation of patients by the Zelen protocol.

noglycosides could be substituted on the basis of in vitro susceptibility results or history of penicillin allergy. Amikacin and gentamicin were acceptable alternatives for tobramycin. Ceftazidime, azlocillin, and imipenem were acceptable alternatives to piperacillin. Serum aminoglycoside concentrations were monitored for all patients.

All patients 18 years or older with one or more blood cultures positive for *P. aeruginosa* were eligible. Patients unable to tolerate oral medications were excluded prior to randomization. Nasogastric or gastric tubes were acceptable oral routes in patients without ileus or obstruction. Nonimmunocompromised patients with the urinary tract as the presumed portal of entry were excluded to eliminate patients with more easily treatable infection and projected low mortality.

Patient entry was stratified according to the following criteria: administration of empiric antipseudomonal antibiotic therapy (extended-spectrum penicillins, expanded-spectrum cephalosporins, and aminoglycosides) within 48 h of the positive blood culture, neutropenia (neutrophils, <1,500 cells/mm^3), possible *Pseudomonas* pneumonia as defined by new pulmonary infiltrate or sputum cultures yielding *P. aeruginosa*, and severity of illness. It was anticipated that these criteria might be independent predictors of clinical efficacy, potentially confounding the issue of rifampin efficacy (2, 11).

Severity of illness was quantified as follows: temperature > 39°C (2 points), mental status (alert = 0 points, disoriented = 1 point, stupor = 2 points, coma = 4 points), hypotension (2 points), mechanical respiratory support (2 points), and cardiac arrest (4 points). Patients were considered to have 4+ illness if they accumulated 4 points or more in the 72 h prior to the identification of bacteremia. This rating index was found to be highly predictive of outcome in a previous study of *P. aeruginosa* bacteremia (11).

Patients were considered immunosuppressed if any one of the following was present: neutropenia (neutrophils, <1,500 cells per mm^3), receipt of oncologic chemotherapy and/or corticosteroids within 1 week of the positive blood culture, or hematologic malignancy.

If the patient was randomized and stratified into the experimental three-drug (rifampin+) group, informed consent was obtained and treatment with rifampin and the beta-lactam agent (usually piperacillin) plus the aminoglycoside (usually tobramycin) was initiated. If the patient was already receiving double-combination therapy empirically, rifampin was added. If the patient was randomized into the control group, the two-drug (standard) therapy (usually piperacillin and tobramycin) was initiated or maintained if empiric antipseudomonal combination therapy had already been initiated.

Study endpoints. Two endpoints were used. The first endpoint was bacteriologic response. Bacteriologic failure was due to either (i) "breakthrough bacteremia," defined as isolation of *P. aeruginosa* from blood while the patient was receiving the study antibiotic regimen or (ii) relapse, defined as isolation of *P. aeruginosa* from blood during the same hospital course following discontinuation of the study antibiotic regimen. The second endpoint was mortality at 5, 10, or 14 days after initial documentation of *P. aeruginosa* bacteremia. Mortality was an objective endpoint, and confining assessment to 14 days or fewer minimized the difficulty of attributing death to infection in severely ill patients in which death results from multifactorial causes. We made no attempt to classify mortality as related or not related to infection, since such an assignment of causation required subjective clinical judgment, with the possible introduction of bias into the assessment of efficacy.

Data were entered into a computer data bank (Prophet System, Division of Research Resources, National Institutes of Health). The chi-square test and Fisher exact test (two tailed) were performed. A stepwise logistic regression analysis was used for multivariate analysis (BMDP, University of California). The two dependent variables assessed were

bacteriologic failures with antibiotic therapy and mortality. The independent variables were antibiotic regimen (standard therapy versus rifampin+), immunosuppression, severity of illness, and pneumonia. Significance was defined as a P value of 0.05 or less.

RESULTS

Sixty-three patients were randomized to the two-drug (standard therapy) group and 58 patients were randomized to the three-drug (rifampin+) group. Six patients refused to enter the three-drug group and received two drugs; as with the Zelen protocol, their outcome was counted in the three-drug group.

Piperacillin plus tobramycin was the most common combination given (89 of 121 [73.6%]), with 44 in the two-drug (standard therapy) group and 45 in the three-drug (rifampin+) group. Other antipseudomonal agents were occasionally substituted on the basis of in vitro susceptibility results or because of a history of penicillin allergy. The next most commonly used combinations were imipenem plus tobramycin (8 of 121), piperacillin plus gentamicin (7 of 121), ceftazidime plus tobramycin (6 of 121), piperacillin plus amikacin (3 of 121), azlocillin plus tobramycin (2 of 121), ceftazidime plus gentamicin (2 of 121), mezlocillin plus gentamicin (1 of 121), mezlocillin plus amikacin (1 of 121), cefoperazone plus tobramycin (1 of 121), and imipenem plus amikacin (1 of 121). All organisms were susceptible in vitro to the beta-lactam and aminoglycoside administered.

Exclusions. 68 patients with *Pseudomonas* bacteremia were excluded from the study. Reasons for exclusion included laboratory failure to identify *P. aeruginosa* within 5 days of obtaining blood culture (12 patients), identification of the urinary tract as the portal of entry in nonimmunosuppressed patients (7 patients), "do not resuscitate" orders such that experimental antibiotic protocols were not considered (12 patients), in vitro resistance of *P. aeruginosa* to the study agents (3 patients), and inability to take oral agents (3 patients). Twenty-five patients died prior to identification of the organism in blood and could not be enrolled. Six patients were inadvertently omitted because of logistic difficulties, including investigator absence.

Stratification variables. A total of 121 patients with *P. aeruginosa* bacteremia were stratified according to four characteristics that were presumed a priori to have an unfavorable impact on outcome in *P. aeruginosa* bacteremia; 94% (114 of 121) of patients received empiric antipseudomonal antibiotics during a 48-h period prior to and/or following the time when the positive blood culture was drawn (Table 1). Twenty-four patients were actually receiving antipseudomonal therapy at the time the blood culture was obtained. Twenty percent (24 of 121) of patients had neutrophil counts ranging from 0 to 1,248 cells/ml (median, 100 cells/ml). Fourteen patients were profoundly neutropenic (neutrophil count, <100 cells/ml); neutrophil counts improved during therapy for 11 of these 14 profoundly neutropenic patients (Table 1). Twenty-five patients in the two-drug therapy (standard therapy) and 27 patients in the three-drug therapy (rifampin+) received corticosteroids at doses of 25 to 5,000 mg (hydrocortisone equivalents) and 20 to 2,500 mg (hydrocortisone equivalents), respectively. Fifty-two percent (63 of 121) of patients had illnesses of 3+ to 4+ (Table 1). Forty-nine percent (59 of 121) of patients were judged to have possible pneumonia at the time of enrollment into the study on the basis of the presence of a pulmonary infiltrate on chest X ray and/or sputum cultures yielding *P. aeruginosa*; this diagnosis was confirmed clinically and bacteriologically during the hospital course in 37 of the original 59 patients (Table 1). Stratification variables were comparable for the two study groups, as expected (Table 1).

TABLE 1. Clinical characteristics of patients receiving two drugs (standard therapy) and of those receiving three drugs (rifampin+)

Clinical parameter	% (Proportion of) patients receiving[a]:	
	Two drugs	Three drugs
Neutropenia[b] (<1,500 cells/ml)	21 (13/63)	19 (11/58)
Profound neutropenia (<100 cells/ml)	13 (8/63)	10 (6/58)
Neutropenia improved during therapy	88 (7/8)	67 (4/6)
Severity of illness[b,c]		
1+	0 (0/63)	4 (2/58)
2+	49 (31/63)	43 (25/58)
3+	17 (11/63)	21 (12/58)
4+	33 (21/63)	33 (19/58)
Immunosuppressed[c]	56 (35/63)	59 (34/58)
Age greater than 65 years	35 (22/63)	29 (17/58)
Diabetes mellitus	17 (11/63)	7 (4/58)
Chronic obstructive pulmonary disease	11 (7/63)	14 (8/58)
Lung malignancy	2 (1/63)	4 (2/58)
Hematologic malignancy	17 (11/63)	17 (10/58)
Nosocomial acquisition[d]	68 (43/63)	76 (44/58)
Polymicrobial bacteremia	29 (18/63)	16 (9/58)
Portal or source		
Pneumonia[b]	24 (18/63)	33 (19/58)
Abdominal/biliary	21 (13/63)	10 (6/58)
Urinary tract	16 (10/63)	9 (6/58)
Intravenous associated	5 (3/63)	2 (1/58)
Vascular	5 (3/63)	7 (4/58)
Wound or skin	6 (4/63)	16 (9/58)
Unknown	19 (12/63)	24 (14/58)
Antipseudomonal antibiotics within 48 h of positive blood culture[b,e]	92 (58/63)	97 (56/58)
Antipseudomonal antibiotics prior to positive blood culture[f]	25 (16/63)	12 (7/58)

[a] For all parameters, P values were not significant by the Fisher exact test (two tailed) (for antipseudomonal antibiotics prior to positive blood culture, $P = 0.07$).
[b] Stratification variable.
[c] See Materials and Methods for definition.
[d] Defined as hospitalization of >3 days.
[e] Forty-eight hours prior to or 48 h after the time when blood culture obtained.
[f] Range of 1 to 20 days (median = 6 days) prior to positive blood culture.

Bacteriologic response. Bacteriologic failure occurred more frequently in the two-drug (standard therapy) group than in the three-drug (rifampin+) group; only 1.7% (1 of 58) of patients receiving three drugs, compared with 14.3% (9 of 63) of patients receiving two drugs, had additional positive blood cultures 3 or more days after the study therapy was initiated. This difference was statistically significant ($P = 0.018$). Multivariate analysis also showed that only the standard regimen was significantly associated with bacteriologic failure ($P < 0.03$) that was independent of other variables, including immunosuppression, severity of illness, and pneumonia.

Of the nine bacteriologic failures in the two-drug group, four were breakthrough bacteremias and five were relapses (with positive blood cultures for *P. aeruginosa* from 11 to 135 days after discontinuation of the two-drug therapy). The patient with relapse at 135 days was considered to have bacteriologic failure because the biliary tract consistently yielded *P. aeruginosa* following two-drug therapy and up

until the time of the repeat positive blood culture 135 days later. Only one of these nine patients died. Seven of nine had focal sites of infection as follows: sacral abscess (one), intra-abdominal abscess (two), septic thrombophlebitis (one), kidney stone (one), biliary obstruction (one), and chronic respiratory colonization (one); six of these seven sites yielded persistent *P. aeruginosa* during therapy. Of the seven sites accessible to surgical drainage, four were drained. On the basis of this finding, the two patient groups were reanalyzed by portal of entry and definable foci of infection to assess whether there may have been significant preexisting differences in the two treatment groups which escaped the stratification scheme; no significant differences could be delineated (Table 1). The one bacteriologic failure in the three-drug group was with a patient with prosthetic aortic valve endocarditis who was not deemed a surgical candidate for valve removal. He was treated for 4 weeks with piperacillin and tobramycin but for only 7 days with rifampin. Bacteremia relapsed 16 days after the cessation of antibiotic therapy.

In 9 of the 10 bacteriologic failures (9 in standard therapy and 1 in rifampin+ therapy), the organisms reisolated from blood were found to have in vitro susceptibility patterns identical to that of the original isolate. In 1 of 10, the MIC of piperacillin rose from 4 to 16 μg/ml. Subtyping of the *P. aeruginosa* isolates was not performed.

For the 37 cases of *Pseudomonas* pneumonia (Table 1), sputum cultures were positive for *P. aeruginosa* prior to therapy in 78% (14 of 18) of patients in the two-drug (standard therapy) group and in 89% (17 of 19) of patients in the three-drug (rifampin+) group; no sputum was produced in 6 patients. Thirty-six percent (5 of 14) of sputum cultures for *P. aeruginosa* remained positive 3 or more days after the initiation of therapy in the two-drug group, while 38% (6 of 16) remained positive in the three-drug group.

Polymicrobial bacteremia occurred in 27 episodes (Table 1). Thirty-two organisms were isolated in conjunction with *P. aeruginosa*; *Escherichia coli* (five cases), *Enterococcus faecalis* (four cases), *Enterobacter* species, (four cases), *Klebsiella* species (four cases), and *Staphylococcus epidermidis* (three cases) were the most common isolates. Bacteriologic failure occurred in 11% of patients with polymicrobial bacteremia in both the two-drug group and the three-drug group. Likewise, mortality was not significantly different for patients experiencing polymicrobial bacteremia in the two treatment groups (data not shown).

Outcome. Mortality was assessed at 5, 10, and 14 days after the initial documentation of bacteremia. No statistically significant difference in mortality was seen between patients randomized to two drugs (standard therapy) and those randomized to three drugs (rifampin+) (Table 2). Likewise, analysis of patient subgroups, including immunosuppression, nosocomial acquisition, presence of pneumonia, and severity of illness, revealed no significant differences in mortality between the two treatment groups (Table 2). Multivariate analysis showed that the severity of illness was significantly associated with mortality ($P < 0.01$) but that antibiotic regimen, immunosuppression, and pneumonia were not.

Antibiotic toxicity. Rifampin was discontinued for two patients because of increasing bilirubin and for a third patient because of nausea and vomiting; all three cases were nevertheless included in the final analysis. An increase in bilirubin was seen with another four patients; this condition resolved after the completion of therapy. Bilirubin increased to 1.5 times above baseline in 53% of the three-drug group versus 22% of the two-drug group, a significant difference ($P < 0.006$ by the Fisher exact test [two tailed]). All abnormalities resolved with the cessation of rifampin treatment. There were no significant differences in the elevations of levels of alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, or serum creatinine between the two treatment groups.

TABLE 2. Mortality at 14 days of patients receiving two drugs (standard therapy) and of those receiving three drugs (rifampin+)

Clinical parameter	% (Proportion) of patients receiving[a]:	
	Two drugs	Three drugs
Mortality at:		
5 days	3 (2/63)	5 (3/58)
10 days	11 (7/63)	21 (12/58)
14 days	17 (11/63)	24 (14/58)
Mortality at 14 days with:		
Immunosuppression	20 (7/35)	29 (10/34)
Neutropenia	23 (3/13)	36 (4/11)
Nosocomial acquisition	23 (10/43)	25 (11/44)
Pneumonia	28 (5/18)	26 (5/19)
1+ illness	0 (0/0)	50 (1/2)
2+ illness	13 (4/31)	16 (4/25)
3+ illness	0 (0/11)	17 (2/12)
4+ illness	33 (7/21)	37 (7/19)

[a] *P* was not significant for all clinical parameters.

DISCUSSION

Despite the introduction of numerous agents with potent antipseudomonal activity over the past several decades, mortality with *P. aeruginosa* bacteremia remains high (2, 5, 13). The difficulty in effectively treating *Pseudomonas* bacteremia is underscored by the fact that 20% of the bacteremic patients in our study were receiving at least one antipseudomonal antibiotic at the time the positive blood culture was drawn! Therefore, the need for more effective treatment for serious *Pseudomonas* infections still exists.

On the basis of encouraging data from in vitro studies (20, 22, 26), animal models (9, 21, 25), and limited clinical experience (18, 23), rifampin was evaluated as part of standard antipseudomonal combination therapy for *P. aeruginosa* bacteremia in this prospective, controlled randomized trial. A total of 121 patients were enrolled. The control group received standard two-drug therapy consisting of an antipseudomonal beta-lactam agent plus an aminoglycoside. The study group received the standard two-drug therapy plus oral rifampin.

Two endpoints were evaluated in this study: bacteriologic response and outcome. Bacteriologic failure occurred significantly more often in patients randomized to two drugs (standard therapy) (9 of 63 [14%]) than in patients randomized to three drugs (rifampin+) (1 of 58 [2%]). In the two-drug group, four of nine patients experienced breakthrough bacteremia during therapy and five of nine relapsed with *P. aeruginosa* bacteremia following discontinuation of therapy. All relapses occurred more than 2 weeks after antibiotics were stopped, and they were later documented to have resulted from uneradicated foci of *P. aeruginosa*. In the three-drug group, the single bacteriologic failure was a relapse 16 days posttherapy in a patient with prosthetic valve endocarditis; he had received only 7 days of rifampin be-

cause of the development of hyperbilirubinemia. Rifampin penetrates extremely well into body fluids, cavities, and cells, especially with the high dose used in this study. Whether this was the reason for the superior bacteriologic response remains to be established. It is important to note that the portal of entry for the organism and the presence of definable foci proved to be similar for the two treatment groups (Table 1).

Despite an apparent bacteriologic advantage for rifampin-treated patients, outcome was not significantly different in either treatment group. The mortality at 14 days postoccurrence of bacteremia for patients randomized to two drugs (standard therapy) was 17% (11 of 63), compared with 24% (14 of 58) for patients treated with three drugs (rifampin+) (Table 2). The lack of a survival benefit conferred by rifampin may have been attributable to several possible factors. Twenty-five patients died in the 48 to 72 h after initial blood cultures were obtained; since *P. aeruginosa* could not be identified at the time the blood cultures were obtained, these patients could not be randomized into the study. Thus, the patients who were presumably the most critically ill and therefore potentially the ones most likely to benefit from improved antibacterial therapy could not be entered into the trial because of the protocol requirement that the identity of bloodstream isolates be established as *P. aeruginosa* prior to enrollment. The patients in the two-drug group who experienced bacteriologic failures were mostly those with persistent uneradicated foci of the organism that ultimately responded to continued therapy and/or surgical drainage.

The following inherent biases against the three-drug regimen occurred during the study. (i) More patients in the two-drug group (25%) had received empiric antipseudomonal therapy for at least 48 h before the positive blood culture was drawn than in the three-drug group (12%) (Table 1). Since there was no significant difference in the severity of illness or underlying disease in the two treatment groups, this may have favored somewhat the outcome of patients who received two drugs (standard therapy). (ii) Rifampin was administered orally, and in some surgical patients absorption may have been suboptimal on the basis of visual inspection of the urine, in which the orange coloration was less intense than expected. (Concentrations of rifampin in serum were not determined.) (iii) Whereas the beta-lactam–aminoglycoside combination was often initiated empirically prior to cultural confirmation, rifampin was not given until *P. aeruginosa* was identified as the bacteremic pathogen, as required by the protocol. Thus, 16% (9 of 58) of patients in the three-drug group actually received rifampin "late" (>72 h after the positive blood culture).

The high doses of rifampin were well tolerated. In only 5.2% (3 of 58) of cases was rifampin prematurely terminated, in two because of hyperbilirubinemia and in one because of nausea and vomiting. Increases in bilirubin occurred significantly more frequently in the three-drug group, but all abnormalities subsided with cessation of therapy. Rifampin can cause hyperbilirubinemia in two ways. First, true elevation can be caused by the displacement of bilirubin by rifampin in the hepatic conjugation enzyme system. Second, colorimetric assays for bilirubin may be artifactually elevated because rifampin colors the serum orange-yellow.

The Zelen protocol. This study employed an innovative design for the enrollment of patients proposed by Zelen (24) (Fig. 1). Patients were randomized to receive either two drugs (standard therapy) or three drugs (rifampin+). In this study design, we were required to seek consent only from patients randomized to the experimental three-drug group. If the patient refused, he or she received the standard therapy. For purposes of analysis, however, the patients randomized to the experimental three-drug group, including those who refused the three-drug therapy, were evaluated together.

The most severe drawback of this protocol in the analysis of the study occurs if many patients refuse the experimental therapy. The scientific interpretation will be clouded by the fact that the outcome for these patients will be counted toward experimental therapy which they did not receive. In our study, only six patients refused the experimental therapy of three drugs (rifampin+); this refusal did not affect the statistical conclusions of the study. No differences in statistical interpretation were seen when the data were analyzed by the Zelen assignment and when they were analyzed by the drugs the patient actually received.

There are legitimate ethical concerns about this protocol, given the fact that the patients randomized to the control group were not informed about their participation in a clinical trial. These issues have been well explored elsewhere (6, 7, 12, 17) and are beyond the scope of this discussion. Nevertheless, our experience with this study design revealed clear-cut advantages to both patient and investigator. The time-consuming process of informed consent (however desirable) was halved and the decision-making process was simplified. Furthermore, unlike standard randomized trials in which the patient is not informed as to which therapy he or she will receive if they accept entry into the study, patients randomized to the experimental therapy were immediately knowledgeable about which therapy they would receive. We cannot help but point out that if our study had not been conducted, all patients would still have received the standard (control) therapy of an antipseudomonal beta-lactam agent and aminoglycoside. No laboratory tests or invasive procedures were performed as part of the study that would not otherwise have been performed in the routine management of patients with *Pseudomonas* bacteremia.

Horwitz and Feinstein (12) listed three other shortcomings of the Zelen protocol. (i) Placebo-controlled trials are not possible. This shortcoming did not apply to our study, since the patients randomized to control therapy received the accepted standard combination of an antipseudomonal beta-lactam agent and aminoglycoside. (ii) A double-blind format is not possible since both physician and patient know which treatment will be used. In this study, blinding was not feasible from the outset, given the fact that rifampin colors body secretions bright orange. (iii) Frequent follow-up visits for the sole purpose of data collection may inconvenience patients randomized to the control group. This was not a problem in our study, given that the endpoints of survival and bacteriological cure were assessed during the hospitalization.

In summary, rifampin contributed to the efficacy of antipseudomonal therapy. Since bacteriologic response was improved when rifampin was combined with standard therapy for *P. aeruginosa* bacteremia, further trials with rifampin as an antipseudomonal agent should be considered. Moreover, development of new rifamycins with more potent in vitro activity against *P. aeruginosa* should be encouraged.

Given the high in vitro MICs against *P. aeruginosa* and the lack of clinical experience in using rifampin for *P. aeruginosa* infection, we recommend confirmation of these promising results by other investigators before widespread use of rifampin for *P. aeruginosa* infection becomes accepted. Rifampin might be considered as an adjunctive treatment in serious *P. aeruginosa* infections that have failed standard

combination therapy. In addition to the elevation of bilirubin caused by rifampin, one should be mindful of the alteration of metabolism for other drugs (coumadin, cyclosporine, etc.).

Finally, we found the Zelen protocol to be particularly well suited for comparative studies of antimicrobial agents in infectious diseases, and wider use of this protocol should be considered.

ACKNOWLEDGMENTS

We thank Shirley Brinker and Linda Gibasiewicz for secretarial assistance and Marilyn Wagener and Susan Snyder for statistical analysis.

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