Original Article

http://dx.doi.org/10.3947/ic.2013.45.3.283
Infect Chemother 2013;45(3):283-291
pISSN 2093-2340 · eISSN 2092-6448

Infection & Chemotherapy

Correlations between Microbiological Outcomes and Clinical Responses in Patients with Severe Pneumonia

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Background: In treatment of pneumonia, microorganisms sometimes persist, appear or reappear despite good clinical responses. On the other hand, recent increasing antibiotic resistance emphases the goal of rapid eradication of pathogen in severe infection. This study was planned to evaluate the correlations between microbiological outcomes and clinical responses in severe pneumonia.

Materials and Methods: Data was gathered from 3 clinical trials regarding severe pneumonia. Microbiological outcomes, determined by serial culture of respiratory tract samples,were compared with clinical outcomes.

Results: In total, 146 bacterial strains from 76 patients were analyzed. While clinical success was generally related to total or partial eradication of isolated organisms, *Acinetobacter*, *Enterobacter*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia* were often not eradicated and yet were observed in 56% of cases considered clinically successful at the end of antibiotic treatment. Most of the non-eradicated strains (71%) already had or developed resistance against the antibiotics used for treatment. Ten patients relapsed during the follow-up period; 7 of these relapses were associated with 10 non-eradicated organisms.

Conclusions: These data raise concern about the pathogenicity of bacteria that persist in the respiratory tract even though good clinical outcomes of pneumonia are achieved, especially when *Acinetobacter*, *Enterobacter*, *P. aeruginosa*, or *S. maltophilia* were involved. Thus, clinical relapse and development of drug resistance by non-eradicated organisms may be raised.

Key Words: Severe pneumonia, Microbiological outcome, Clinical outcome, Resistance development

Introduction

In certain kinds of infection, the persistence, appearance, or reappearance of microorganisms during antibiotic treatment may not correlate with the clinical response to treatment. We can readily differentiate non-pathogenic organisms that do not generally cause infections. However, even organisms that frequently cause infections may exist as bystanders or colo-

Received: August 22, 2013 **Revised:** September 10, 2013 **Accepted:** September 17, 2013
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nizers rather than true pathogens. Furthermore, organisms characterized as true pathogens may persist or relapse unrelated to clinical response. In most infections at non-sterile sites, especially when foreign bodies are involved, it is not easy to differentiate true pathogens from non-pathogens. Therefore, changes in clinical findings are usually preferred over microbiological findings to define the outcomes of antibiotic treatment for severe pneumonia requiring mechanical ventilation.

Because the prevalence of resistance is increasing in many important clinical pathogens, pathogen eradication has received more emphasis in recent trials [1-8]. Clinical success achieved without microbiological eradication may increase the selection for antimicrobial resistance or the initiation of subsequent infections [9]. Antibiotics that maximize bacterial eradication prevent the emergence of resistance, as dead microorganisms cannot mutate [8]. More rapid the bacterial eradication, better the possibility of avoiding the selection for resistance among subpopulations.

However, it remains unclear whether microbiological eradication should be a goal of antibiotic treatment in addition to good clinical response, especially for infections at non-sterile sites such as the lower respiratory tracts of patients in intensive care units. Therefore, we conducted an analysis of the correlations between clinical responses and microbiological eradication among patients with severe pneumonia.

Materials and Methods

Three clinical trials conducted at the Millard Fillmore Hospital between 1984 and 1993 were reviewed: (i) an open-label study of cefmenoxime therapy, where the goal was dosage optimization targeted to achieve bacterial eradication in 4 days by dual individualization with doses ranging between 500 and 2,000 mg q 4–8 h; (ii) a double-blinded, randomized trial comparing intravenous ciprofloxacin to intravenous imipenem, with dosages of 200–400 mg q 8–12 h and 250–1,000 mg q 6–12 h, respectively, depending on creatinine clearance and susceptibility; (iii) an open-label, randomized controlled study of intravenous ciprofloxacin versus intravenous ceftazidime, with ciprofloxacin and ceftazidime dosages of 400 mg q 8 or 12 h and 1–2 g q 8 or 12 h, respectively, where doses were optimized to a target area under the inhibitory curve (AUIC) of 250, which represented the 24 h area under the concentration versus time curve (AUC)/MIC ratio. In the last study, piperacillin and tobramycin were added to ciprofloxacin and ceftazidime, respectively, if the target AUIC of 250 could not be achieved with the starting doses of the monotherapy regimens. Subsets of the results from these studies have been included in other published studies [10-12].

Physicians evaluated clinical outcomes at the end of antibiotic treatment and during the follow-up period, up to 2 weeks after antibiotic treatment. Daily clinical scoring (pneumonia score) was used to evaluate the clinical response more objectively and quantitatively. The pneumonia score consists of 10

Table 1. Pneumonia score[a]

	1	2	3	4
Rales/crackles	None	Mild	Moderate	Severe
Decreased breath sounds	None	Mild	Moderate	Severe
Oxygen use	Room air	Mask aerosol T vent (≤40%)	Ventilator (41–60%)	Ventilator (≥ 61%)
WBC count (peripheral)	< 10K	10K–15K	15.1K–30K	> 30K
Differential, % band neutrophils	< 5	5.1-15	15.1–39.9	≥ 40
CNS status	Alert and fully oriented	Alert but not fully oriented	Not alert, responsive only to pain	Non-responsive
Tube sign[b] (number of tubes)	0-2	3-5	6-9	≥ 10
Sputum or tracheal secretions	None	Suction every shift or cough occasionally	Suction every 2-3 hours or cough continuously	Suction every 0.5-1 hour
Temperature (maximum, °F)	97.0–99.0	99.1–100.9	101.0–102.9	≥ 103.0
Serum albumin (gm/dL)	≥ 3.9	3.0-3.8	1.9-2.9	≤ 1.8

[a]Modified from references 20 and 23.
[b]Tubes include endotrachael tube, foley catheter, ureteral stent, indwelling venous catheter, nasogastric tube, central line, Swan-Ganz catheter, and surgical drainage tubes, etc.

Table 2. Demographic data and microbiological outcomes of patients by clinical response

Demographic data & microbiological outcomes	Clinical outcome (end of treatment)		Clinical outcome (follow up)	
	Cured	Failed	Cured	Failed
Number of patients	55	19	45	29
Age (SD) (yr)	68.5 (13.2)	67.3 (14.2)	67.7 (14.3)	69.0 (12.1)
Sex (male:female)	34:21	13:6	27:18	20:9
Height (SD) (cm)	170.9 (11.1)	168.4 (10.8)	171.1 (11.0)	168.9 (11.1)
Weight (SD) (kg)	74.8 (26.4)	71.2 (15.3)	74.9 (27.4)	72.3 (17.8)
Charlson Weighted Index (SD)	2.0 (1.5)	2.7 (2.3)	2.0 (1.5)	2.6 (2.1)
Trauma	1	0	1	0
Operation/procedure	28	16[a]	22	22[a]
Steroid	5	1	2	4[a]
Hemodialysis	1	2[a]	0	3[a]
Mechanical ventilation	49	18	39	28
Endotracheal tube/tracheostomy	49	19	39	29[a]
Bacteremia	1	0	1	0
Microbiological outcome (end of treatment)				
All organisms eradicated	26	1[a]	23	4[a]
All or part of organisms eradicated	47	9[a]	41	15[a]
Microbiological outcome (follow up)				
All organisms eradicated	24	1[a]	21	4[a]
All or part of organisms eradicated	44	9[a]	38	15[a]

SD, standard deviation.
[a]*P*-value < 0.1.

Table 3. Multivariate analysis of factors contributing to clinical outcomes

Contributing factors	Clinical outcome (end of treatment)		Clinical outcome (follow up)	
	Odds ratio	*P*-value	Odds ratio	*P*-value
Operation/procedure	0.185–0.235	0.020–0.047	0.245–0.332	0.027–0.084
Microbiological eradication, all or part of organisms eradicated	5.639	0.007	6.007	0.005
Microbiological eradication, all organisms eradicated	18.279	0.009	7.446	0.005

clinical parameters, which are shown in Table 1. Drop of pneumonia score to 4 was considered the threshold for good clinical response.

Sputum samples or tracheal aspirates were cultured daily and tested for antibiotic sensitivity. Microbiologic outcomes were determined using guidelines from the Infectious Diseases Society of America [13, 14] as follows: microbiologic eradication, elimination of the organism determined by 2 consecutive negative cultures; microbiologic persistence, failure to eradicate the causative organism; microbiologic relapse, recurrence of the same organism within 5 days after discontinuation of treatment or during treatment after 2 consecutive negative cultures; superinfection, development of new pneumonia with signs and symptoms due to a new or resistant pathogen other than the original causative organisms; colonization, development of a positive culture of a bacterial strain other than the primary causative isolate that appeared >48 h after initiation of therapy that persists in at least 2 repeated cultures and is not associated with fever, leukocytosis, persistence, or progression of pneumonia; indeterminate, circumstances where it was not possible to categorize the microbiologic response. Presumed microbiological eradication or presumed microbiological persistence were not considered endpoints in these trials, as all assessments were based on actual cultures.

Table 4. Comparison of microbiological outcomes and clinical responses at the end of antibiotic treatment by microorganisms

Microbiological outcomes	Clinical outcome (end of treatment)			Clinical outcome (follow up)			Total
	Cured	Failed	Indeterminate	Cured	Failed	Indeterminate	
Acinetobacter spp.							11
Eradication	1	0	0	0	1	0	1
Persistence	1	2	0	0	3	0	3
Colonization	7	0	0	4	3	0	7
Enterobacter spp.[a]							12
Eradication	3	2	0	3	2	0	5
Persistence	2	1	0	2	1	0	3
Relapse	4	0	0	3	1	0	4
Escherichia coli							14
Eradication	13	1	0	12	2	0	14
Klebsiella spp.[b]							16
Eradication	8	3	2	8	3	2	13
Persistence	0	1	0	0	1	0	1
Relapse	1	1	0	1	1	0	2
Proteus spp.[c]							11
Eradication	7	1	0	6	2	0	8
Relapse	2	0	0	2	0	0	2
Superinfection	0	1	0	0	1	0	1
Pseudomonas spp.[d]							31
Eradication	7	1	0	6	2	0	8
Persistence	5	12	0	3	14	0	17
Relapse	5	0	0	4	1	0	5
Superinfection	0	1	0	0	1	0	1
Serratia marcescens							11
Eradication	7	0	0	4	3	0	7
Persistence	0	2	0	0	2	0	2
Relapse	1	0	0	0	1	0	1
Indetermined	0	1	0	0	1	0	1
Staphylococcus aureus							13
Eradication	7	2	0	6	3	0	9
Persistence	0	1	0	0	1	0	1
Relapse	1	1	0	1	1	0	2
Colonization	1	0	0	1	0	0	1
Stenotrophomonas maltophilia							14
Eradication	4	0	0	4	0	0	4
Persistence	0	2	0	0	2	0	2
Relapse	1	1	0	1	1	0	2
Colonization	2	0	0	2	0	0	2
Superinfection	1	3	0	0	4	0	4
Others[e]							13
Eradication	9	2	1	8	3	1	12
Colonization	1	0	0	1	0	0	1

( ) represents the number of isolates.
[a]*E. aerogenes* (5), *E. cloacae* (7).
[b]*K. oxytoca* (4), *K. pneumoniae* (12).
[c]*P. mirabilis* (9), *P. vulgaris* (2).
[d]*P. aeruginosa* (29), *P. fluorescens* (2).
[e]Strains for which the total number of isolates was less than10; *Alcaligenes xylosoxidans* (1), *Citrobacter freundii* (4), *Haemophilus influenza* (3), *Morganella morganii* (1), *Streptococcus* (4).

Table 5. Susceptibility of microorganisms by microbiological outcomes

Microbiological outcomes	Susceptible	Resistant	Development of resistance	Total
Acinetobacter				11
Eradication	1	0	0	1
Persistence	1	2	0	3
Colonization	0	7	0	7
Enterobacter spp.[a]				12
Eradication	4	0	1	5
Persistence	0	0	3	3
Relapse	0	0	2	2
Colonization	0	2	0	2
Escherichia coli				14
Eradication	14	0	0	14
Klebsiella spp.[b]				16
Eradication	13	0	0	13
Persistence	0	0	1	1
Relapse	0	0	2	2
Proteus spp.[c]				11
Eradication	8	0	0	8
Relapse	1	0	1	2
Superinfection	1	0	0	1
Pseudomonas spp.[d]				31
Eradication	7	1	0	8
Persistence	4	4	9	17
Relapse	1	0	4	5
Superinfection	1	0	0	1
Serratia marcescens				11
Eradication	7	0	0	7
Persistence	2	0	0	2
Relapse	0	0	1	1
Indeterminate	0	0	1	1
Staphylococcus aureus				13
Eradication	9	0	0	9
Persistence	0	1	0	1
Relapse	0	2	0	2
Colonization	0	1	0	1
Stenotrophomonas maltophilia				14
Eradication	2	0	1	4[e]
Persistence	1	1	0	2
Relapse	0	1	1	2
Colonization	0	1	0	2[e]
Superinfection	2	1	0	4[e]
Others[f]				13
Eradication	12	0	0	12
Colonization	0	1	0	1

( ) represents the number of isolates.
[a]*E. aerogenes* (5), *E. cloacae* (7).
[b]*K. oxytoca* (4), *K. pneumoniae* (12).
[c]*P. mirabilis* (9), *P. vulgaris* (2).
[d]*P. aeruginosa* (29), *P. fluorescens* (2).
[e]Susceptibility tests were not performed in some cases.
[f]Strains for which the total number of isolates was less than10; *Alcaligenes xylosoxidans* (1), *Citrobacter freundii* (4), *Haemophilus influenza* (3), *Morganella morganii* (1), *Streptococcus* (4).

Statistical analysis

Patients' baseline underlying disease states and demographic characteristics were compared to clinical outcomes. The effect of categorical data on the clinical outcomes was evaluated using Chi-square and Fisher's exact tests where appropriate. Continuous data were compared using Student's *t*-test and Kruskal-Wallis one-way analysis of variance. For multivariate factor analysis, data sets with *P*-values < 0.1 were subjected to logistic regression analysis using SYSTAT software (Systat, Inc., Evanston, Ill.).

Results

A total of 146 bacterial strains were isolated from 76 patients and included in the analysis. Baseline characteristics of patients by clinical outcomes are listed in Table 2. Two patients with indeterminate treatment responses were excluded from the analysis. There was no statistical difference between patients with different clinical outcomes in the sex ratio, age, height, weight, or Charlson weighted index, which represents comorbid illnesses that predict the risk of mortality [15]. The incidence of several predisposing conditions — recent operations or procedures (within 30 days preceding antibiotic treatment), use of corticosteroids, hemodialysis, insertion of endotracheal tubes, or tracheostomy — showed differences in the prevalence between patients with favorable clinical outcomes and those with poor clinical outcomes. Although chemotherapy, pregnancy, neutropenia, splenectomy, transplantation, and peritoneal dialysis were also included in the list of predisposing conditions, no patients reported those conditions. APACHE II scores were not compared because scores were not available for every patient. Microbiological eradication, whether total or partial, was more often associated with patients who were classified as cured. Multivariate analysis identified microbiological eradication and recent operations or procedures as independent factors contributing to favorable clinical outcomes (Table 3).

However, many cases achieved clinical success but not microbiological elimination (Table 4). While microbiological outcomes showed 81 instances of microbiological eradication (55.5%), 29 microbiological persistence (19.9%), 16 microbio-

Table 6. Summary of patients who clinically relapsed after discontinuation of antibiotic treatment

Patient	Organisms	Microbiological outcomes	Development of resistance	Time of clinical relapse (days after discontinuation of antibiotics)
Case 1	*Acinetobacter*	Persistence	No	3
	Enterobacter aerogenes	Relapse	Yes	3
Case 2	*Serratia marcescens*	Eradication	No	2
Case 3	*Acinetobacter*	Superinfection	No[a]	9
	Serratia marcescens	Relapse	Yes	9
Case 4	*Acinetobacter*	Superinfection	No[a]	6
	Pseudomonas aeruginosa	Relapse	Yes	6
	Serratia marcescens	Eradication	No	6
Case 5	*Pseudomonas aeruginosa*	Persistence	No	1
Case 6	*Acinetobacter*	Superinfection	No[a]	3
	Proteus mirabilis	Eradication	No	3
	Serratia marcescens	Eradication	No	3
Case 7	*Acinetobacter*	Eradication	No	12
	Pseudomonas aeruginosa	Eradication	No	12
Case 8	*Pseudomonas aeruginosa*	Persistence	No	14
Case 9	*Escherichia coli*	Eradication	No	4
Case 10	*Haemophilus influenzae*	Eradication	No	13
	Staphylococcus aureus	Eradication	No	13
	Stenotrophomonas maltophilia	Superinfection	NA[b]	13

[a]Resistant from the start of antibiotic treatment.
[b]Not available.

logical relapse (11.0%), 13 colonization (8.9%), 6 superinfection (4.1%), and 1 indeterminate (0.7%), failed eradication was frequent in cases of infection with *Acinetobacter* (10/11), *Enterobacter* (7/12), *P. aeruginosa* (23/29), and *S. maltophilia* (10/14). When only organisms isolated more than 5 times were counted, there was no case with good clinical outcome where *E. coli* persisted. *Klebsiella pneumoniae, Proteus mirabilis,* and *Serratia marcescens* were associated with just a few (1 or 2 cases per each organism) of the observed discrepancies between clinical and microbiological outcomes. In contrast, the organisms with frequent eradication failure, *Acinetobacter*, *Enterobacter*, *P. aeruginosa*, and *S. maltophilia*, were often associated with a mismatch of clinical outcomes — 28 of 50 non-eradicated strains of these gram-negative bacteria persisted, relapsed, or colonized in 24 patients, despite good clinical outcome.

Eradication failure was often associated with resistance against the antibiotics used for treatment (46/65, 70.8%) (Table 5). While most of the resistance in non-eradicated strains of *Acinetobacter* (9/9) and *S. maltophilia* (4/5) was observed in the initial cultures, other microorganisms, including *Enterobacter* (5/7) and *P. aeruginosa* (13/17), developed antibiotic resistance during treatment. In addition, while clinical relapses occurred in 10 patients during the follow-up period, 7 of these relapses were associated with 10 organisms that were not eradicated (Table 6): *Acinetobacter* (4), *Enterobacter* (1), *P. aeruginosa* (3), *S. maltophilia* (1), and *S. marcescens* (1).

Discussion

In this study, many discrepancies were observed between microbiological outcomes and clinical responses in patients with severe pneumonia. The discrepancies were noted primarily as failures to eradicate in association with good clinical responses. *Acinetobacter, Enterobacter, P. aeruginosa, and S. maltophilia* continued to be isolated even when clinical improvements were observed, whereas other organisms were generally eradicated when good clinical responses were achieved. Many organisms persisting along with good clinical responses were associated with the presence or development of resistance to the antibiotic used for treatment.

The reason for the discrepancy between failed eradication and good clinical response is not known. It might be a consequence of reduced pathogenicity of the organisms harboring resistance determinants [16-23], or fewer pathogenic organisms (i.e., inoculum reduction at the infection site). The organisms might also be sequestered in surface biofilms established in the respiratory tract or on foreign bodies, a well-known phenomenon with *P. aeruginosa* [24-26]. We may ignore the existence of organisms when clinical findings are improving with antibiotic treatment in severe pneumonia. However, that a significant number of organisms persisting in patients with good clinical responses resulted in clinical relapses and that most of the persisting organisms were resistant to the initial antibiotics used for treatment is greatly concerning.

Although there were also cases that worsened clinically despite microbiological eradication, no definite trend was found between different organisms. Underlying diseases, medications, or complications other than pneumonia may have caused the unfavorable clinical responses that were observed.

This study has some limitations. Clinical trials included in this study were performed 20–30 years ago; clinical situations such as levels of antibiotic resistance, antibiotic treatment regimens, and quality of supportive care could differ from current standards. Another limitation of this study was that quantitative or semi-quantitative cultures of respiratory specimens were not tried. The reason for selecting these particular clinical trials was the comprehensive data on severe pneumonia, including serial respiratory culture and clinical responses based on a scoring system. Study design of the 3 trials was nearly same in most aspects other than antibiotic regimen and randomization. As the discrepancy between clinical responses and respiratory cultures, performed from sputum or tracheal suction, is still a problem that clinicians confront daily, the results of this study present information relevant to clinicians who treat patients with severe pneumonia.

This study supports the questionable pathogenicity of some bacteria in severe pneumonia when they exist in the setting of a good clinical response. However, the potential for clinical relapse and the increased incidence of antibiotic resistance by non-eradicated bacteria is of clinical concern. Serial quantitative cultures and biomarkers such as procalcitonin have been tried to more objectively determine microbiologic and clinical outcome in pneumonia; their usefulness in clinical settings warrants further investigation [27].

Acknowledgment

This work was supported by Grant from Inje University, 2011.

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