Eur J Clin Microbiol Infect Dis (2011) 30:813–818
DOI 10.1007/s10096-011-1161-x

ARTICLE

The effect of empiric antibiotic therapy on mortality in debilitated patients with dementia

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Received: 4 November 2010 / Accepted: 4 January 2011 / Published online: 26 January 2011

Abstract The purpose of this investigation was to assess the effect of empirical antibiotic treatment on 30-day mortality among debilitated inpatients with dementia and Gram-negative bacteremia. A retrospective cohort study in the years 2005–2007 was undertaken. Data were collected through patient chart review. The association between individual variables and 30-day mortality was assessed through univariate analysis. Variables significantly associated with mortality ($p<0.05$) were entered into a logistic regression analysis. Adjusted odds ratios (ORs) for mortality with 95% confidence intervals (CIs) are shown. Subgroup analysis of patients with and without decubitus ulcers was performed. In our cohort of 378 patients with dementia and Gram-negative bacteremia, the 30-day mortality was 39% overall and 61% in the subgroup of patients with decubitus ulcers. Inappropriate empirical therapy was associated with higher mortality, although this effect was not statistically significant (OR 1.41, 95% CI 0.86–2.29). Inappropriate empirical therapy did not affect mortality in the subgroup of patients with decubitus ulcers (OR 0.37, 95% CI 0.11–1.28). Other factors found to independently affect mortality included age, co-morbidities, source of infection, sepsis severity, and hospital-acquired infection. Appropriate empirical antibiotic therapy for patients with dementia and severe bacterial infection did not have a clear advantage, especially in the sickest group of patients with decubitus ulcers.

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Introduction

Dementia is a fatal disease with dismal short-term prognosis [1]. The toll on the individual person is difficult to assess and personal preferences most commonly are not known. Frequently, in view of the short-term prognosis and suffering of the patients, physicians try to refrain from invasive interventions such as mechanical ventilation, major surgery, or chemotherapy. Antibiotic therapy for febrile illness, on the other hand, is viewed as minimally invasive, inexpensive, and devoid of ill consequences to the patient [2]. These assumptions should be scrutinized. The cost of therapy is higher than the direct antibiotic cost; resistance induction affecting the individual treated and the society at large and side effects of antibiotic treatment, such as *Clostridium difficile*-associated colitis, are much more costly [3]. Hospitalization in a foreign environment is destabilizing and stressful for the elderly demented patient.

Many of the questions relating to the ethics and possible futility of curing infections among patients with dementia are difficult to answer. Prior to addressing these questions, we sought to determine whether appropriate empirical antibiotic treatment confers a survival benefit among debilitated patients with dementia. Appropriate empirical therapy was shown to improve survival in most studies

assessing patients with sepsis, including those with septic shock [4–7]. To our knowledge, no previous studies have focused on this group of patients, although elderly people from nursing homes consume a significant proportion of the antibiotic treatment in hospitals. We based our assessment on a highly selected group of patients with Gram-negative bacteremia, infections that are associated with the highest mortality. We assumed that a benefit for early appropriate antibiotic treatment, if existent, should be identified in this group of patients.

The objective of this study was to assess the effect of the appropriateness of empirical antibiotic treatment, given in the first 48 h prior to the availability of culture results, on 30-day mortality among debilitated inpatients with dementia and Gram-negative bacteremia.

Methods

Setting

Meir Medical Center is a 700-bed community hospital which serves a population of 600,000.

Design

Retrospective cohort study. Patients were identified through the microbiology laboratory records and data were extracted through patient chart review.

Participants

Patients, without age restriction, hospitalized between the years 2005 and 2007. We included patients with Gram-negative bacteremia, a diagnosis of dementia in their admission or discharge notes, and a bed-ridden functional status. In case of recurrent bacteremia, only the first episode was included.

Exposure variable

Empirical antibiotic treatment, defined as therapy started during the first 48 h after blood cultures were taken.

Definitions

a. Hospital-acquired infection was defined as an episode of bacteremia manifesting more than 72 h after the patient's admission.
b. Definitive antibiotic therapy was defined as therapy administered more than 48 h after blood cultures were taken, after pathogen identification and susceptibility results became available.
c. Appropriate therapy was identified when the pathogen was found to be sensitive in vitro to the antibiotic treatment, and the therapy was given taking into account the patient's renal function, with appropriate dosing and schedule.

The medical charts of all patients were reviewed and the following data were recorded:

1. Demographics: sex, year of birth, and place of residence (home or nursing home).
2. Clinical data: co-morbidities, previous hospitalizations (during the year and the month before bacteremia), previous antibiotic therapy (during the month before hospitalization), fever and its duration, and source of bacteremia.
3. Laboratory data: white blood cell count, blood creatinine, and albumin at sepsis presentation.
4. Bloodstream isolate and antibiotic susceptibilities.
5. Antibiotic therapy.
6. Outcomes: mortality at 30 days following the blood culture date. Mortality data were accessed through a national population registry maintained by the Ministry of Interior.

Statistical methods

The association between individual variables and 30-day mortality was assessed through univariate analysis. Categorical variables were as assessed using a chi-square test (Mantel–Haenszel unadjusted odds ratio [OR] given for inappropriate empirical antibiotic treatment). Continuous variables were assessed using the *t*-test or the Mann–Whitney *U*-test if not distributed normally. Variables significantly associated with mortality ($p<0.05$) and not significantly correlated were entered into a logistic regression analysis using forward stepwise conditional analysis. Inappropriate empirical treatment was forced into the model on the first step. Adjusted ORs for mortality with 95% confidence intervals (CIs) are shown. Subgroup analysis of patients with and without decubitus ulcers was performed.

Results

Between 1 January 2005 and 31 December 2007, 2,962 blood cultures turned positive with Gram-negative bacteria, and 654 of those were from debilitated patients with dementia. One hundred and seventy-six patients had more than one positive blood culture and 39 patients had more than one Gram-negative bacteremic episode in this 3-year period (31 patients with two episodes each, six patients with three episodes each, one patient with four episodes,

and one patient with five episodes). We excluded six episodes judged to be contaminants and clinical data were not accessible for five of the patients (Fig 1).

Patient characteristics

The mean patient age was 84.3 years (standard deviation [SD] 7.4), 57% were female, and 61% were admitted from a nursing home. All patients but one had co-morbidities, and in 18.3% of the patients, decubitus ulcers were present at the time of admission (Table 1).

Fifty-seven percent of the patients were hospitalized in the 6 months prior to the current admission and 31% were hospitalized during the previous month. One-third of the patients received antibiotics in the month prior to the current hospitalization.

Forty percent (151/378) of patients received inappropriate empirical therapy, 14 of whom did not receive antibiotics empirically.

Antibiotic use

The most frequently used antibiotics for empirical therapy were a second-generation cephalosporin or amoxicillin–clavulanate, which, together, compromised 80% of the empirical therapy given. These two antibiotics compromised the majority of the definitive treatment, but their relative proportion decreased to 60%. More than 10% of the patients received a carbapenem as definitive therapy (Table 2).

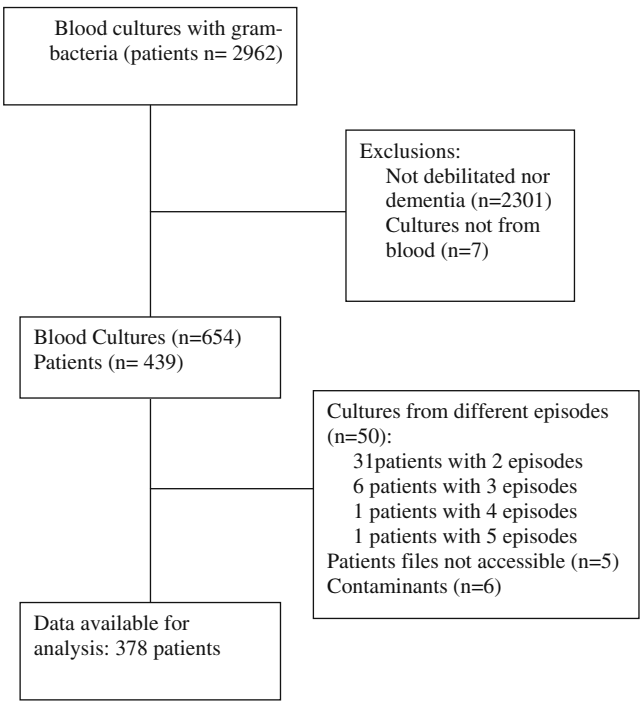

Fig 1 Flow diagram of the patient inclusion for this study

Mortality

One hundred and forty-six patients (38.6%) died in the 30 days following bacteremia. Inappropriate empirical antibiotic treatment was significantly associated with mortality without adjustment to other risk factors for mortality; 81/232 (34.9%) who remained alive versus 70/146 (47.9%) who died received inappropriate empirical antibiotic treatment (p=0.012, unadjusted OR 1.72, 95% CI 1.13–2.62). Other risk factors for mortality on univariate analysis included older age, acquisition of infection in the hospital and number of days in he hospital prior to infection, several background conditions, the source and pathogen causing infection, and lower albumin levels at the onset of infection (Table 1). Previous hospitalization as well as residence in nursing homes did not increase the mortality. Out of 378 patients, 18 (who were alive after 48 h) did not receive appropriate definite therapy and this was significantly associated with mortality.

Patients given inappropriate definite antibiotic treatment were excluded from the logistic regression analysis, since this variable was highly correlated with the appropriateness of empirical antibiotic treatment. Thus, multivariate analysis was conducted on 360 patients receiving appropriate definitive antibiotic treatment. Inappropriate empirical treatment was associated with a higher 30-day mortality without statistical significance (p=0.17, OR 1.41, 95% CI 0.86–2.29. Older age, congestive heart failure, previous stroke, hypoalbuminemia, and source of infection remained significantly associated with higher mortality (Table 3).

This analysis was repeated for the subgroups of patients with or without decubitus ulcers, receiving appropriate definitive treatment (Table 2). Among patients without decubitus ulcers, the 30-day mortality was 32.6% (97/298 patients), and inappropriate empirical therapy was significantly associated with higher mortality at 30 days (unadjusted OR 2.26, 95% CI 1.37–3.73, adjusted OR 1.92, 95% CI 1.08–3.41, p=0.027). In the subgroup of the more debilitated patients with decubitus ulcers, the 30-day mortality rate was 59.7% (37/62 patients), and inappropriate empiric therapy was not associated with increased mortality (unadjusted OR 0.27, 95% CI 0.09–0.79, p=0.02, adjusted OR 0.37, 95% CI 0.11–1.28, p=0.12 adjusted only for creatinine, albumin, and source of infection).

Discussion

This study focused on the characteristics and outcome of 378 debilitated patients with dementia and Gram-negative

Table 1 Demographic, clinical, and laboratory data on the patients and 30-day mortality

		Alive at 30 days (%)	Deceased at 30 days (%)	Total	*p*-value
Number of patients		232	146	378	
Inappropriate empirical treatment		81 (34.9%)	70 (47.9%)	151 (39.9%)	0.012
Mean age (SD)		82.8 (7.2)	85.1 (7.5)	84.3 (7.4)	0.003
Males		92 (39.7)	71 (48.6)	163 (43.1)	0.086
Resident of nursing home		143 (61.6%)	89 (61%)	232 (61.4%)	0.895
Hospitalizations during the previous 6 months		130 (56%)	87 (59.6%)	217 (57.4%)	0.496
Hospitalizations during the previous month		69 (29.7%)	47 (32.2%)	116 (30.7%)	0.615
Hypertension		122 (52.6%)	80 (54.8%)	202 (53.4%)	0.675
Diabetes mellitus		77 (33.2%)	43 (29.5%)	120 (31.7%)	0.447
Heart disease (ischemic, congestive heart failure, atrial fibrillation)		101 (43.5%)	85 (58.2%)	186 (49.2%)	0.005
Ischemic heart disease		60 (25.9%)	50 (34.2%)	110 (29.1%)	0.081
Congestive heart failure		31 (13.4%)	36 (27.4%)	67 (17.7%)	0.005
Atrial fibrillation		50 (21.6%)	40 (24.7%)	90 (23.8%)	0.194
Previous CVA		69 (29.7%)	58 (39.7%)	127 (33.6%)	0.045
Chronic kidney disease		42 (18.1%)	33 (22.6%)	75 (19.8%)	0.286
Chronic lung disease		29 (12.5%)	18 (12.3%)	47 (12.4%)	0.961
Malignancy		37 (15.9%)	25 (17.1%)	62 (16.4%)	0.764
Decubitus ulcers		27 (11.6%)	42 (28.8%)	69 (18.3%)	<0.001
Peptic disease		13 (5.6%)	12 (8.2%)	25 (6.6%)	0.319
Chronic liver disease		4 (1.7%)	2 (1.4%)	6 (1.6%)	0.788
Other co-morbidities		187 (80.6%)	111 (76%)	298 (78.8%)	0.289
Antibiotic treatment during previous month		73 (31.5%)	55 (37.7%)	128 (33.9%)	0.214
Foreign body	Total	65 (28%)	39 (26.7%)	104 (27.5%)	0.782
	Urinary catheter	47 (20.3%)	29 (19.9%)	76 (20.1%)	0.926
	Artificial joint or permanent pacemaker	9 (3.9%)	6 (4.1%)	15 (4%)	0.911
	Central venous catheter	8 (3.4%)	4 (2.7%)	12 (3.2%)	0.702
	Endotracheal tube	5 (2.2%)	5 (3.4%)	10 (2.6%)	0.454
Renal failure[a]		109 (47.2%)	90 (63.8%)	199 (53.5%)	0.002
Fever or hypothermia[a]		196 (84.5%)	118 (80.8%)	314 (83.1%)	0.355
Source of infection	Urinary tract	122 (52.6%)	37 (25.3%)	159 (42.1%)	<0.001
	Respiratory tract	17 (7.3%)	25 (17.1%)	42 (11.1%)	
	Abdominal cavity	21 (9.1%)	8 (5.5%)	29 (7.7%)	
	Skin	6 (2.6%)	19 (13%)	25 (6.6%)	
	CVC	3 (1.3%)	0 (0%)	3 (0.8%)	
	Unknown origin	63 (27.2%)	57 (39%)	120 (31.7%)	
Escherichia coli infection		105 (45.3%)	37 (25.3%)	142 (37.6%)	<0.001
Pseudomonasaeruginosa infection		11 (4.7%)	8 (5.5%)	19 (5%)	0.749
Anaerobic infection		6 (2.6%)	14 (9.6%)	20 (5.3%)	0.003
Polymicrobial infection		35 (15.1%)	25 (17.1%)	60 (15.9%)	0.598
AmpC or ESBL resistance		45 (19.4%)	41 (28.1%)	86 (22.8%)	0.05
Hospital-acquired infection		28 (12.1%)	38 (26%)	66 (17.5%)	0.001
Median creatinine[a] (range)		1.25 (0.4–11.7), 230 patients included	1.50 (0.5–8.9), 142 patients included	1.3 (0.4–11.7), 372 patients included	0.003
Median albumin ± SD level[a]		2.8 (±0.4), 230 patients included	2.6 (±0.5), 139 patients included	2.7 (±0.47)	<0.001
Median leukocyte count ± SD level[a]		15.5 (±10.02), 232 patients included	15.2 (±9.2), 146 patients included	15.4 (±9.7)	0.71
Length of hospital stayprior to bacteremia(days) median, range		0 (0–285)	0 (0–74)	0 (0–285)	0.1
Inappropriate definitivetreatment (out of 324patients surviving more than48 h)		6 (2.6%)	12 (13.2%)	18 (5.6%)	<0.001

[a] Values refer to those measured at the onset of infection ±48 h

Table 2 Antibiotics given to the patients as empirical and definitive therapy

	Empirical therapy (n=378)	Definitive therapy, alive at 48 h (n=322)
Second-generation cephalosporin	180 (47.5%)	130 (40.4%)
Amoxicillin–clavulanate	124 (32.8%)	64 (19.9%)
Aminoglycosides	29 (7.7%)	42 (13%)
Quinolones	13 (3.4%)	23 (7.1%)
Piperacillin or piperacillin–tazobactam	16 (4.2%)	17 (5.2%)
Third-generation cephalosporin	7 (1.8%)	4 (1.2%)
Carbapenems	1 (0.3%)	37 (11.5%)
Other	12 (3.2%)	7 (2.2%)
None	14 (3.7%)	

bacteremia, a diagnosis which carries a high mortality rate, especially in this frail population. This was exemplified in our study with a 30-day mortality of 39% in the whole group and 61% in the subgroup of patients with decubitus ulcers. Overall, inappropriate empirical therapy was associated with increased mortality, although this effect was not statistically significant (adjusted OR 1.41, 95% CI 0.86–2.29). Inappropriate empirical therapy did not affect mortality in the subgroup of patients with decubitus ulcers (adjusted OR 0.37, 95% CI 0.11–1.28), but was significantly associated with mortality in the subgroup of patients with no decubitus ulcers (adjusted OR 1.9, 95% CI 1.08–3.41). Other factors found to influence mortality were age, co-morbidities, source of infection, sepsis severity, and hospital-acquired infection. Of note, 57% (38/66) of the patients who acquired their infection in the hospital died within 30 days (adjusted OR 2.13, 95% CI 1.16–3.9).

Our findings are in agreement with those reported by Fabiszewski et al., who studied the effect of antibiotic therapy on the outcome of febrile episodes in institutionalized Alzheimer patients and found that, for the patients with severe Alzheimer's, there was no effect on survival between treated and untreated patients [8]. This study included all patients with febrile episodes, some of which might have been non-infectious or viral in origin. In our study, we show that, even in the extreme case of proven Gram-negative sepsis, empirical antibiotics had no effect on the sickest group of patients, those with decubitus ulcers. Further support to our results comes from another study that assessed the effect of inappropriate therapy on the outcome of bacteremic patients. Among 87 patients with dementia and decubitus ulcers, inappropriate empirical antibiotic treatment, using similar definitions, did not have a statistically significant effect on the in-hospital mortality (OR 1.36, 95% CI 0.50–3.76) [7].

This cohort consisted of an elderly population with multiple risk factors for bacterial resistance; 61% of patients resided in nursing homes, 27% carried a foreign body, one-third received antibiotics, and one-third were hospitalized in the month prior to the current hospitalization. Dementia and

Table 3 Independent determinants of death by 30 days. Multivariate analysis: all patients (360 patients receiving appropriate definitive antibiotic treatment if alive) and patients without decubitus ulcers (298 patients)

Factor	All patients[a]			Patients with no decubitus ulcers[b]		
	OR	95% CI	p-value	OR	95% CI	p-value
Inappropriate empirical treatment	1.409	0.865–2.293	0.168	1.919	1.079–3.412	0.027
Age	1.066	1.03–1.103	<0.001	1.078	1.035–1.123	<0.001
CHF	2.071	1.138–3.771	0.17	1.96	1.025–3.746	0.042
CVA	1.762	1.06–2.928	0.029	1.875	1.045–3.364	0.035
Creatinine				1.259	1.004–1.581	0.046
Albumin	0.363	0.214–0.615	<0.001			
Hospital-acquired infection	2.125	1.156–3.904	0.015	3.022	1.37–6.667	0.006
Source: pulmonary	3.562	1.620–7.830	0.002	4.008	1.668–9.627	0.002
Source: UNK/skin	2.499	1.478–4.227	0.001	2.042	1.107–3.77	0.022

[a] Three hundred and sixty patients receiving appropriate definitive antibiotic treatment. Hosmer–Lemeshow goodness of fit test for the model df=8, p=0.64

[b] Two hundred and ninety-eight patients with no decubitus ulcers, receiving appropriate definitive antibiotic treatment. Hosmer–Lemeshow goodness of fit test for the model df=8, p=0.15

non-ambulatory status, per se, have also been described as risk factors for multidrug-resistant Gram-negative bacteria [9]. This is reflected in the high percentage of inappropriate empirical antibiotic therapy seen in our study and in the substantial number of patients who needed a carbapenem for their definitive therapy. The outcome of an effort to improve the percentage of appropriate empirical antibiotic therapy in this population would be a dramatic increase in the use of broad-spectrum antibiotics. Most febrile episodes are probably non-bacterial. Recommending broader-spectrum antibiotics to this population for all febrile episodes carries considerable personal and ecological cost. On the individual level, broad-spectrum antibiotics will increase the risk for *C. difficile* colitis and will promote colonization with resistant bacteria. Moreover, as was shown in our study, infection acquired during hospitalization dramatically increases the risk of mortality in the elderly patient. On the community level, broad-spectrum antibiotics given to all febrile, debilitated, demented patients will increase the burden of resistant bacteria in hospitals. A direct correlation between the amount of antibiotics given in a specific ward in the hospital to bacterial resistance in the ward has been shown [10].

Hospitalization with aggressive therapy is inconsistent with the palliative approach of care directed towards comfort, as suggested for debilitated patients with dementia [1]. It is clear that febrile and infectious episodes become more frequent near death in this population, and, although they precipitate death, dementia is the underlying cause of death [1, 11].

Our study suffers from several limitations; the subgroup analysis of patients with decubitus ulcers included only 62 patients, thus, the conclusions are less robust than those for the group of patients with no decubitus ulcers. In our analysis, we grouped together 14 patients who received no empirical antibiotics with patients who received inappropriate empirical therapy. Administering antibiotics to which the subsequently isolated causative bacteria are resistant might lead to worse outcomes than no treatment, due to the further promotion of resistance, *C. difficile*, and other adverse events. However, our data are insufficient to address this point.

Targeting appropriate empirical therapy among debilitated patients dementia is an ethical problem, complicated by the futility, even for the very short term, of antibiotic treatment and the considerable ecological cost of broad-spectrum antibiotics needed to achieve high rates of appropriate empirical therapy. In light of the grave prognosis and increased stress for the patients, we suggest reassessing the indication of hospitalization for the febrile, debilitated, demented patient. In case of hospitalization for febrile illness, no treatment or narrow-spectrum antibiotic can be started until culture the results become available. Fewer hospitalizations will minimize greatly the inconvenience to the patient and a more conservative approach will decrease the use of broad-spectrum antibiotics, without greatly affecting the short-term mortality.

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