Experience with ESBL-Producing Enterobacteriaceae Treated with Carbapenems Compared to Other ß-Lactams: Outcomes Report from the SENTRY Antimicrobial Surveillance Program

K-706

ICAAC 2003
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ABSTRACT

Background: The emergence and increase of ESBL-producing Enterobacteriaceae (ENT) worldwide has compromised treatment by a variety of enzyme-sensitive ß-lactams, but no carbapenems (CARB). The SENTRY Program initiated an outcomes analysis of isolates from participant centers with confirmed ESBL isolates in 2001 - 2002.

Methods: Isolate-specific Case Report Forms (CRF) were initiated for confirmed ESBL ENT isolates and CRFs were completed by 27 participant sites in North America (8), Latin America (9) and Europe (10). Forms were reviewed by 3 medical observers and outcomes assigned (success = cured or improved; failure) to regimens used for ≥ 3 days. 109 cases were screened and 82 were considered evaluable.

Results: Cases treated by ß-lactams (BL) were specifically compared: CARB ± co-drug (aminoglycoside or quinolone; 49) versus other BL ± co-drug (16). Demographics included: age (ave 53, range 0-82); male sex (53%), hosp. LOS (ave, 20 d), and ICU LOS (ave, 10 d). Clinical failures were 16% overall with a mortality of 19% (attributable mortality of only 8%). Success was 80 and 81% for CARB and BL groups, respectively, with identical fatality rates (19%). Risk factors (variables) trending toward significance in predicting failures were: malignancy or transplantation (BL), urinary cath or vent assistance (CARB) and age/no. of treatment drugs (all cases). Site of infection (blood or lung) and organism species (*Klebsiella*, *E. coli*, *P. mirabilis*) did not effect outcomes.

Conclusions: ESBL-producing ENT continues to be a difficult infection to detect in the laboratory and therapy options still remain controversial. CARB and other BL regimens (cephalosporins alone or in combination, enzyme inhibitor combinations) produced equivalent clinical success rates. Only a minority of cases failed when other BLs were used at appropriate PD-directed doses.

INTRODUCTION

Infection with ESBL-producing *Escherichia coli* or *Klebsiella pneumoniae* has been associated with a significantly longer duration of hospital stay and greater hospitalization costs. Some studies have also suggested that bacteremia caused by ESBL-producing strains is associated with a higher mortality rate and that early administration of appropriate antimicrobials may reduce fatal illnesses.

Other studies, however, have shown that the clinical outcome may be related to the type and/or the number of ESBLs produced. Patients with bacteremia caused by *E. coli* or *K. pneumoniae* strains that produce a single ESBL will have a greater likelihood of a favorable outcome than patients infected with isolates that produce multiple ß-lactam-resistance mechanisms. Favorable responses to treatment with non-ceftazidime extended-spectrum cephalosporins when the causative pathogen produced either TEM-6 or TEM-12 have been documented. These results suggest that the production of an ESBL does not necessarily preclude successful treatment with cephalosporin if the doses conform to pharmacodynamic principals of adequate target attainment.

In summary, information regarding the efficacies of broad-spectrum cephalosporins is limited and the prognosis of bacteremia caused by a member of the family Enterobacteriaceae depends on several factors such as the underlying disease, the clinical severity at the time of administration of antimicrobials, and the antimicrobial regimen utilized. In the present study we performed an outcome analysis of patients infected with confirmed ESBL-producing *E. coli* or *K. pneumoniae* in medical centers participating in the SENTRY Antimicrobial Surveillance Program.

MATERIALS AND METHODS

Organisms. All isolates were taken from the SENTRY Program collection in 2001 - 2002, each strain originating in participant medical centers (27 sites) in North America (eight sites), Latin America (nine sites) and Europe (10 sites). All organisms selected for the study were identified by reference methods in two locations including the monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA). Only strains of *E. coli* and *Klebsiella* spp. from bacteremia or pneumonia cases were considered for the protocol.

Susceptibility test methods. Selected strains were tested by the NCCLS M7-A6 (2003) broth microdilution method using 27 antimicrobial agents. Organisms meeting the screening criteria as a possible extended-spectrum ß-lactamase (ESBL) producer were further tested by the confirmatory clavulanate-inhibition method. The applied screening criteria were: aztreonam or cefotaxime or ceftazidime or ceftriaxone MIC at ≥ 2 μg/ml. Two confirming tests were used (disk approximation with four ß-lactam substrates; ESBL Etest with two substrates). Confirmed strains using NCCLS guidelines were entered into the study protocol.

MATERIALS AND METHODS (Continued)

Study design. Confirmed ESBL organisms initiated an isolate-specific Case Report Form (CRF) that was returned to the participant laboratory/pharmacy for retrospective chart review. Complete microbiology profiles from reference MIC tests and epidemiologic typing were provided to the participant institution. The forms required the determination of:

1. Patient demographics;
2. Assessment of numerous risk factors (independent variables);
3. Antimicrobial therapy before and after the isolation of the ESBL-producing strain (all doses were recorded);
4. Clinical outcome;
5. Adverse drug reactions; and
6. Mortality (total and attributable).

Each completed report form was examined by three medical observers and two Doctors of Pharmacology for evaluability. Each patient episode had to receive ≥ three days of treatment to be tabulated. Of the 109 original CRFs received, 82 were evaluable and are reported here. Approximately 30 additional cases have been obtained since the completion of this analysis and will be reported later.

Data/case analysis. Comparisons of patient characteristics and outcomes among treatment regimens were carried out using the Chi square statistic or Fisher's exact test.

RESULTS

- Patients varied widely in age (0 - 82 years) with mean and median ages of 46 and 53 years, respectively.
- Length of hospital stay was prolonged overall and, on the average, one-half of the hospitalization for each patient was spent in the ICU (mean, 17 days).
- The clinical failure rate (16%) of all treatments was less than the mortality rate (19%) and the attributable mortality to the ESBL infection was only 9% (Table 1).
- The most studied species was *K. pneumoniae* (69 cases) among 74 total cases infected with *Klebsiella* spp. (Table 1). No significant differences in clinical outcomes were noted between the studied enteric species.
- The risk factors (independent variables) recorded most often for patients with ESBL infection were: 1) hospital stay at > 10 days (92%); 2) prior antimicrobials (81%); 3) various indwelling catheters (64 - 66%); and 4) ventilator assistance (62%). All other key risk factors occurred in ≤ 31% of patients (Table 1).
- Most risk factors (independent variables; Table 2) were not significantly associated with clinical failure or patient mortality rates. Only "transplantation" was significantly correlated with death (p = 0.02) and a trend toward a correlation was observed for "prior antimicrobials" for clinical failures (p = 0.11) and mortality (p = 0.28).
- Only 21% of ESBL-infection episodes were treated with combination therapy (Table 3).
- The most often selected antimicrobial class for therapy was the carbapenems (imipenem and meropenem) used alone (39 cases; 48%) or in combination with a fluoroquinolone or an aminoglycoside (12%; see Table 3).
- Clinical failure rates varied from 0.0% for monotherapies with piperacillin/tazobactam, aminoglycosides and fluoroquinolones to 40.0% for the limited number of cases (five) treated with cephalosporins alone. All organisms in these patients were highly resistant (MIC, ≥ 32 μg/ml) to the treatment agent or treated with suboptimal dosing regimens (Table 3; data not shown).
- "Collapsed" data comparisons (all carbapenem treatments versus all other ß-lactam therapies) showed nearly identical clinical failure and mortality results (Table 3).
- Risk factors effecting outcomes (Table 4) when comparing "collapsed" and carbapenem treatment groups indicated an influence of malignancy (p = 0.04) and transplantation (p = 0.15) on the failures of "collapsed" group therapy (especially for cephalosporins), and ventilator assistance was a near significant factor among carbapenem treated patients (p = 0.08).

RESULTS

Table 1. Observations available for analyses among evaluable cases (n=82).

Variable or parameter (no.)	Mean/median (range)	%
Age (81)	46/53 (0-82 y)	-
Length of hospital stay (66)	40/20 (0-464 d)	-
Length of ICU stay (71)	17/10 (0-143 d)	-
Clinical failure (82)		16
Mortality (81)		19
Attributable (7)		9
Organisms		
Klebsiella spp. (74)		90
E. coli (7)		9
P. mirabilis (1)		1
Risk factors		
Diabetes		24
Emergency intra-abdominal surgery		25
Gastrostomy or jejunostomy tube		31
Hospital stay at > 10 days		92
ICU stay at > 10 days		46
IV catheters		64
Malignancy		22
Prior antimicrobials		81
Prior extended care facility stay		8
Sex (male)		53
Transplantation		6
Urinary catheters		66
Ventilator assistance		62

Table 2. Clinical failures or deaths associated with 12 independent variables or risk factors (82 evaluable cases).

	p value	
Independent variable	Clinical failure	Death
Diabetes	0.72	0.33
Emergency intra-abdominal surgery	0.72	0.33
Gastrostomy or jejunostomy tube	1.00	0.74
Hospital stay at > 10 days	0.58	0.58
ICU stay at > 10 days	0.76	1.00
IV catheters	1.00	0.68
Malignancy	1.00	0.73
Prior antimicrobials	0.11	0.28
Prior extended care facility stay	1.00	1.00
Transplantation	0.49	0.02
Urinary catheters	0.31	0.76
Ventilator assistance	0.52	1.00

Table 3. Clinical failure and death rates indexed by selected treatment groups.

Treatment group (no.)	% failures/deaths
Monotherapy	
Carbapenems (39)	20.5/18.4
Cephalosporins (5)	40.0/40.0
Fluoroquinolone (FQ) or aminoglycoside (AG; 12)	0.0/8.3
Piperacillin/Tazobactam (4)	0.0/0.0
Other agents (5)	0.0/40.0
Combinations	
Carbapenem + FQ or AG (10)	20.0/20.0
Cephalosporin + FQ or AG (7)	14.3/14.3
All carbapenem therapies[a] (49)	20.8/18.8
All other ß-lactam therapies[a] (16)	18.8/18.8

a. Includes mono and combination therapies.

Table 4. Independent variable distributions for the largest "collapsed" treatment group (cephalosporin or piperacillin/tazobactam ± co-drug) and carbapenem therapies (49 cases).

	Proportion by treatment group		
Independent variable (no.)	Collapsed group	Carbapenem	p value
Diabetes (59)	19	23	1.00
Emergency intra-abdominal surgery (59)	33	25	0.52
Gastrostomy or jejunostomy tube (56)	21	33	0.51
Hospital stay at > 10 days (54)	100	98	1.00
ICU stay at > 10 days (56)	36	52	0.36
IV catheters (60)	87	89	0.82
Malignancy (61)	44	16	0.04
Prior antimicrobials	93	87	1.00
Prior extended care facility stay (60)	7	9	1.00
Transplantation (57)	14	2	0.15
Ventilator assistance (62)	44	70	0.08
Clinical failures (%)	18.8	20.4	1.00
Total mortality (%)	18.8	18.8	1.00

CONCLUSIONS

- ESBL-producing isolates among the Enterobacteriaceae (*E. coli*, *Klebsiella* spp., *P. mirabilis*) continue to produce significant morbidity and mortality (8 - 19%) among patients associated with long hospitalizations and receiving prior antimicrobial therapy.
- Carbapenem treatment, alone or in various combinations, has become the dominant regimen (60%) for ESBL infections in Europe and the Americas.
- Successful treatment was achieved for 84% of all cases, 80% for carbapenem-containing regimens, and 75% for cephalosporin regimens. Highest success rates were noted for non-ß-lactam or ß-lactamase inhibitor combination treatments.
- Continuation of this protocol to approximately 150 evaluable cases (with susceptible case controls) should ultimately assist in the understanding of: 1) appropriate susceptibility breakpoint concentrations for the ß-lactams; and 2) outcomes related to pharmacodynamic targets in human subjects.

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