Evaluation of Patients with ESBL- and Non-ESBL-Producing Enterobacteriaceae: Outcomes Report from the SENTRY Antimicrobial Surveillance Program

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ABSTRACT

Background: As extended-spectrum ß-lactamase (ESBL)-producing Enterobacteriaceae continue to emerge worldwide, selection of empiric treatment modalities is an increasing challenge. The SENTRY Antimicrobial Surveillance Program initiated an outcomes analysis of isolates (blood or respiratory) from centers with confirmed ESBL- and non-ESBL-producing Enterobacteriaceae isolates (2001 - 2002). In this analysis, we compared outcomes and risk factors for poor outcome between ESBL and non-ESBL cases.
Methods: Case report forms were completed by 48 centers in North America (18), Latin America (11) and Europe (19). Forms were reviewed by 3 medical observers and clinical outcome (success=cure or improvement; failure), mortality, and treatment regimens (used for ≥ 3 days) attributable to outcome were assessed.
Results: 412 cases were screened and 177 were considered evaluable. Demographics (median, range or %) were: age (54, newborns-90 years), male sex (59%), prior length of hospital stay (21, 2-464 days) and prior length of ICU stay (6, 0-158 days). Failures were 17.5% with an overall mortality of 21.0% (attributable of only 6.8%). Treatment regimens (%) included carbapenem mono- (28.8) and combination-therapy (10.2), cephalosporin mono- (10.2) and combination-therapy (7.9), fluoroquinolone (11.9), and ß-lactam/ß-lactamase inhibitor combinations (9.6). Clinical success was 83% (113/136) for ESBL and 80% (33/41) for non-ESBL cases. Clinical success by treatment group for ESBL and non-ESBL cases for carbapenem and cephalosporin monotherapy were 81.8% vs 85.7% and 84.6% vs 80.0%, respectively. Factors associated with poor outcome (p-value) included prior nursing home stay (0.14), presence of an intravascular catheter (0.13), transplantation (0.08) and ventilator assistance (0.07). The presence of these factors was comparable between ESBL and non-ESBL cases except ventilator assistance (64.3% vs 37.1%, p=0.004).
Conclusions: While Enterobacteriaceae infections are associated with significant mortality, ESBL production alone does not appear to be an independent risk factor for treatment failure with several drug regimens, including cephalosporin monotherapy.

INTRODUCTION

Outbreaks of infection with Enterobacteriaceae producing extended-spectrum ß-lactamases (ESBLs), particularly those caused by *Klebsiella pneumoniae* and *Escherichia coli*, have been increasingly observed worldwide. Depending on the type of ESBL, organisms expressing these enzymes can exhibit various levels of *in vitro* resistance to cephalosporins and even resistance to several other classes of antimicrobial agents.

Reports of treatment failure due to infecting isolates with apparent *in vitro* susceptibility have raised concerns about the use of extended-spectrum cephalosporins for the treatment of serious infections arising from ESBL-producing Enterobacteriaceae. While epidemiologic data describing clinical outcomes for ESBL infections after empiric treatment with commonly prescribed antimicrobial regimens are generally lacking, studies have shown a favorable impact on outcome in critically-ill patients with Gram-negative bacteremia when appropriate therapy is initiated early.

Previously, we have reported outcomes for 82 patients with ESBL-producing Enterobacteriaceae infections treated with carbapenems and other broad-spectrum ß-lactams. The objective of these analyses was to describe the outcomes for a larger cohort of patients infected with confirmed ESBL- and non-ESBL-producing Enterobacteriaceae collected from medical centers participating in the SENTRY Antimicrobial Surveillance Program.

METHODS

Organisms: All Enterobacteriaceae isolates (bloodstream or respiratory [pneumonia] cultures) originating from medical centers in North America, Latin America and Europe participating in the SENTRY Antimicrobial Surveillance Program between 2001-2002 were eligible for inclusion. Organisms were identified by reference identification and susceptibility testing methods in two locations including the monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA).

Susceptibility Testing Methods: All Enterobacteriaceae strains were tested by the NCCLS M7-A6 (2003) broth microdilution method using 27 antimicrobial agents. In addition, ESBL testing included the following:

1. Organisms meeting the NCCLS screening criteria as a possible ESBL producer were further tested by the confirmatory clavulanate-inhibition method.
2. The applied screening criteria were: aztreonam or cefotaxime or ceftazidime or ceftriaxone MIC at ≥ 2 µg/mL.
3. Two confirming tests were used: disk approximation for four ß-lactam substrates, and ESBL Etest (AB BIODISK, Solna, Sweden) with two substrates.
4. Confirmed strains using NCCLS guidelines were entered into the study protocol.

Study Design: Using retrospective chart review, case report forms were completed by participating laboratory and/or pharmacy investigators for cases with non-ESBL- and confirmed ESBL-producing Enterobacteriaceae. Non-ESBL- and confirmed ESBL-producing Enterobacteriaceae cases were matched by gender and age (to the extent possible) and time of occurrence (i.e., same quarter of the same year) within medical centers. Complete microbiology profiles from reference MIC tests and epidemiologic typing were provided to the participant institution.

Case report forms required assessment of the following:

1. Patient demographics
2. Assessment for the presence of numerous risk factors in the 30 days prior to the index culture (independent variables)
3. Antimicrobial therapy before and after the isolation of the non-ESBL- and ESBL-producing strain (all doses were recorded)
4. Clinical outcome
5. Adverse drug reactions
6. Mortality (all-cause and attributable)

Completed case report forms were reviewed by 3 independent medical observers to determine cases considered evaluable and therapy attributable to outcome using the following definitions:

1. Attributable agent(s) must have been used for at least three days post culture.
2. Antimicrobial therapy must have been started or replaced or continued in an interval responsive to the culture report (five days).
3. Having a recorded outcome (clinical success=cure or improvement; clinical failure) and mortality (all-cause and attributable).

Data Analysis: Comparisons of patient characteristics and outcomes among treatment regimens were carried out using the Chi square statistic or Fisher's exact test for categorical variables and using the Wilcoxon rank sum test for continuous variables.

RESULTS

- Of the 412 original case report forms received, 177 were considered evaluable. Demographic characteristics for these cases are presented in Table 1.
  - Patients varied widely in age (newborns - 90 years) with mean and median ages of 48 and 54 years, respectively.
  - Overall, patients had a prolonged hospital stay (median 21 days).
  - Approximately 50% of patients were in the ICU prior to culture; of these patients, 50% spent close to 90% of their prior hospitalization in the ICU.
  - The organisms most frequently isolated were *K. pneumoniae* (85.3%) and *E. coli* (11.3%).
  - 82% of cases had infections due to ESBL-producing Enterobacteriaceae isolates (18% of non-ESBL-producing control cases were selected from those hospitals also having ESBL-producing cases).
- Successful clinical outcomes were observed for a high proportion of cases (82.5%). Attributable and all-cause mortality were 6.8 and 21.0%, respectively.
- With the exception of gastrostomy/jejunostomy tubes and need for ventilator assistance, the proportion of underlying co-morbidities and potential risk factors was similar among non-ESBL and ESBL cases (Table 2). In the case of these two risk factors, a significantly higher proportion of ESBL cases had a gastrostomy or jejunostomy tube or required ventilatory assistance as compared to non-ESBL cases.
- As shown in Table 3, the antimicrobial class for therapy most often selected for treatment of both ESBL and non-ESBL cases was the carbapenems (imipenem and meropenem), used alone 28.8% (51 cases).
  - Among ESBL cases, carbapenem monotherapy and combination therapy (with a fluoroquinolone or an aminoglycoside) accounted for 32.4 and 13.2% of regimens, respectively.
  - Among non-ESBL cases, fluoroquinolones and ß-lactam/ß-lactamase inhibitor combination accounted for highest proportion of treatment regimens (24.4 and 22.0%, respectively).
- As shown in Table 4, outcomes were similar between non-ESBL and ESBL cases for clinical response as well as attributable and all-cause mortality.
- Clinical response by treatment group for non-ESBL and ESBL cases was similar (Table 5). For example, clinical success for carbapenem and cephalosporin monotherapy among non-ESBL and ESBL cases was 85.7 vs 81.8% and 80.0 vs 84.6%, respectively.
- Risk factors (independent variables) associated with poor outcome (p-value) included prior nursing home stay (0.14), presence of an intravascular catheter (0.13), transplantation (0.08), and ventilator assistance (0.07) (Table 6). Most risk factors examined were not significantly associated with clinical failure. As shown in Table 2, the presence of these particular risk factors was comparable between ESBL and non-ESBL cases except ventilator assistance (64.3 vs 37.1%, p = 0.004).
- Of the risk factors evaluated, only presence of intravascular catheters was associated with all-cause mortality; mortality was 23.6 and 4.8% in those patients with and without an intravascular catheter, p = 0.05.

Table 1. Summary of clinical characteristics and potential risk factors among all evaluable cases (n=177).

Variable	Mean, Median (Range)	%
Age	48, 54 (<1, 90)	
Prior length of hospital stay	34, 21 (2, 464)	
Prior length of hospital stay ≥ 10 days		84.0
Prior length of ICU stay	14, 6, (0, 158)	
Prior ICU stay		59.6
Clinical Success		82.5
Attributable mortality		6.8
All-cause mortality		21.0
Organisms		
K. pneumoniae		85.3
K. oxytoca		1.7
K. ozaenae		0.56
Klebsiella spp.		0.56
E. coli		11.3
P. mirabilis		0.56
ESBL-producing strains		76.8
Diabetes		22.8
Emergency intra-abdominal surgery		19.9
Gastrostomy or jejunostomy tube		25.3
Malignancy		21.2
Presence of intravascular catheters		87.0
Presence of urinary catheters		69.2
Prior antibiotics		86.6
Prior nursing home stay		9.0
Sex (% male)		59.3
Transplantation		6.5
Ventilator assistance		58.4

Table 2. Comparison of potential risk factors among ESBL and non-ESBL cases.

Independent Variable	Presence of Independent Variable: Non-ESBL (n=41)	ESBL (n=136)	p-value
Diabetes	22.2	23.0	0.93
Emergency intra-abdominal surgery	11.4	22.3	0.16
Gastrostomy or jejunostomy tube	6.4	30.2	0.007
Prior length of hospital stay ≥ 10 days	85.4	83.6	0.79
Prior ICU stay	42.5	65.1	0.01
Malignancy	25.7	20.0	0.46
Presence of intravascular catheters	86.1	87.2	0.79[a]
Presence of urinary catheters	60.0	71.9	0.18
Prior antibiotics	81.8	87.9	0.39[a]
Prior nursing home stay	12.1	8.2	0.50[a]
Transplantation	5.9	6.7	1.00[a]
Ventilator assistance	37.1	64.3	0.004

a. Fisher's exact test was computed in place of Pearson Chi-square since more than one-fifth of fitted cells were sparse (frequency < 5).

Table 3. Summary of treatment regimens among non-ESBL, ESBL, and all cases.

Treatment Group	% (n): non-ESBL (n=41)	ESBL (n=136)	All (n=177)
Carbapenem alone	17.1 (7)	32.4 (44)	28.8 (51)
Carbapenem + aminoglycoside or fluoroquinolone	0	13.2 (18)	10.2 (18)
Cephalosporin alone	12.2 (5)	9.6 (13)	10.2 (18)
Cephalosporin + aminoglycoside or fluoroquinolone	9.8 (4)	7.4 (10)	7.9 (14)
ß-lactam/ß-lactamase inhibitor combination	22.0 (9)	5.9 (8)	9.6 (17)
Fluoroquinolone	24.4 (10)	8.1 (11)	11.9 (21)
Carbapenem + 2nd ß-lactam	0	3.7 (5)	2.8 (5)
Aminoglycoside	4.9 (2)	2.2 (3)	2.8 (5)
Trimethoprim/Sulfamethoxazole + Other	2.4 (1)	3.7 (5)	3.4 (6)
Other	7.3 (3)	14.0 (19)	12.4 (22)

Table 4. Summary of outcomes among non-ESBL and ESBL cases.

Outcome	% non-ESBL (n=41)	ESBL (n=136)	p-value
Clinical success	80.5	83.1	0.7
Attributable mortality	12.2	5.2	0.15[a]
All-cause mortality	22.0	20.6	0.85

a. Fisher's exact test was computed in place of Pearson Chi-square since more than one-fifth of fitted cells were sparse (frequency < 5).

Table 5. Summary of clinical outcome by treatment regimens among non-ESBL and ESBL.[a]

Treatment Group	% (number of successes/total number of cases): non-ESBL (n=41)	ESBL (n=136)
Carbapenem alone	85.7 (6/7)	81.8 (36/44)
Carbapenem + aminoglycoside or fluoroquinolone	-	88.9 (16/18)
Cephalosporin alone	80.0 (4/5)	84.6 (11/13)
Cephalosporin + aminoglycoside or fluoroquinolone	-	80.0 (8/10)
ß-lactam/ ß-lactamase inhibitor combination	77.8 (7/9)	87.5 (7/8)
Fluoquinolone	100 (10/10)	81.8 (9/11)
Carbapenem + 2nd ß-lactam	0	100 (5/5)
Aminoglycoside	-	-
TMP + Other	-	80.0 (4/5)
Other	-	73.7 (14/19)

a. Clinical outcome for a treatment group for either non-ESBL or ESBL cases was not computed for cohort sample sizes < 5.

Table 6. Univariate evaluation of factors associated with clinical success.

Independent Variable	Presence of Independent Variable: Yes	No	p-value
Diabetes	83.3	81.1	0.77
Emergency intra-abdominal surgery	83.9	80.8	0.69
Gastrostomy or jejunostomy tube	81.6	82.1	0.94
Prior length of hospital stay ≥ 10 days	81.7	85.2	0.79[a]
Prior ICU stay	82.8	80.6	0.71
Malignancy	85.3	81.0	0.56
Presence of intravascular catheters	80.7	95.2	0.13[a]
Presence of urinary catheters	80.6	87.5	0.29
Prior antibiotics	80.1	90.5	0.37[a]
Prior nursing home stay	64.3	83.0	0.14[a]
Transplantation	60.0	83.3	0.08[a]
Ventilator assistance	76.6	88.1	0.07

a. Fisher's exact test was computed in place of Pearson Chi-square since more than one-fifth of fitted cells were sparse (frequency < 5).

CONCLUSIONS

- Enterobacteriaceae infections were associated with significant morbidity (clinical failure rate = 17.5%) and mortality (7-21%).
- Clinical outcome and mortality among patients with ESBL- and non-ESBL-producing Enterobacteriaceae infections were similar.
- Carbapenems, as monotherapy or in various combinations, accounted for nearly 50% of treatment regimens, while cephalosporin mono- or combination- therapy accounted for 17% of treatment regimens among ESBL cases collected in North America, Latin America and Europe.
- Clinical success was achieved for 83.1% of ESBL and 80.5% of non-ESBL cases. Outcomes by treatment group for ESBL and non-ESBL cases for carbapenem and cephalosporin monotherapy were 81.8 vs 85.7% and 84.6 vs 80.0%, respectively.
- ESBL production alone does not appear to be an independent risk factor for treatment failure with several drug regimens, including cephalosporin monotherapy.
- Although the size of the non-ESBL control group and certain cohorts by treatment regimen were limited in the present analyses, outcomes were examined for a large number of ESBL cases collected worldwide; examination of datasets such as these will allow for a further understanding of the relationship between outcome and treatment choice, including dosing levels and MIC value of the pathogen. Such information may be used to support pharmacokinetic-pharmacodynamic analyses and decisions for susceptibility breakpoints.

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