Clinical Impact of De-escalation to Ertapenem in Enterobacteriaceae infections in Intensive Care Units from Seven Hospitals in Colombia

Blanco VM[1], Vallejo M[1,2], Hernandez C[1], Cuesta D[2], Maya JJ[1], Motoa G[1], Correa A[1], Rosso F[3], Matta L[4], Muñoz M[5], Flórez E[6], Quinn JP[7], Villegas MV[1]

[1]Centro Internacional De Entrenamiento e Investigaciones Médicas (CIDEIM), Cali, Colombia; [2]Universidad Pontificia Bolivariana, Medellin, Colombia; [3] Fundación Clínica Valle del Lili, Cali, Colombia; [4]Clínica Comfenalco Universidad Libre, Cali, Colombia; [5]Centro Médico Imbanaco, Cali, Colombia; [6]Hospital General de Medellín, Medellín, Colombia; [7]AstraZeneca, Waltham, MA.

Maria V. Villegas, MD, MSc.
Carrera 125 # 19 – 225 Cali, Colombia.
mariavirginia.villegas@gmail.com
(572) 555-2164

Background: The increasing emergence and uncontrolled spread of antimicrobial resistance worldwide threatens patient outcomes and raises overall healthcare costs. Antimicrobial De-Escalation (DE) requires that initial optimal broad-spectrum therapy be narrowed within 48 to 72 hours after the pathogen and its antibiotic susceptibility is known. ETP has proven to be effective for ESBL-producing EB but lacks activity against non-fermenters; DE to this antibiotic may reduce the development of resistance to *P. aeruginosa* (Pa). Herein, we evaluated the clinical impact of DE to ETP in infections caused by EB in ICUs from 7 hospitals from 4 Colombian cities.

Methods: A cohort prospective study was carried out between February 2008 and June 2012. Adult ICU patients diagnosed with an EB infection and in whom empiric antibiotic therapy against Pa was started, were included in the study. Patients were assigned to 3 different groups: DE to ETP (group A), changed to an antibiotic different from ETP (group B) or not DE and continued on the same empirically anti-pseudomonas antibiotic (group C). Overall mortality, length of ICU stay (LOS), and clinical failure defined as the persistence of signs and symptoms of active infection at day 7 of antibiotic therapy, were analyzed.

Results: From a total of 1536 patients assessed for eligibility, 316 were included. Of those, 148 were assigned to group A, 63 to group B and 105 to group C. Patients in group A had a more severe condition at the moment of ICU admission, median APACHE II score = 20 compared to score ≤15 for B and C (p=0.0001). LOS was similar for the 3 groups. The overall mortality was 9% for group A versus 32% and 24% for groups B and C, respectively (p=0.003). Kaplan-Meier curves showed higher survival rates for group A (mean = 66 days, 95% CI 58 - 74) than for B or C, mean of 41 and 56 days, respectively (p=0.000). Patients from group A had a much lower relative risk of clinical failure when compared to group B (RR 0.454; 95% CI 0.239 - 0.861; p=0.019).

Conclusion: Patients DE to ETP had a lower mortality rate, a greater survival time, and a lower proportion of clinical failures than patients who were either changed to other antibiotics or continued the same initial therapy. DE o ETP should be considered as part of antimicrobial stewardship programs at the ICUs whenever the clinical condition and culture results allow

OBJECTIVE

To evaluated the clinical impact of De-escalating to Ertapenem in infections caused by Enterobacteriaceae in critically ill patients from 7 hospitals in Colombia.

MATERIALS & METHODS

- **Study design:** A prospective cohort study
- **Setting:** Intensive Care Units (ICU) and Intermediate Care Units (IMCU) between February 2008 and June 2012 in seven intermediate and high-complexity Colombian hospitals from different cities.
- **Participants:** adults ≥18 years with an Enterobacteriaceae infection confirmed by a microbiological culture, in whom empiric antibiotic therapy (EAT) against *P. aeruginosa* was started. Patients whose empirical antibiotics were changed before ICU/IMCU admission were excluded.
- **Groups:** Patients who were either de-escalated to Ertapenem (Group A), switched from to an antiobiotic different to Ertapenem (Group B), or did not change the EAT (Group C, reference).
- **Main outcomes:** Clinical response to active infection on day 7 after the microbiological culture report, overall mortality, length of ICU/ IMCU stay (LOS).
- **Measurement:** Socio-demographic variables, APACHE-II score, and presence of co-morbidities were recorded at the time of admission to the ICU/IMC. First bacterial culture during ICU stay, source and type of infection, LOS prior to initiating EAT and selection of the antibiotic therapy was also measured.
- **Statistical methods:** To evaluate the clinical response the relative risk (RR) with a 95% confidence interval (CI) was estimated and logistic regression was done by GEE (Generalized Estimating Equations). The Hazard Ratio (HR) for death by any cause and its 95% CI were determined using Cox proportional hazards model. The differences in median of days of ICU/IMCU stay was determined using Mann-Whitney test and Kruskal-Wallis test.

RESULTS

Table 1. Baseline characteristics of ICU/IMCU subjects with an Enterobacteriaceae infection

Characteristics	De-escalated to Ertapenem n = 148	Changed to other ATB n = 63	Not Changed ATB empirical n = 105	P-value
Age, median [IQR] years	57 [41-73]	57 [35-70]	67 [53-75]	**0.004**
Gender, male- n(%)	64 (43)	31 (49)	56 (53)	0.277
APACHE II score, median [IQR]	20 [15-27]	15 [12-19]	15 [12-19]	**0.0001**
Comorbid conditions n(%)				
High Blood Pressure	49 (33)	27 (43)	49 (47)	0.079
Heart disease	31 (21)	13 (21)	27 (26)	0.621
Diabetes	29 (20)	13 (21)	21 (20)	0.985
Kidney disease	22 (15)	9 (14)	11 (10)	0.579
Immunosuppression	15 (10)	8 (13)	5 (5)	0.163
Chronic obs. pulmonary disease	14 (9)	3 (5)	7 (7)	0.453
Liver disease	1 (1)	6 (9)	5 (5)	**0.007**
Other	36 (24)	6 (9)	4 (4)	0.545
Type of Infection - n(%)				
Blood stream infection	53 (36)	29 (46)	32 (30)	**0.005**
Urinary tract infection	42 (28)	9 (14)	28 (27)	
Intra-abdominal infection	22 (15)	4 (6)	6 (6)	
Nosocomial pneumonia	20 (14)	11 (18)	22 (21)	
Skin/Soft tissue infection	5 (3)	8 (13)	15 (14)	
Other	6 (4)	2 (3)	2 (2)	
Bacteria - n(%)				
K. pneumoniae	66 (45)	23 (36)	37 (35)	0.330
E. coli	43 (29)	19 (30)	34 (32)	
E. cloacae	13 (9)	7 (11)	10 (10)	
S. marcescens	6 (4)	6 (10)	13 (12)	
P. mirabilis	4 (3)	3 (5)	6 (6)	
Other	15 (10)	5 (8)	5 (5)	
Length of ICU/IMCU stay before empirical ATB, median days (IQR)	3 (0-10)	2 (0-8)	0 (0-6.5)	0.095

Table 2. Antibiotic therapy in ICU/IMCU subjects with an Enterobacteriaceae infection

Characteristics	De-escalated to ertapenem n = 148	Changed to other ATB n = 63	Not Changed ATB n = 105	P-value
Empiric antibiotic monotherapy	100 (68)	60 (95)	98 (93)	**<0.0001**
Days of empiric antibiotic therapy, days, (IQR)	3 (2-4)	3 (2-5)	-	0.674
Empiric antibiotic*				
Cefepime	63 (43)	17 (27)	39 (37)	0.101
Meropenem	34 (23)	14 (22)	30 (29)	0.524
Amikacin	26 (18)	6 (10)	7 (7)	**0.026**
Pip/Tazobactam	24 (16)	24 (38)	22 (21)	**0.002**
Imipenem	17 (12)	0 (0)	4 (4)	**0.003**
Other	33 (22)	5 (8)	10 (10)	**0.004**
Total of ATB used				
Median (IQR)	2.5 (2-3)	2 (2-2)	1 (1-1)	**<0.0001**

Table 3. Clinical response and overall mortality by study group in ICU/IMCU subjects with an Enterobacteriaceae infection

Study Group	CLINICAL RESPONSE		Relative Risk (CI 95%) crude	Odds Ratio (CI 95%) adjusted*	DEATH	Relative Risk (CI 95%) crude	Hazard Ratio (CI 95%) adjusted**
	Failure or parcial response	Cure					
De-escalated to Ertapenem, n (%)	59 (39.9)	89 (60.1)	1.44 (0.99-2.08)	0.73 (0.61 - 0.88)	13 (9)	0.36 (0.19 - 0.68)	0.29 (0.10 – 0.84)
Changed to other ATB, n (%)	23 (36.5)	40 (63.5)	1.32 (0.84-2.07)	0.84 (0.70- 1.009)	20 (32)	1.33 (0.81 - 2.19)	1.46 (0.69 – 3.06)
Not changed ATB empirical, n (%)	29 (27.6)	76 (72.4)	1	1	25 (14)	1	1

*Logistic regression by Generalized Estimating Equations: odds ratio was adjusted by hospital grouping effect and propensity score of Ertapenem, APACHE II score, kidney disease, diabetes mellitus, ICU/IMCU stay before beginning empirical ATB, isolated bacteria, use of Cefepime, Amikacine, Imipenem, Piperacillin/Tazobactam as empirical antibiotics and total antibiotics received

**Cox proportional hazards model: hazard ratio was adjusted by hospital grouping effect and age, APACHE II score, kidney disease, diabetes mellitus, chronic obstructive pulmonary disease, high blood pressure, empirical antibiotic monotherapy, ICU/IMCU stay before beginning empirical therapy and the use of Aztreonam, Ciprofloxacin, Meropenem, Cefepime, Piperacillin/Tazobactam as empirical antibiotics

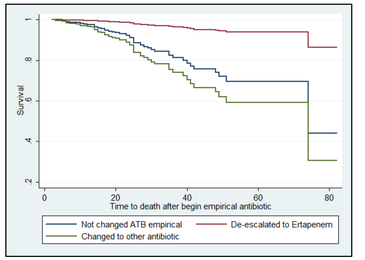

Figure 1. Cox proportional hazard regression

Table 4. Length Of ICU/IMCU Stay by study group of patients with an Enterobacteriaceae infection

LENGTH OF STAY (LOS) IN THE ICU/IMCU	De-escalated to Ertapenem n = 148	Changed to other ATB n = 63	Not Changed ATB n = 105	P value
LOS from admission to discharge, median days (IQR)	22 (14 - 32)	19 (12 - 31)	20 (12 - 35)	0.504
LOS from initiation of empiric antibiotic to discharge, median days (IQR)	16* (9 - 24)	14 (10 - 26)	14 (7 - 28)	0.751
Survival time after begin empirical antibiotic, mean days (CI 95%)	66 (59 - 72)	34 (28 - 40)	50 (42-58)	0.001

***P value between Group A and Group C: 0,040**

CONCLUSIONS

- ✓In the ICU, empiric antibiotic therapy against *P. aeruginosa* is needed, but once culture comes back positive for an Enterobacteriaceae, DE to a non antipseudomonal antibiotic should be done once the patient is hemodynamically stable .
- ✓Patients who DE to ETP had a lower mortality rate, a greater survival time, and a lower proportion of clinical failures than patients who were either changed to other antibiotics or continued on the same initial therapy.
- ✓DE to ETP should be considered as part of antimicrobial stewardship programs at the ICUs whenever the clinical condition and culture results allow.

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