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# Therapeutic drug monitoring in patients with infective endocarditis treated with amoxicillin plus ceftriaxone

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## Introduction

The current European guidelines for managing *Enterococcus faecalis* infective endocarditis (EFIE) do not mention dosage adjustment of AMOXICILLIN (AMX) plus CEFTRIAZONE (CRO) to creatinine clearance (CrCl). In addition, these guidelines recommend dosage regimen at AMX: 200mg/kg/day i.v. in 4-6 doses plus CRO: 4g/day i.v. or i.m. in 2 doses. However, high-doses of beta-lactams could have renal and/or neurological toxicity. Moreover, the minimal trough concentrations (C<sub>0</sub>) of AMX and CRO associated with bactericidal synergy activity against *E. faecalis* are not known for treating patients with EFIE.

## Objective

We aimed to assess the clinical efficacy and toxicity according to the first C<sub>0</sub> of AMX and CRO in patients treated for EFIE.

## Patients & Methods

### Data collection

- Five-years (2016 – 2021) retrospective analysis of therapeutic drug monitoring (TDM) data from patients who were treated for EFIE with AMX + CRO.
- Biological and clinical data were collected using laboratory software and medical records.
- Two groups were compared according to the occurrence of an initial antibiotic overdose: **Group A: No-overdose**; **Group B: Overdose**.

### Outcomes

- Primary outcome: 30-days all causes mortality.
- Secondary outcomes: Acute kidney injury (AKI); duration of bacteremia and 1-year all causes mortality.

### Definitions

- AMX and CRO toxic thresholds were respectively defined as 80 mg/L and 100 mg/L according to French guidelines<sup>1</sup>.
- AKI was defined as a sudden increase ( $\leq 48$ h) in serum creatinine of  $\geq 26.5 \mu\text{M}$  or an increase of  $\geq 50\%$  over baseline creatinine (KDIGO).

## Results

Antibiotics C<sub>0</sub> were determined using tandem mass spectrometry coupled with liquid chromatography (LC MS/MS)

Patients treated with AMX plus CRO (n= 76)

Exclusion:  
Polymicrobial infection (n= 3)  
Meningitis (n= 1)

Patients treated for EFIE (n= 72)  
No. C<sub>0</sub> (AMX)= 194 No. C<sub>0</sub> (CRO)= 147

First C<sub>0</sub>

**Group A**  
n= 30

C<sub>0</sub> (AMX) < 80 mg/L  
**And**  
C<sub>0</sub> (CRO) < 100 mg/L

**Group B**  
n= 42

C<sub>0</sub> (AMX)  $\geq 80$  mg/L  
**Or/And**  
C<sub>0</sub> (CRO)  $\geq 100$  mg/L

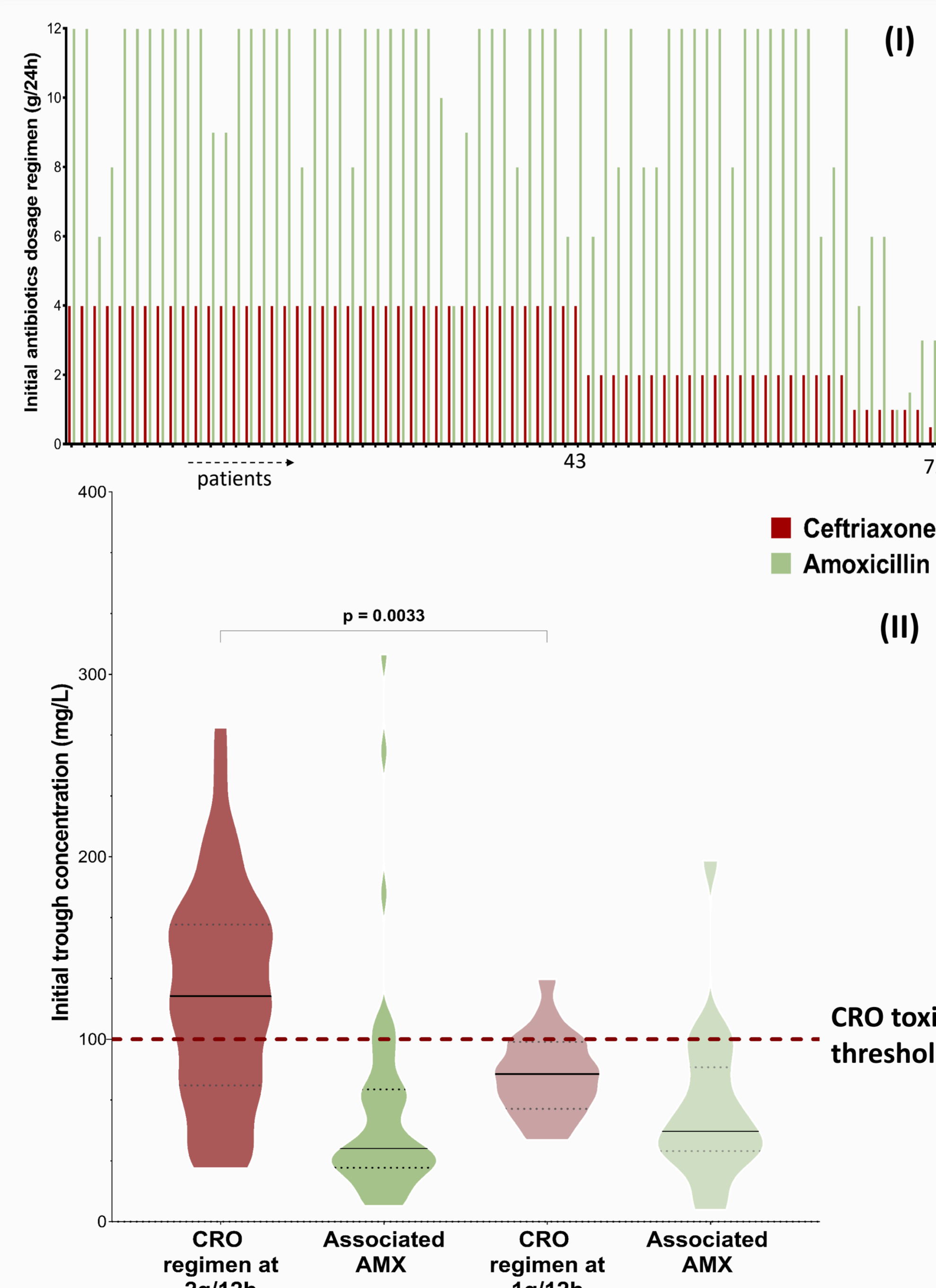


Fig 2. (I) Initial AMX and CRO dosage regimen of 72 patients treated for EFIE. (II) Initial C<sub>0</sub> of AMX and CRO according to antibiotics dosage regimen.

Variables	Group A No-Overdose n= 30	(%) or (SD)	Group B Overdose n= 42	(%) or (IQR)	p-Value
Male	21	70	32	80	p > 0.5
Mean of age (years)	77.1	6.7	79.8	8.5	p < 0.5
Mean of Charlson Comorbidity Index	4.2	1	4.6	1	p > 0.5
Chronic kidney diseases	15	50%	32	76%	p < 0.5
Haemodialysis	3	10%	0	0%	p > 0.5
Diabetes	13	43%	12	28.5%	p > 0.5
Mean of IMC (Kg/m <sup>2</sup> )	28.5	6	27	4.7	p > 0.5
CRO dosage regimen (2g/12h)	17	56%	26	62%	p > 0.5
Device therapy (TAVI, Prosthetic valve and cardiac implantable electronic device)	22	73%	29	69%	p > 0.5
Surgery	6	20	5	12%	p > 0.5
IE complications	6	20%	14	33%	p > 0.5
Septic shock	5	83%	3	21%	ND*
Systemic emboli	0	0%	4	28.5%	ND
Heart failure	6	100%	7	50%	ND
Baseline of eGFR (mL/min/1,73m <sup>2</sup> )	69.1	36	45.1	21.6	p < 0.01
Baseline of creatinine (mg/L)	135	116.7	177	124.6	p < 0.01
<b>30-days mortality</b>	<b>1</b>	<b>0.3%</b>	<b>1</b>	<b>0.23%</b>	<b>p &gt; 0.5</b>
<b>AKI under treatment**</b>	<b>5</b>	<b>17%</b>	<b>22</b>	<b>55%</b>	<b>p &lt; 0.01</b>
<b>Mean days of bacteremia (days)</b>	<b>3.7</b>	<b>2.2</b>	<b>3.5</b>	<b>2.6</b>	<b>p &gt; 0.5</b>
<b>1-year mortality</b>	<b>4</b>	<b>13%</b>	<b>10</b>	<b>24%</b>	<b>p &gt; 0.5</b>

Table 1. Clinical and biological characteristics and outcomes of 72 patients treated for EFIE according to antibiotics C<sub>0</sub>.

\*ND: Not Done; \*\*Hemodialyzed patients were not included in the statistical analysis.

## IV- Conclusion

The European guidelines for managing patients treated for EFIE do not provide antibiotics dosage adjustment to weight (for CRO) or to creatinine clearance (for AMX and CRO). Nevertheless, overdose appears to be frequent and associated with the occurrence of adverse events such as AKI. TDM of patients treated for EFIE seems to be important and could allow to define a plasma C<sub>0</sub> targets of these two antibiotics.

## Reference

<sup>1</sup> Guilhaumou R, Benaboud S, Bennis Y, et al. Optimization of the treatment with beta-lactam antibiotics in critically ill patients—guidelines from the French Society of Pharmacology and Therapeutics (Société Française de Pharmacologie et Thérapeutique—SFPT) and the French Society of Anaesthesia and Intensive Care Medicine (Société Française d'Anesthésie et Réanimation—SFAR). *Crit Care*. 2019;23(1):104. doi:10.1186/s13054-019-2378-9