Linezolid Toxicity in Clinical Practice: Towards a Better Detection of at-risk Patients?

Interim Analysis of a Prospective Multicentric Study

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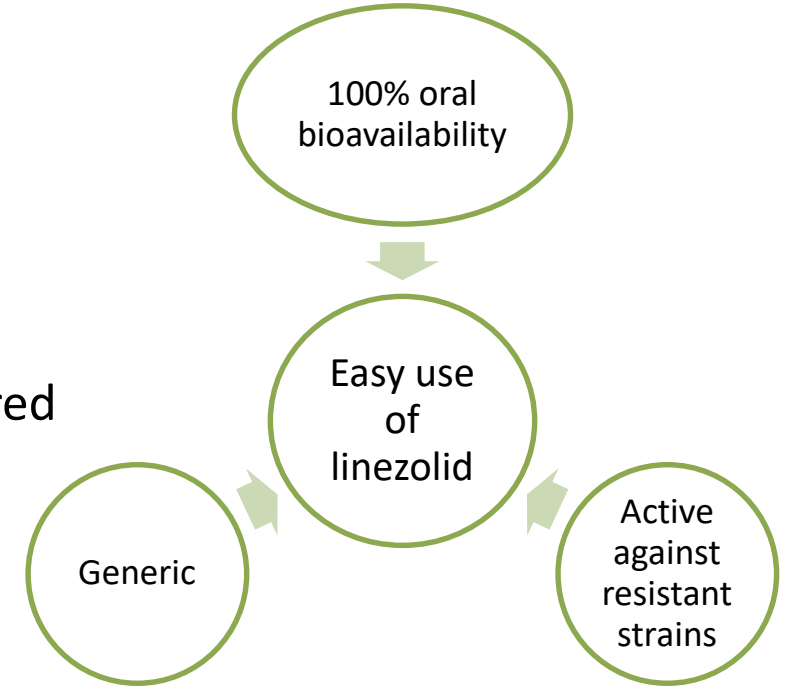
Copenhagen, Denmark
15–18 April 2023
33rd ECCMID
EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Linezolid (LZD)

- Oxazolidinone: **Gram positive** bacteria
- Inhibition of the **protein synthesis**
- Skin and soft tissue infections + nosocomial and community-acquired pneumonia
- Maximum of **28 days** of treatment
- 600 mg 2x/day

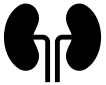


Linezolid toxicity

- **Hematological** disorders (anemia – thrombocytopenia)
  → Weekly blood test recommended
- Lactic acidosis
- Peripheral and optic **neuropathy**

Higher level of hematological disorders than in the SmPC

Risk factors: Treatment duration – renal impairment - comorbidities

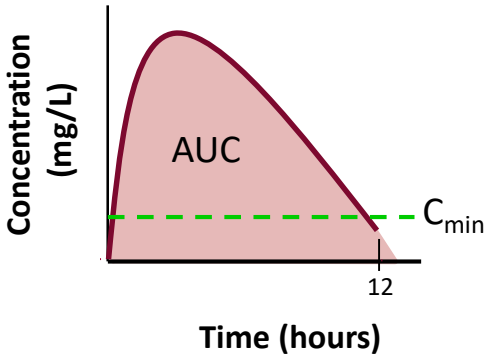




Thirot et al (2021), Antibiotics 10(5):530
SmPC = Summary of product characteristics

Linezolid monitoring

- **AUC/CMI** = PK/PD parameter driving efficacy

- **C_{min}**
  - Safety indicator
  - Currently recommended range = **2 – 7 mg/L**
  - **C_{min} > 9 mg/L** = increasing risk of developing hematological toxicity



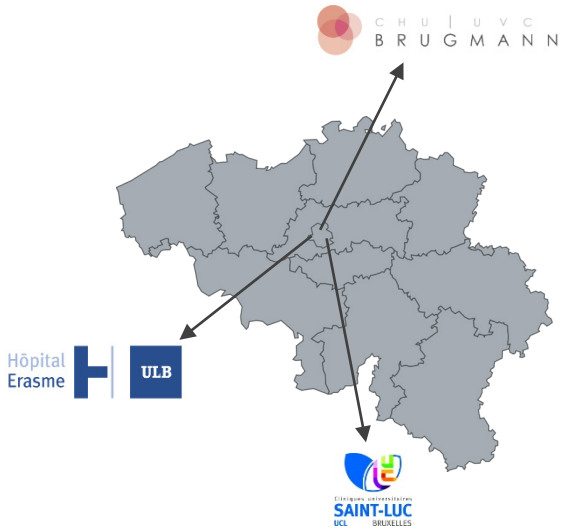
Cattaneao (2016) Int J Antimicrob Agents 48(6):728-731
Fage et al (2021) Talanta; Vol 221 (121641)

Objectives

- Assess the rate of LZD adverse drug reactions (ADRs) in clinical practice
- Highlight risk factors associated with the development of ADRs
- Assess the link between C_{min} and the development of ADRs

Methodology

Prospective interventional study (3 Belgian hospitals)



Inclusion criteria:

- Adult patients (> 18 years)
- Treated with linezolid for at least 3 days
- Hospitalized or ambulatory patients

Exclusion criteria:

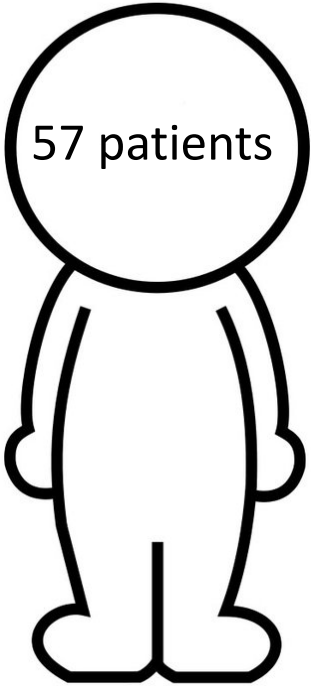
- Platelets level < 75,000 / mm^3 and/or hemoglobin < 8g/dl

Monitoring:

Blood sampling the day of the follow-up consultation

Blood sampling once a week (according to the duration of the therapy)

Patients' characteristics



61 treatments

22 (36.1%)	39 (63.9%)	65 (31 - 97)
85 kg (40-154)	72 ml/min (5 -134)	1 mg/dl (0.32-8.16)
Charlson index 2 (0-6)	46 (75.4%)	15 (24.6%)
600 mg 2x/d	7 54	13 (4 – 117)

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Type of infections and LZD duration

Infection	N (%)	Median treatment duration (range)
BJI	22 (36.1)	28 (9-121)
SSTI	10 (16.4)	11 (8-17)
Secondary bacteremia	8 (13.1)	10.5 (5-23)
Endocarditis	6 (9.8)	14 (9-14)
Septic shock	5 (8.2)	8 (6-10)
UTI	3 (4.9)	7 (5-7)
Pneumonia	2 (3.3)	8.5 (7-10)
Others	5 (8.2)	

BJI = bone and joint infection – **SSTI** = skin and soft tissue infection – **UTI** = urinary tract infection

Adverse drug reactions

ADRs	N (%)	% based on ADR in EU SmPC
Thrombocytopenia	18 (29.5)	1 - 10
Anemia	10 (17.5)	1 - 10
Metallic taste	9 (15.8)	1 – 10
Gastro intestinal disorders	17 (28.8)	1 - 10
Tinnitus	1 (1.75)	0.1 - 1
Mycosis	2 (3.5)	1 - 10
Paresthesia	1 (1.75)	0.1 - 1
Hepatic disorders	1 (1.75)	1 - 10

- **30**  with at least 1 ADR
- Between 1 and 4 ADRs

- 11 stops for toxicity (10 hematological toxicity and 1 paresthesia)
- Hematological toxicity : Stop after 9 to 34 days

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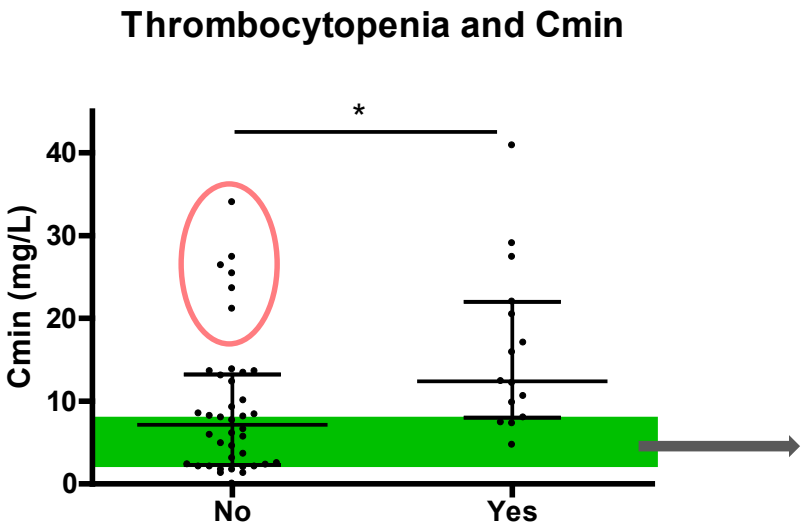
Adverse drug reactions



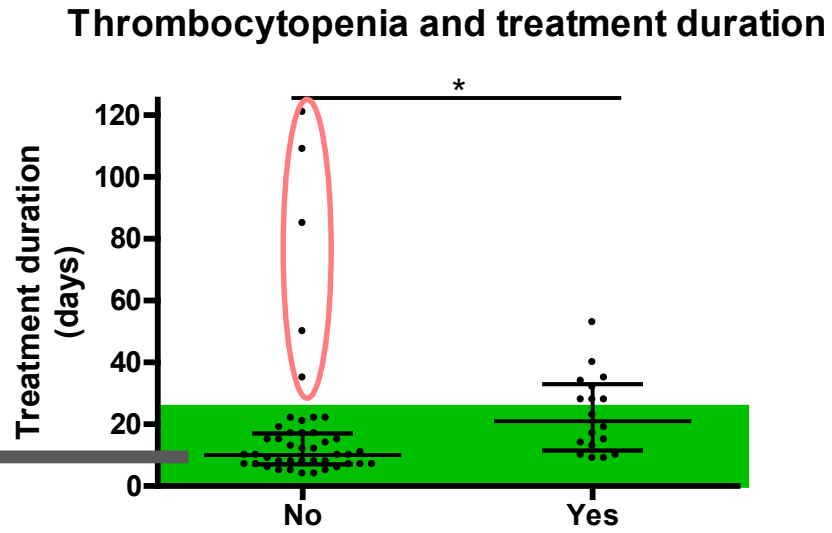
Clinically recommended range (2-7 mg/L)

	No	Yes
Median (range)	7.1 (0-34)	12.4 (4.7-40.85)

* Mann-Whitney U test

Adverse drug reactions

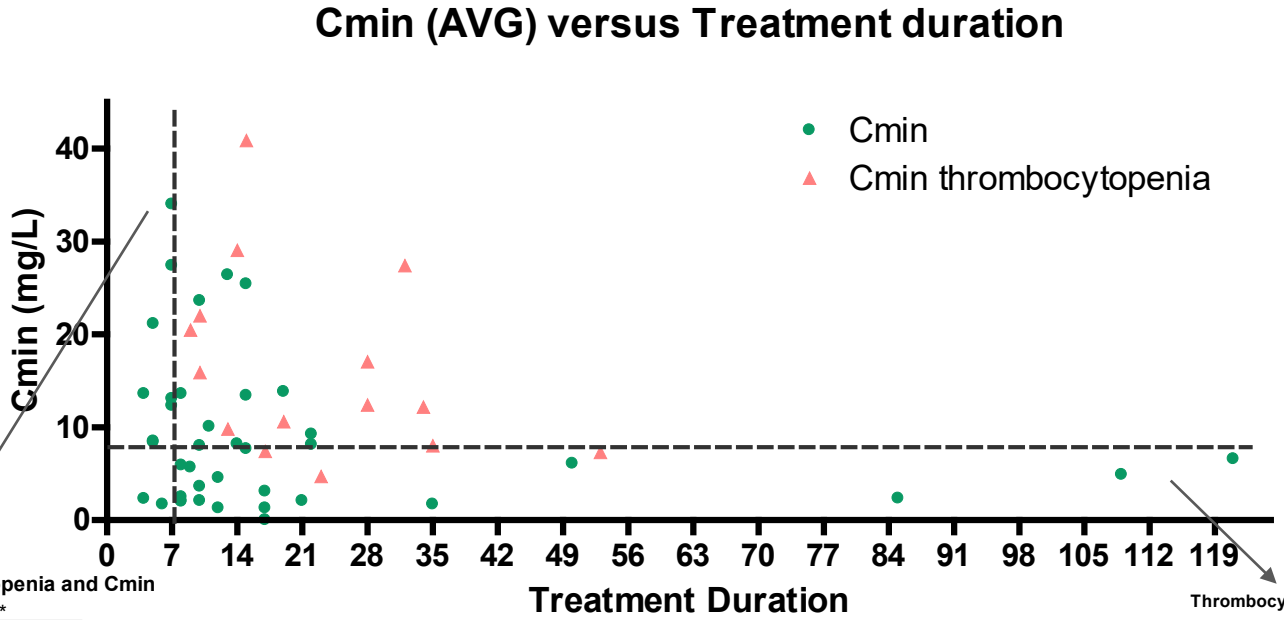
Treatment duration < 28 days

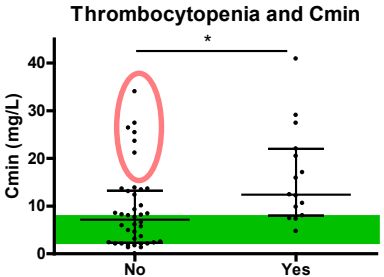


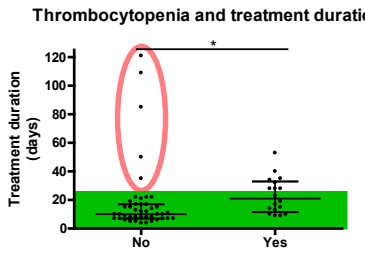
	No	Yes
Median (range)	10 (4-121)	21 (9-53)

* Mann-Whitney U test

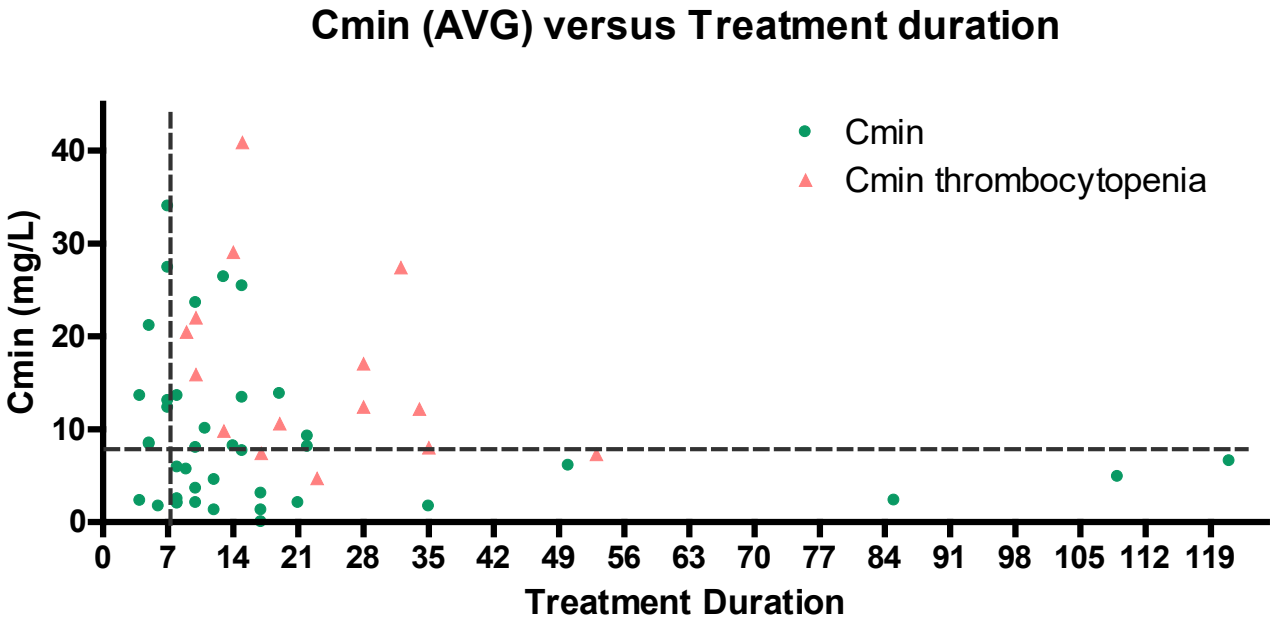
Linezolid monitoring and ADRs





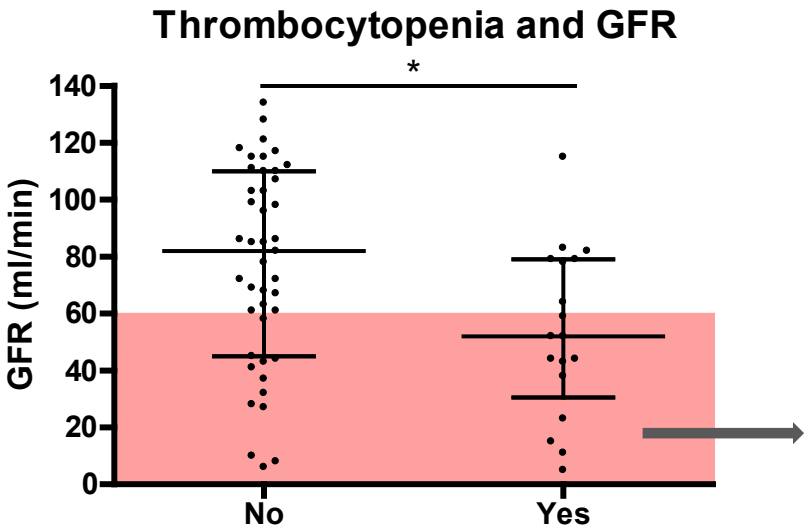


Linezolid monitoring and ADRs



- Patients with the **longest treatment duration** are patients **without** any ADRs
- Platelet decrease is observed between 7 and 14 days
- Patients with high C_{min} → No toxicity observed because short treatment?

Adverse drug reactions



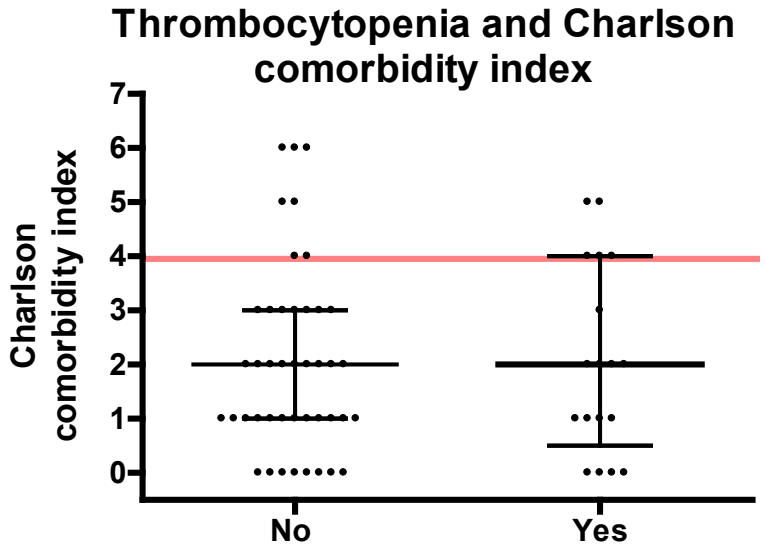
Glomerular filtration rate < 60 ml/min
→ Renal insufficiency

	No	Yes
Median (range)	82 (6-134)	52 (5-115)

* Mann-Whitney U test

Adverse drug reactions

Charlson comorbidity index ≥ 4



	No	Yes
Median (range)	2 (0-6)	2 (0-5)

* Mann-Whitney U test

Key messages

- More **frequent** ADRs
  - → Hematological toxicity (discontinuation)
  - → Metallic taste

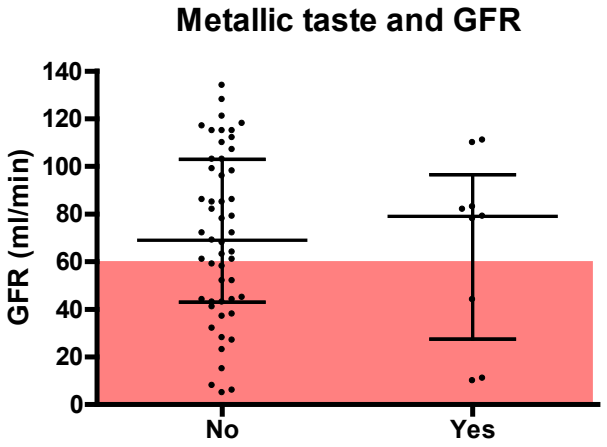
- Parameters: C_{min} – renal impairment – longer treatment duration

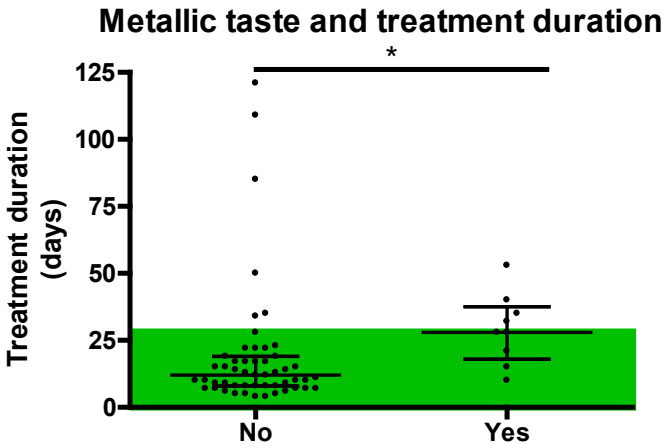


- Patients can have long treatment duration without ADR
  → C_{min} in the therapeutic range

Thank you!

Metallic taste

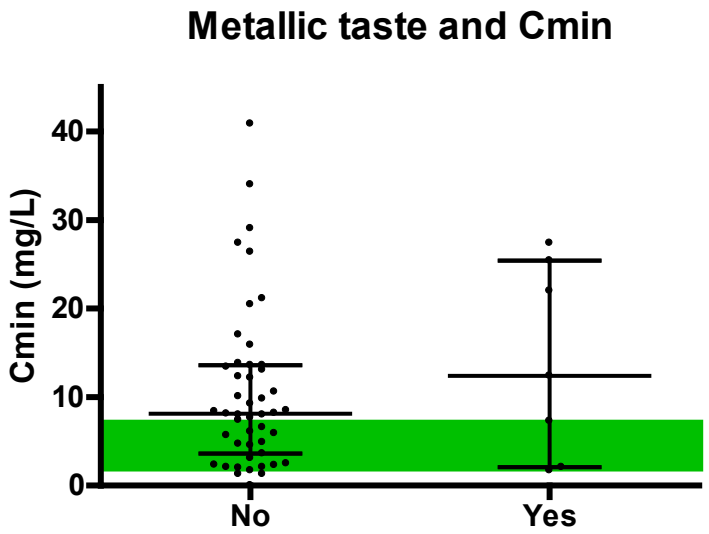




	No	Yes
Median (range)	69 (5-134)	79 (10-111)

	No	Yes
Median (range)	12 (4-121)	28 (10-53)

Metallic taste



	No	Yes
Median (range)	8.1 (0-40.85)	12.4 (1.7-27.4)

GFR and Cmin