Dosing cycloserine: analysis of therapeutic drug monitoring results among patients with drug-resistant tuberculosis in California

Phil Lowenthal[1], Neha Shah[1,2], Lisa True[1], Leslie Henry[1], Pennan Barry[1]

[1]Tuberculosis Control Branch, California Department of Public Health; [2]Centers for Disease Control and Prevention

Background

- Cycloserine remains a recommended drug for the treatment of drug-resistant tuberculosis (DR-TB) despite the potential for side effects in high serum concentration.
- Uncertainty and variability exist in dosing recommendations for cycloserine.
- The California MDR-TB Service routinely recommends therapeutic drug monitoring (TDM) to adjust cycloserine dose.

Objectives

- Analyze initial cycloserine dosing among TB patients by evaluating clinical and laboratory data collected by the California MDR-TB Service.
- Detect patient characteristics that might predict plasma cycloserine drug concentration and potentially improve initial cycloserine dosing strategy.

Methods

- We analyzed MDR-TB service consult data for TB patients reported during 2009-2015 with a peak cycloserine concentration available.
- Peak concentration was labeled as "peak" in medical or consultation records, or documented collected at 2 hours past medication ingestion.
- The Cockcroft-Gault formula, which incorporates patient age, weight, gender and serum creatinine concentration was used to determine patient creatinine clearance.
- Goal peak plasma cycloserine concentration was 20-35 µg/ml[1].

Results

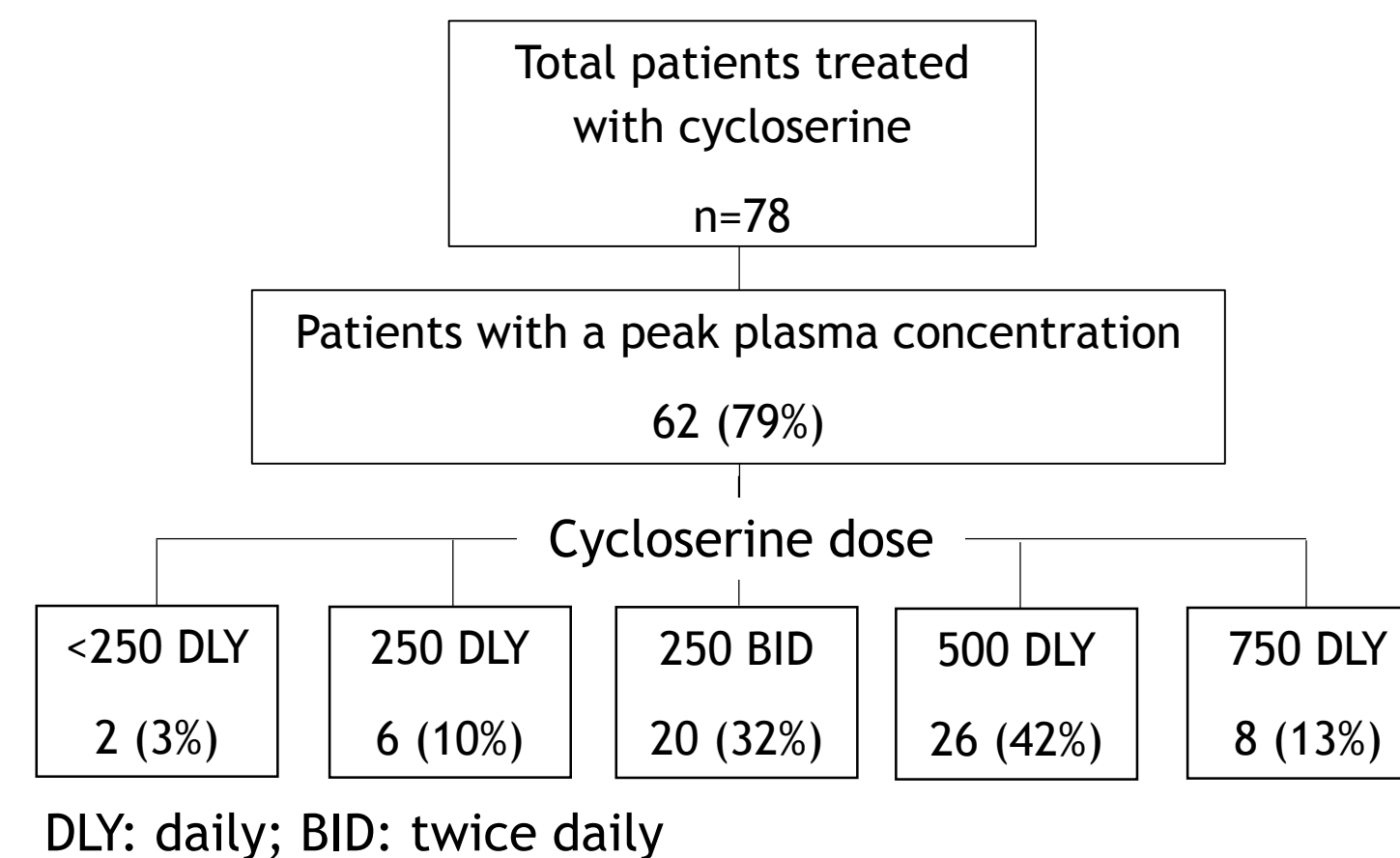**Figure 1. Tuberculosis patients treated with cycloserine, 2009-2015**

Total patients treated with cycloserine
n=78

Patients with a peak plasma concentration
62 (79%)

Cycloserine dose

<250 DLY	250 DLY	250 BID	500 DLY	750 DLY
2 (3%)	6 (10%)	20 (32%)	26 (42%)	8 (13%)

DLY: daily; BID: twice daily

Table 1: Characteristics of patients treated with cycloserine who had a peak plasma concentration

Characteristic (n=62 patients)	n (%)
Sex	
Male	36 (58)
Female	26 (42)
Age (years), median [IQR]	38.9 [27-56]
5-14	1 (2)
15-24	10 (16)
25-44	27 (44)
45-64	17 (27)
≥65	5 (8)
Unknown	2 (3)
Non-U.S.-born	55 (89)
Diabetes	16 (26)
HIV	1 (2)
Patient weight (kg), median [IQR]	58.2 [51-68]
Initial cycloserine treatment to peak drug plasma concentration (days) [IQR]	20 [14-40]

IQR: interquartile range

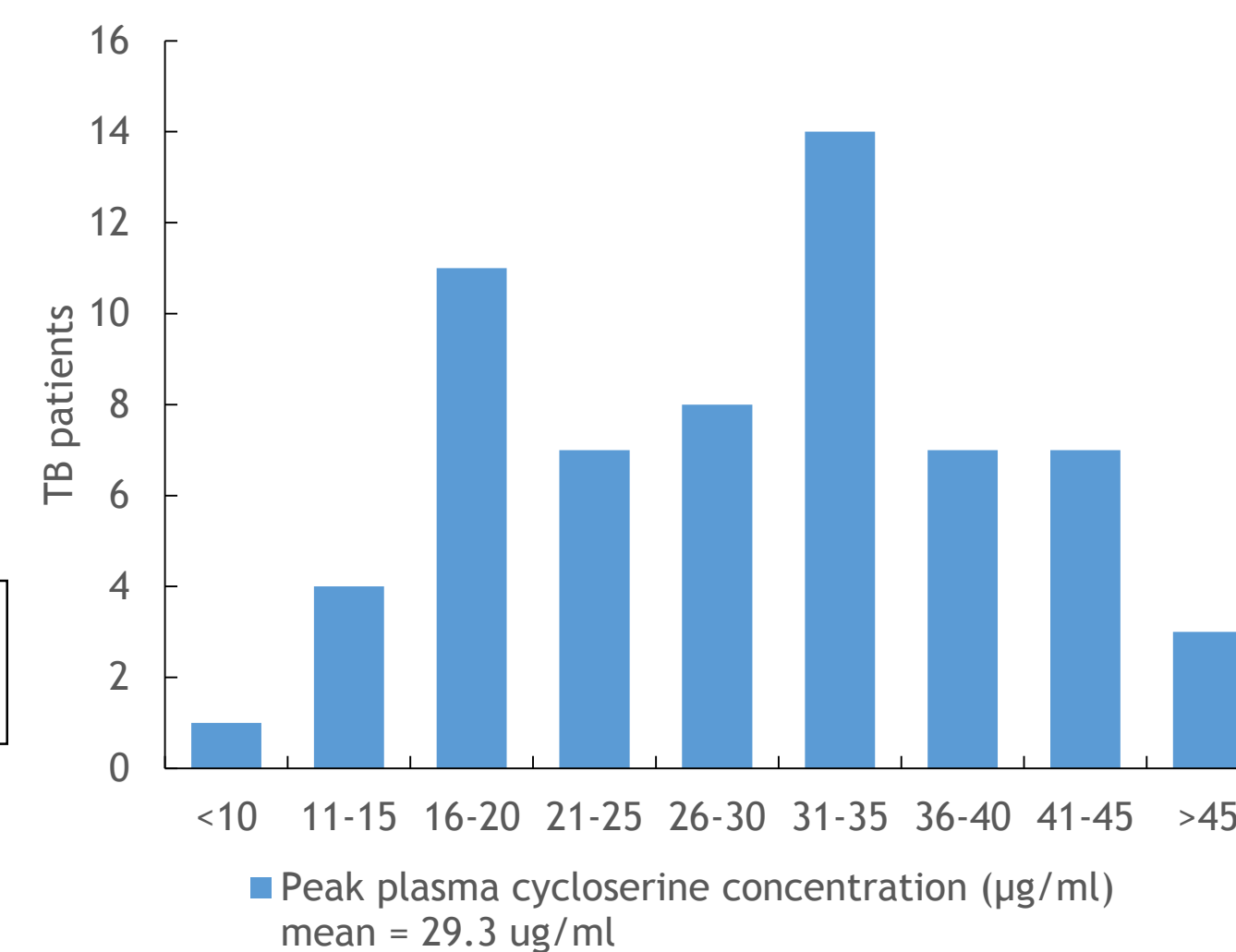**Figure 2: Peak plasma cycloserine concentration (n=62 patients)**

Peak plasma cycloserine concentration (µg/ml)
mean = 29.3 ug/ml

Table 2: Patient characteristics by cycloserine plasma concentration

n=62 patients	<20 µg/ml (n=16)	20-35 µg/ml (n=28)	>35 µg/ml (n=18)	P value
Age, years, mean	35.5	39.7	51.2	**0.0069**
Male sex n (%)	9 (56)	16 (57)	11 (61)	0.9512
Diabetes mellitus, n (%)	4 (19)	6 (20)	8 (42)	0.3249
Renal clearance, mean	102.1	99.0	70.1	**0.0018**
Dose mg/kg/day, mean	7.8	9.0	9.3	0.2358

Conclusions

- We found that more than half of patients had an initial cycloserine peak concentration outside the expected range regardless of initial dosing strategy.
- Greater patient age and lower creatinine clearance were associated with higher than normal cycloserine plasma concentration.
- TDM is important to identify patients with peak concentration outside targeted range.

Limitations

- Exact time from ingestion to blood draw was not known for XX%.

Reference
1. Asultan A, Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis: an update. Drugs. 2014 Jun;74(8):839-54.