Optimized Chemotherapy with Linezolid for TBM

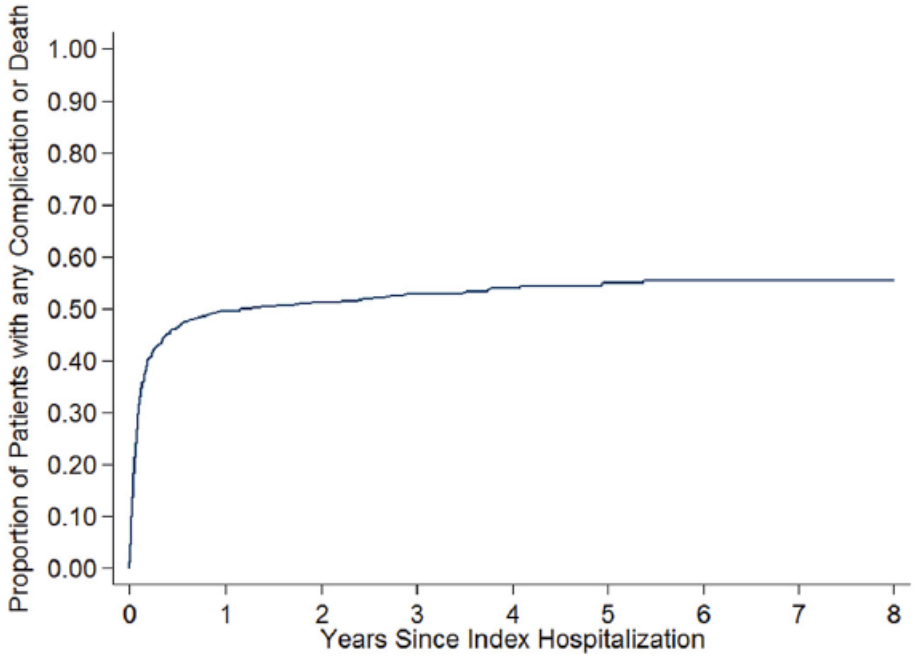
Wen-Hong ZHANG

Fudan University Hospital, China

Mortality of TBM is high even in well treated patients

Tuberculous meningitis (TBM) is the most severe form of infection caused by Mycobacterium tuberculosis.

Death or disability in more than half of TBM patients.



Merkler A E, et al. 2017

Retrospective cohort study in USA

All patients 18 years or older hospitalized for TBM in California (2005~2010), New York (2006~2012), and Florida (2005-2012).

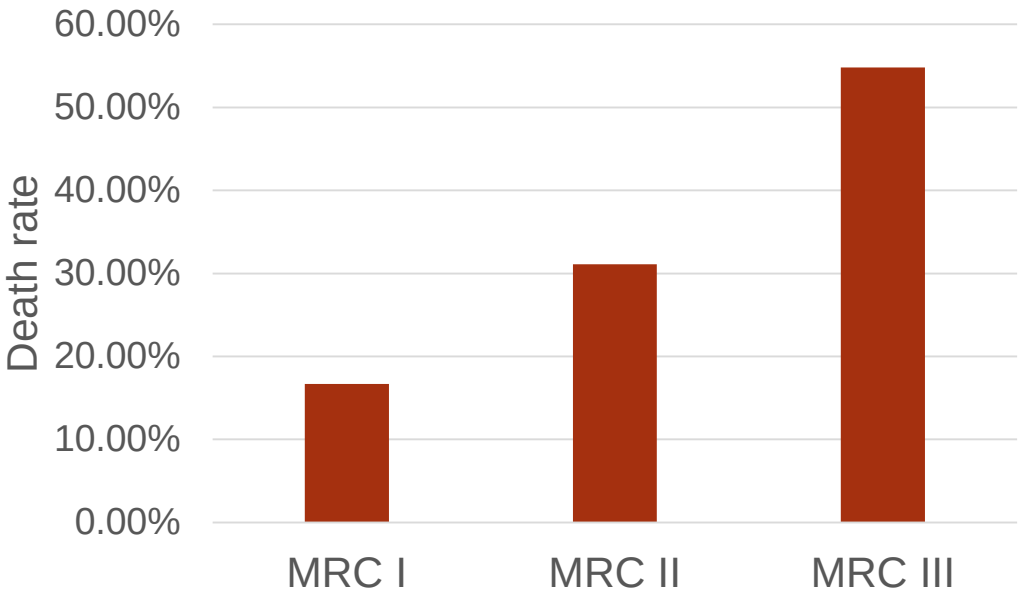
N=806

Even in developed countries like the US, the prognosis remains relatively **poor**.

Merkler A E, et al. Journal of the Neurological Sciences, 2017,375:460-463.

TBM grade of severity is associated with mortality

Grade 1	GCS of 15 with no focal neurology
Grade 2	GCS of 15 with a focal neurological deficit or a GCS of 11–14
Grade 3	GCS of ≤10



MRC grade is strongly related to survival rate.

Is current guideline rational for TBM Treatment?

Are we using the right drugs and doses?

WHO 2010: Treatment of tuberculosis guidelines(4th edition)

Intensive phase treatment	Continuation phase
2 month of HRZE	4 month of HR

(Presumed, or known, to have drug-susceptible TB)

ATS/CDC/IDSA 2016: Drug-Susceptible Tuberculosis guideline

Intensive phase treatment	Continuation phase
2 month of HRZE	7-10 month of HR

WHO. Treatment of tuberculosis: guidelines[M]. World Health Organization, 2010.
Official ATS/CDC/IDSA practice guidelines: treatment of drug-susceptible tuberculosis[J]. Clin Infect Dis, 2016,63:e147-e195.

CSF penetration of available anti-TB drugs

	Standard daily dose for adults	Estimated ratio of CSF to plasma concentration	Comments
Isoniazid	300 mg	80–90%	Essential drug; good CSF penetration throughout treatment
Rifampicin	450 mg (weight <50 kg) or 600 mg (weight ≥50 kg)	10–20%	Essential drug, despite relatively poor CSF penetration; higher doses might improve effectiveness
Pyrazinamide	1·5 g (weight <50 kg) or 2·0 g (weight ≥50 kg)	90–100%	Excellent CSF penetration throughout treatment
Ethambutol	15 mg/kg	20–30%	Poor CSF penetration once meningeal inflammation resolves
Streptomycin	15 mg/kg (1 g maximum)	10–20%	Poor CSF penetration once meningeal inflammation resolves
Kanamycin	15 mg/kg	10–20%	Poor CSF penetration once meningeal inflammation resolves
Amikacin	15–20 mg/kg	10–20%	Poor CSF penetration once meningeal inflammation resolves
Moxifloxacin	400 mg	70–80%	Good CSF penetration
Levofloxacin	1000 mg	70–80%	Good CSF penetration
p-Aminosalicylic acid	10–12 g	No data	Probably very poor CSF penetration unless meninges are inflamed
Ethionamide or protionamide	15–20 mg/kg (1 g maximum)	80–90%	Good CSF penetration
Cycloserine	10–15 mg/kg	80–90%	Good CSF penetration
Linezolid	1200 mg	40–70%	Variable interindividual CSF pharmacokinetics
Capreomycin	15–20 mg/kg	No data	..

Thwaites G E, et al. Lancet Neurol, 2013,12(10):999-1010.

Optimization of Current Treatment

Intensive strategy

High-dose of rifampicin and isoniazid

New drug combination

Fluoroquinolones

Linezolid

High-dose of rifampicin

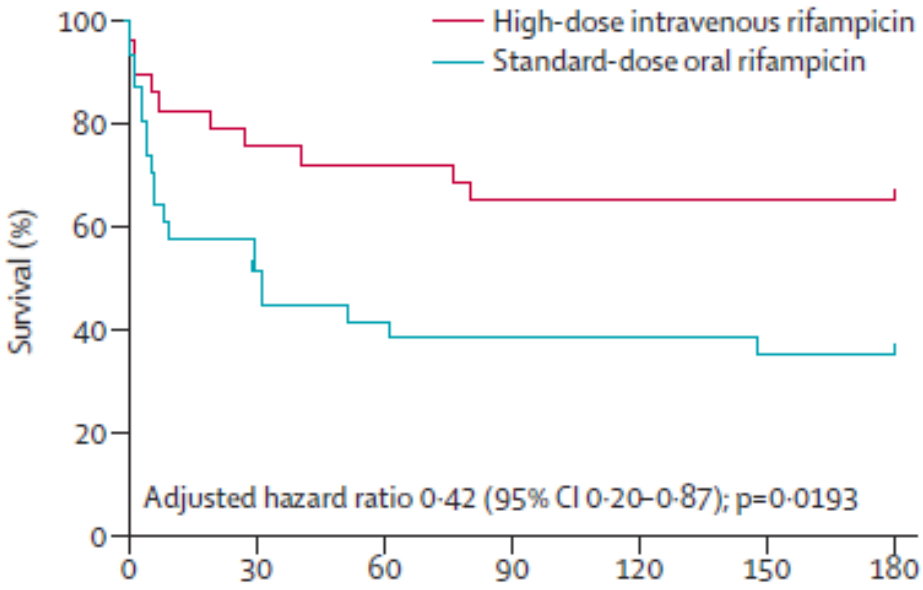
Investigation in Indonesia. 2013

Open-label, RCT trail

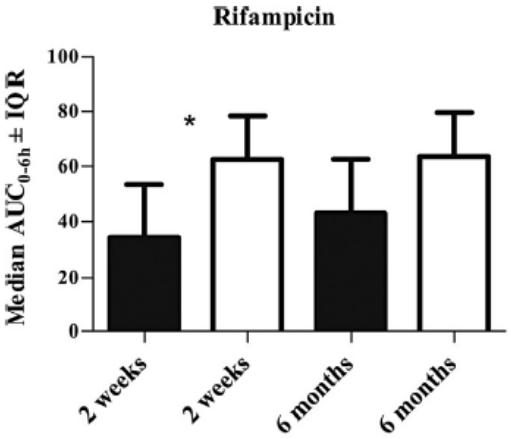
N=60

standard dose (450 mg, ~10 mg/kg) **orally**

high dose (600 mg, ~13 mg/kg) **intravenously**



	600 mg, intravenous (n=26)	450 mg, oral (n=26)	Ratio of intravenous to oral	p value
Plasma				
AUC_{0-6} (mg.h/L)	78·7 (71·0–87·3)	26·0 (19·0–35·6)	3·0 (2·2–4·2)	<0·0001*
C_{max} (mg/L)	22·1 (19·9–24·6)	6·3 (4·9–8·3)	3·5 (2·6–4·8)	<0·0001*
C_{max} (≥8 mg/L)	26 (100%)	13 (50%)	..	<0·0001†
T_{max} (h; median, range)	2 (1–2)	2 (1–6)	..	0·048‡
CSF				
C_{max} (mg/L)§	0·60 (0·46–0·78)	0·21 (0·16–0·27)	2·92 (2·03–4·20)	<0·0001*



Ruslami R, et al. Lancet Infect Dis, 2013,13(1):27-35. Te Brake L, et al. International Journal of Antimicrobial Agents, 2015,45(5):496-503.

High-dose of rifampicin

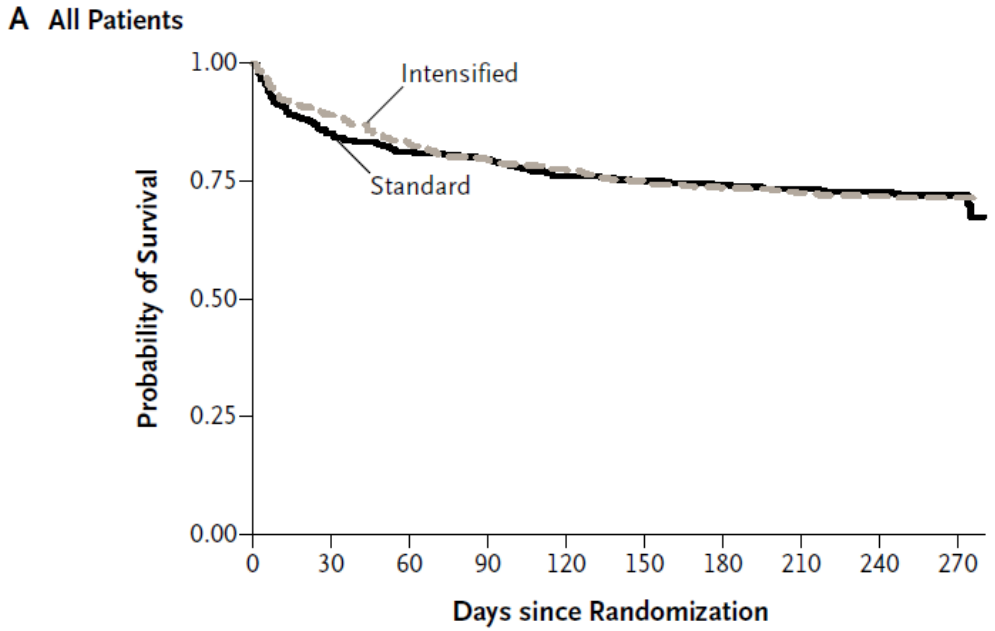
Investigation in Vietnam. 2016

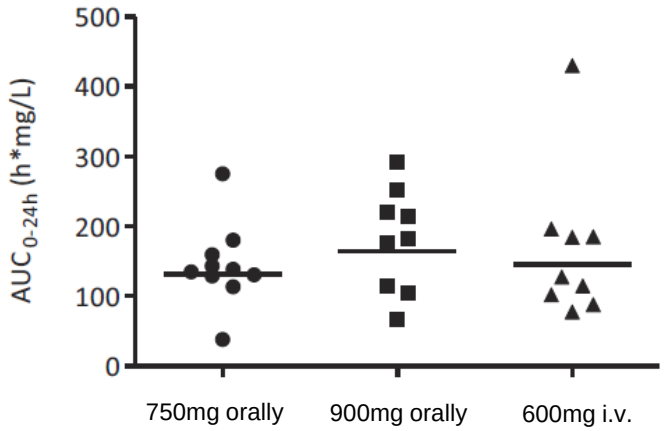
Double blind, RCT trail

N=817

Standard dose (~10 mg/kg) orally
High dose (~15 mg/kg) orally

Rifampicin CSF exposures may not have been as high as those achieved in the Indonesian study when the drug was given intravenously





Yunivita V, et al.2016

Higher oral doses of ~17 and ~20mg/kg lead to rifampicin exposures equivalent to intravenous rifampicin at ~13mg/kg

Heemskerk A D, et al. N Engl J Med, 2016,374(2):124-134. Yunivita V, et al. International Journal of Antimicrobial Agents, 2016,48(4):415-421.

Limitation of High-dose of rifampicin

May be more effective

In Vietnam study

~15mg/kg orally may not **high** enough

Potentially more toxic

Tolerability

may vary among ethnic groups

Fluoroquinolones: controversy of the dosage

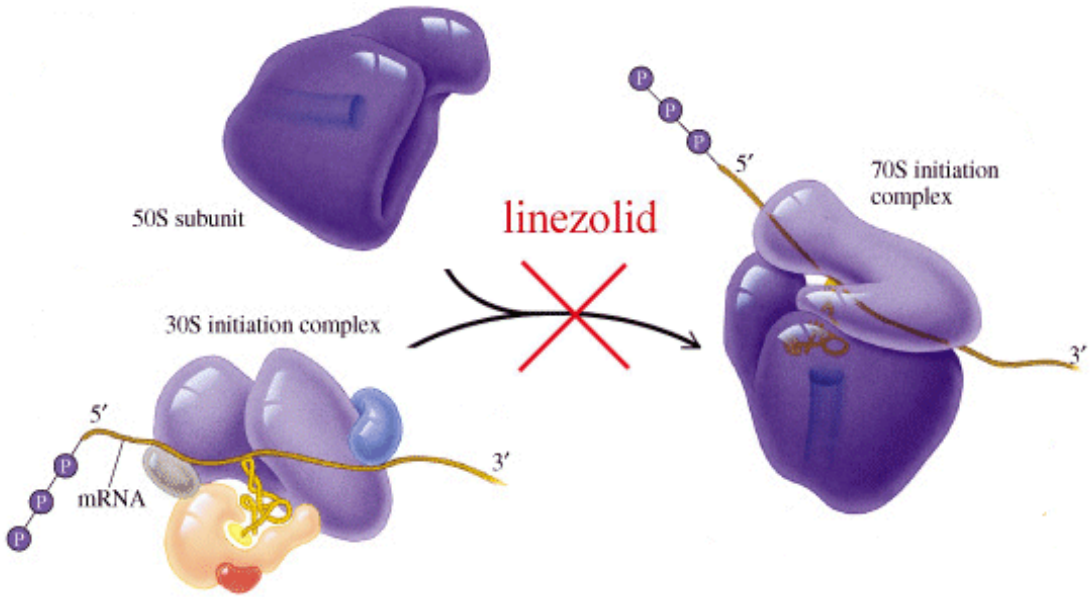
Investigation in Indonesia. 2013

No Mfx **vs** Mfx 400mg **vs** Mfx 800mg

	Deaths	Univariable	Multivariable	p value
Oral rifampicin 450 mg (n=31)	20 (65%)	1·00	1·00	0·03*
Intravenous rifampicin 600 mg (n=29)	10 (34%)	0·42 (0·20–0·91)†	0·42 (0·20–0·91)†	..
No moxifloxacin (n=22)	10 (45%)	1·00	1·00	0·55‡
Moxifloxacin 400 mg (n=19)	8 (42%)	0·74 (0·29–1·89)§	0·76 (0·30–1·94)§	..
Moxifloxacin 800 mg (n=19)	12 (63%)	1·40 (0·60–3·25)§	1·27 (0·53–3·02)§	..
HIV positive (n=7)	4 (57%)	..	1·80 (0·59–5·53)	0·31
Glasgow Coma Scale at baseline	..	..	0·82 (0·68–0·99)	0·04

Ruslami R, et al. Lancet Infect Dis, 2013,13(1):27-35. Heemskerk A D, et al. N Engl J Med, 2016,374(2):124-134.

Intensified regimens with Linezolid



Oxazolidinone antibiotic

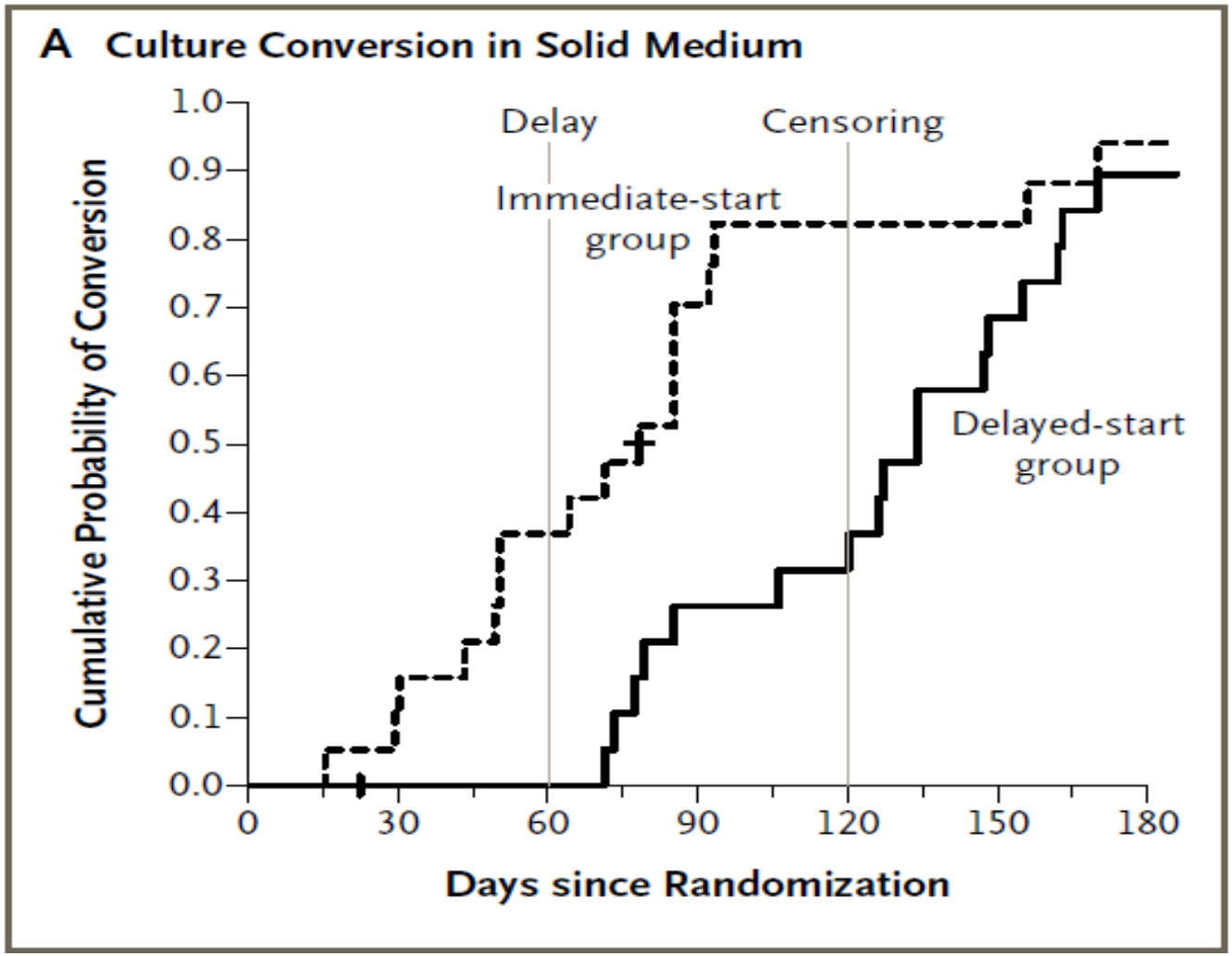
Interaction with 50S

for use against G+ bacteria, including MRSA and VRE

oral bioavailability is approximately 100%

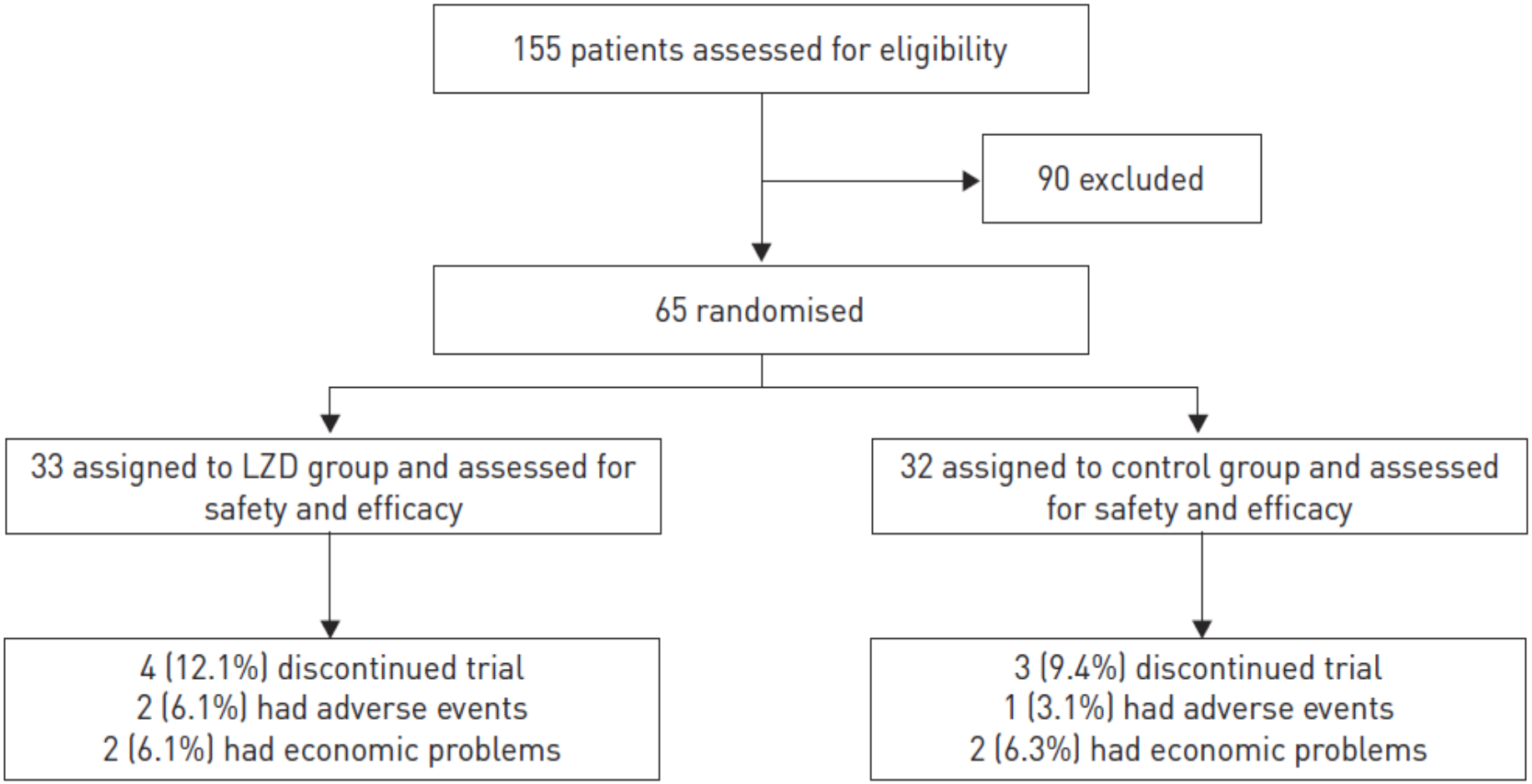
allowing a shift from the intravenous route to the oral route without dose adjustment

Linezolid for XDR-TB



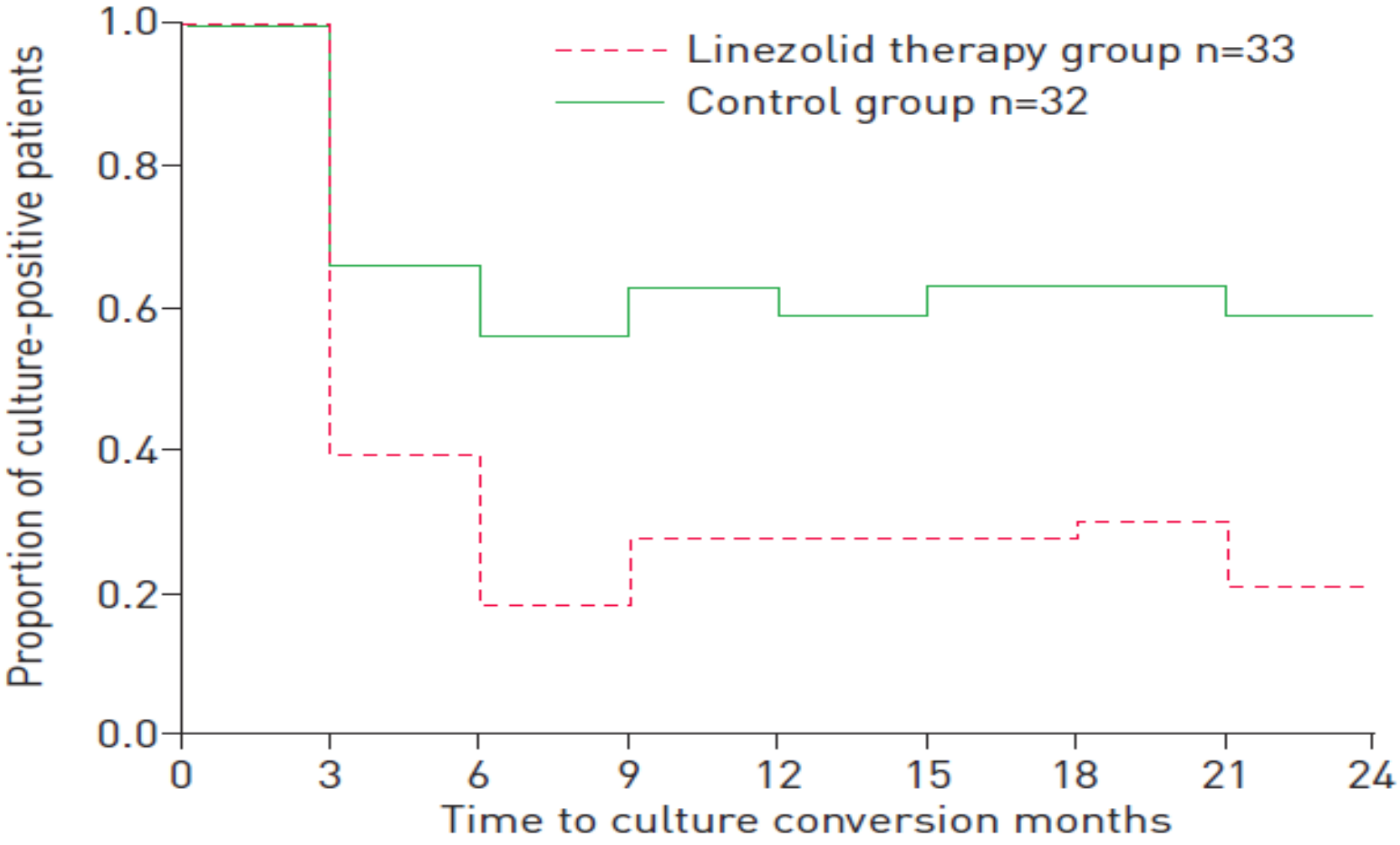
Lee, M., et al. New England Journal of Medicine, 2012. 367(16): p. 1508-1518.

Efficiency, safety and tolerability of linezolid for the treatment of XDR-TB: a study in china

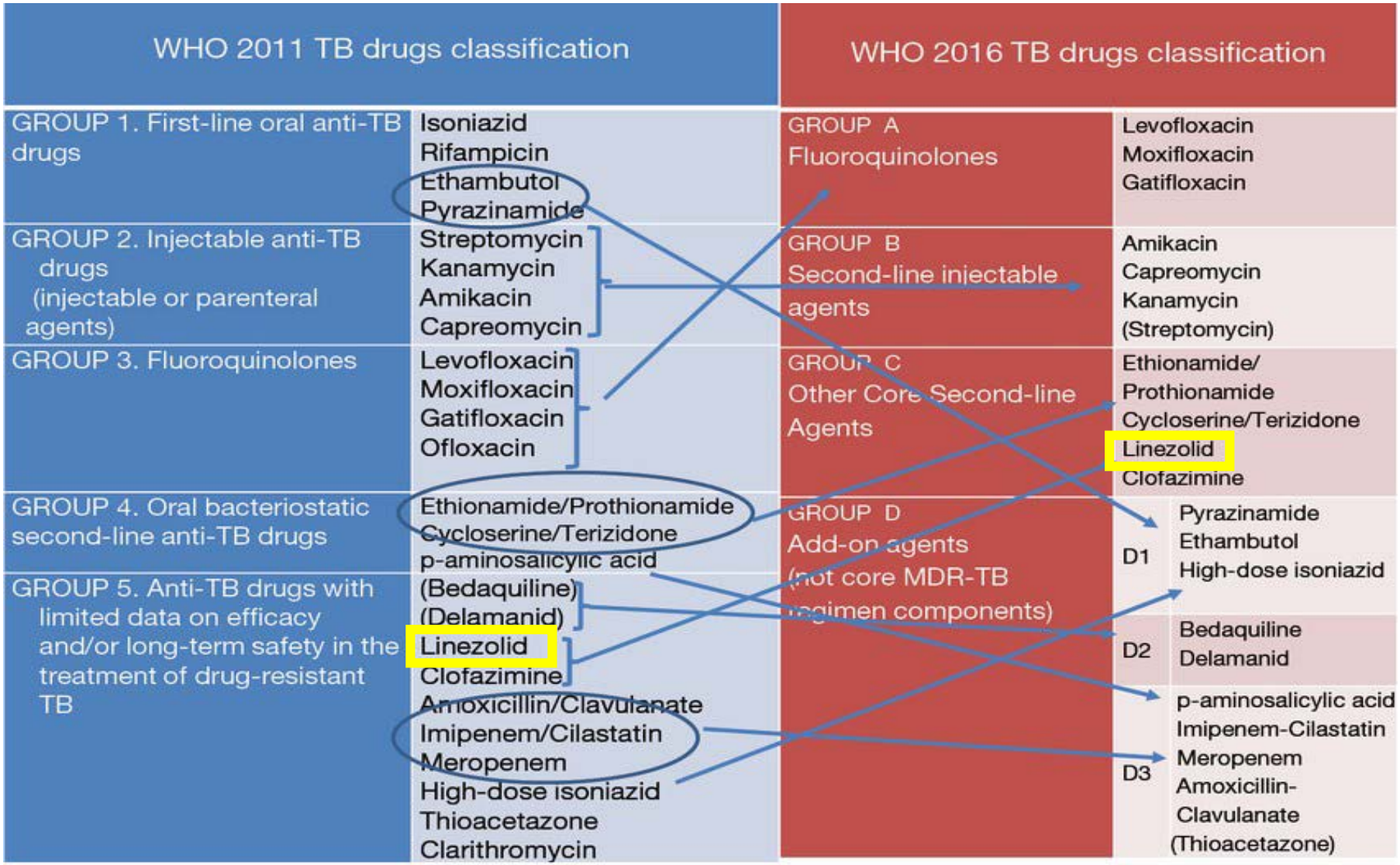


Eur Respir J 2014;

High Culture Conversion with Linezolid treatment



LZD: for limited data to core agents



WHO. WHO treatment guidelines for drug-resistant tuberculosis 2016 update[J]. 2016.
Rendon A, et al. Journal of Thoracic Disease, 2016, 8(10): 2666..

PK/PD of LZD in CSF

Myrianthefs, P., et al. 2006

14 neurosurgical patients given linezolid
at 600 mg twice daily (1h intravenous infusion)
for the treatment of CNS infections caused by gram-positive pathogens.

TABLE 3. Mean ± SD steady-state CSF linezolid pharmacokinetic variables following intravenous administration of 600 mg twice daily to critically ill neurosurgical patients[a]

Patient no.	C_{max} (μg/ml)	C_{min} (μg/ml)	T_{max} (h)	$t_{1/2}$ CSF[b] (h)	AUC_{CSF} (μg · h/ml)	Ratio of AUC_{CSF} to AUC_{serum}
3	5.9	1.2	1.5	4.9	37.7	0.7
4	6.2	1.9	1.5	6.2	46.2	0.7
5	5.7	1.9	4	5.2	46.8	0.6
7	9.3	5.1	4	9.6	88.7	0.7
8	20.4	12.7	2.5	24.8	192.6	0.7
9	16.8	10.8	2.5	13.0	171.5	0.6
10	7.8	6.3	2.5	33.3	86.8	0.6
11	8.0	5.7	2.5	62.9	77.8	0.5
14	17.5	9.6	2.5	12.4	165.9	0.7
Mean	10.8	6.1	2.6	19.1	101.6	0.7
SD	5.7	4.2	0.9	19.0	59.6	0.1

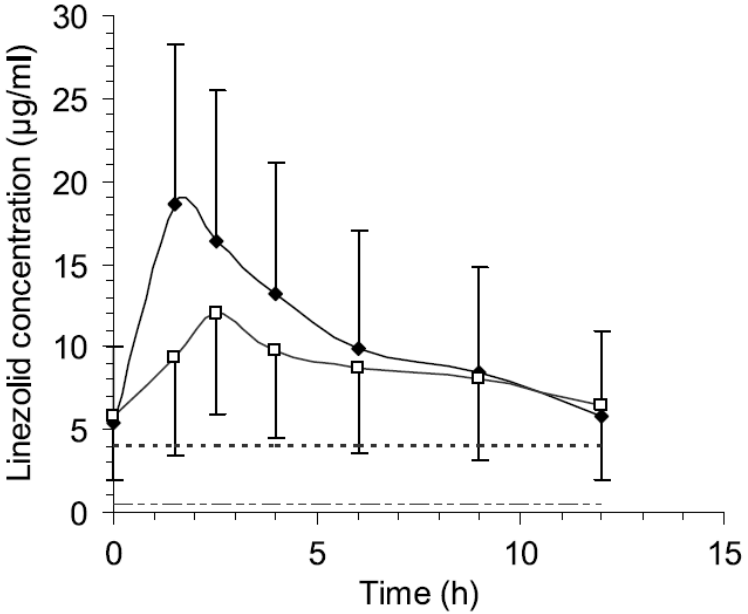


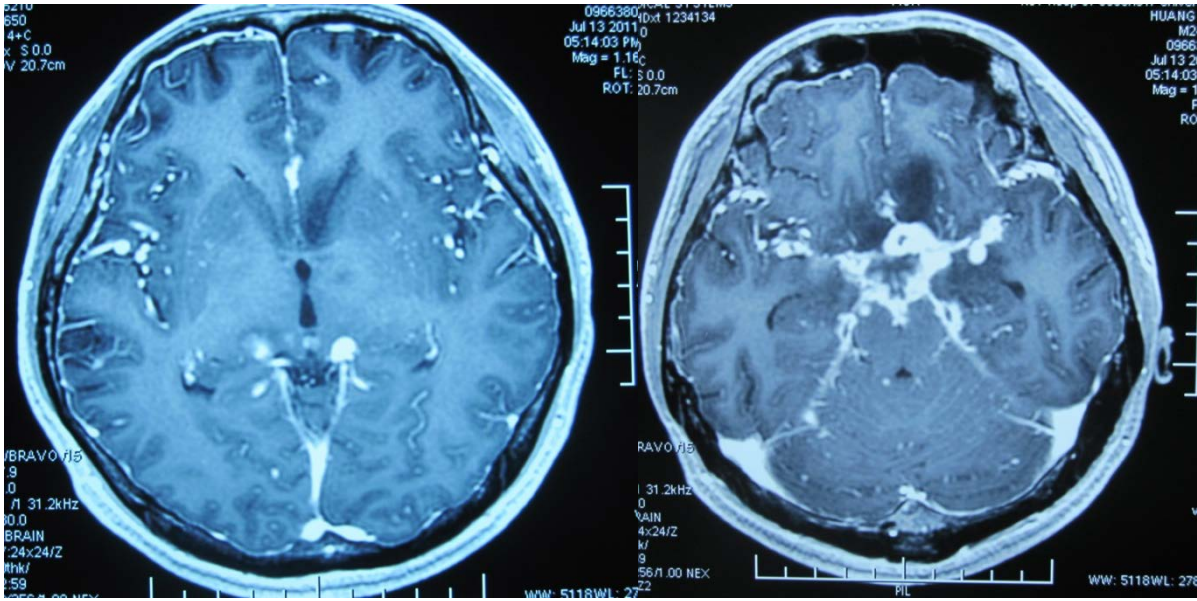
FIG. 1. Mean ± SD concentration-time profiles of linezolid in serum (◆; $n = 14$) and CSF (□; $n = 9$) after a study dose. The maximum inhibitory concentration (dotted line; 4 μg/ml) and the MIC (dashed line; 0.5 μg/ml) of linezolid for common pathogens are also shown (26).

Myrianthefs, P., et al. Antimicrobial Agents and Chemotherapy, 2006. 50(12): p. 3971-3976.

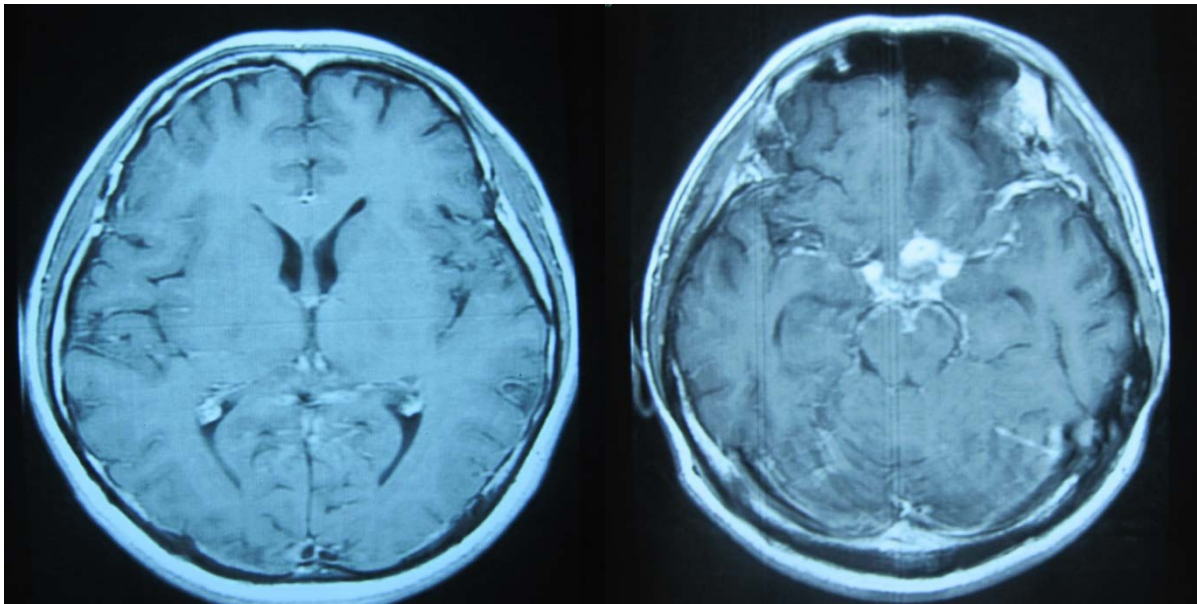
First try of LZD in DR- TBM

2011.7

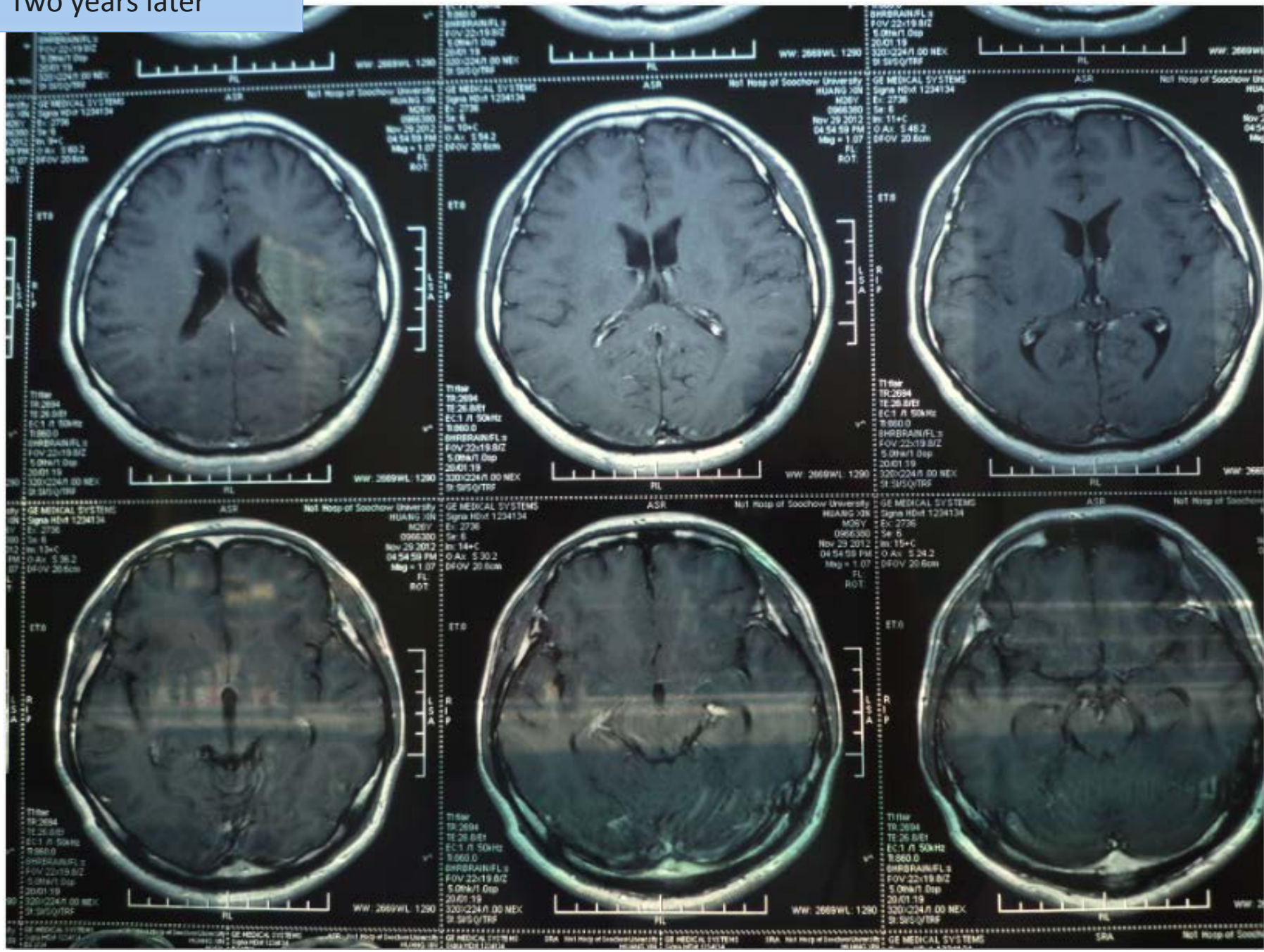
MDR-TBM
HREZ plus Linezolid
(1 month)



one month later



Two years later

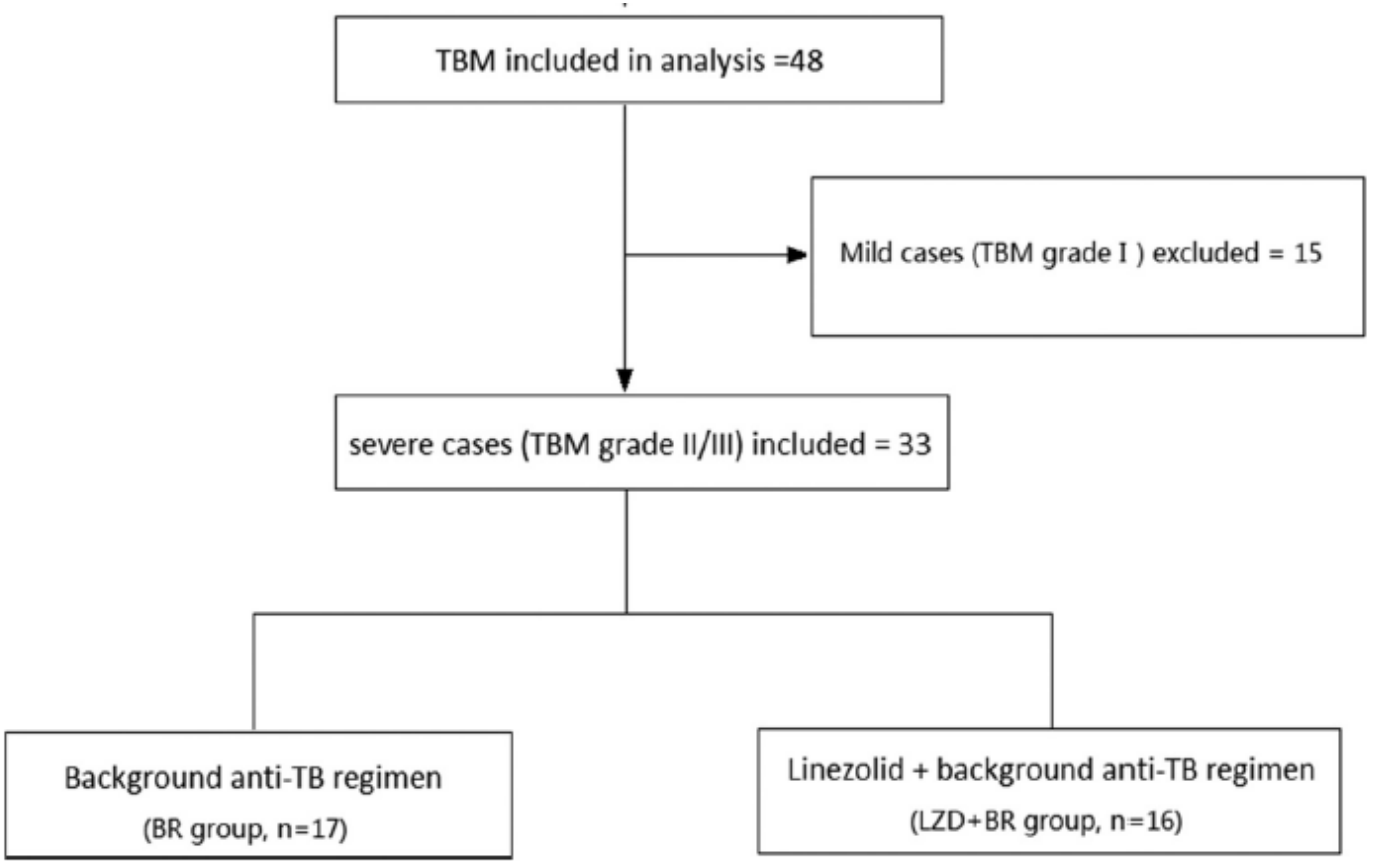


LZD in Adult TBM Patients

Huashan hospital (2010-2012)

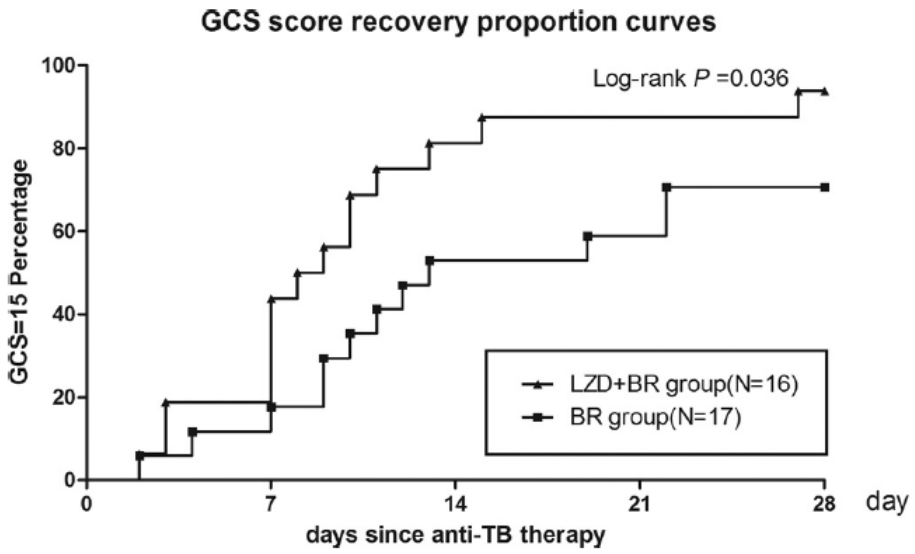
Retrospective cohort study

33 TBM patients of MRC grade II/III



Sun, F., et al. Antimicrobial Agents and Chemotherapy, 2014. 58(10): p. 6297-6301.

LZD in Adult TBM Patients



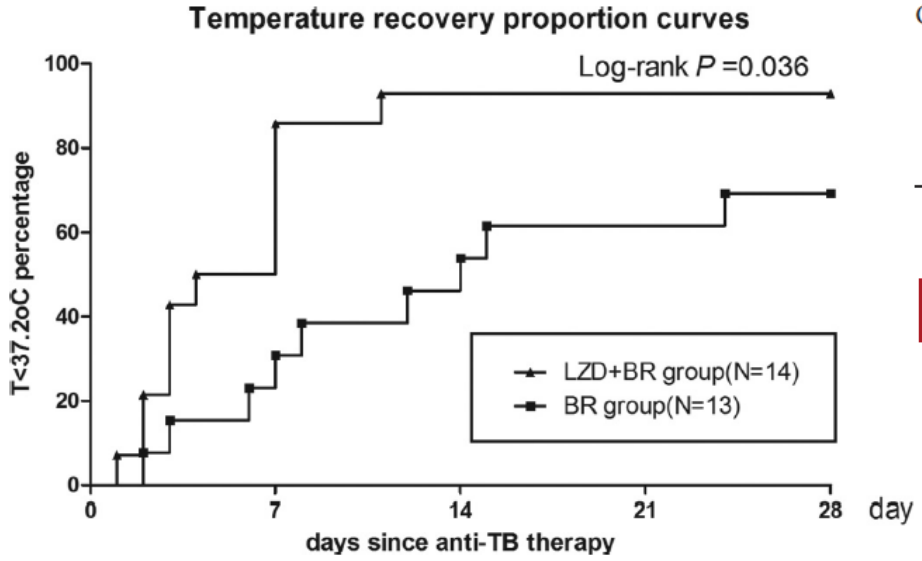


TABLE 2 Serial CSF findings in TBM patients from the LZD-BR and BR groups[a]

Finding	LZD-BR group data (median [IQR][c])	BR group data (median [IQR])	*P* value[b]
CSF/blood glucose ratio			
Baseline	0.26 (0.17–0.36)	0.28 (0.19–0.33)	0.79
After 2-wk treatment	0.29 (0.26–0.33)	0.33 (0.25–0.40)	0.35
After 4-wk treatment	0.40 (0.35–0.47)	0.34 (0.27–0.36)	0.04
CSF white blood cell count ($\times 10^6$/liter)			
Baseline	110 (50–255)	130 (52–250)	0.97
After 2-wk treatment	42 (9–80)	86 (25–120)	0.14
After 4-wk treatment	17 (8–40)	42 (23–105)	0.02
CSF protein concentration (g/liter)			
Baseline	2.23 (1.56–3.87)	1.55 (1.37–2.16)	0.10
After 2-wk treatment	1.44 (1.21–2.13)	1.33 (0.95–1.75)	0.55
After 4-wk treatment	1.07 (0.64–1.81)	1.41 (0.73–1.62)	0.52

Result

Short-term LZD supplementation may be a more effective treatment for life-threatening TBM

LZD in Childhood TBM Patients

Beijing Children's Hospital

Retrospective cohort study

86 childhood TBM patients younger than 15 years old

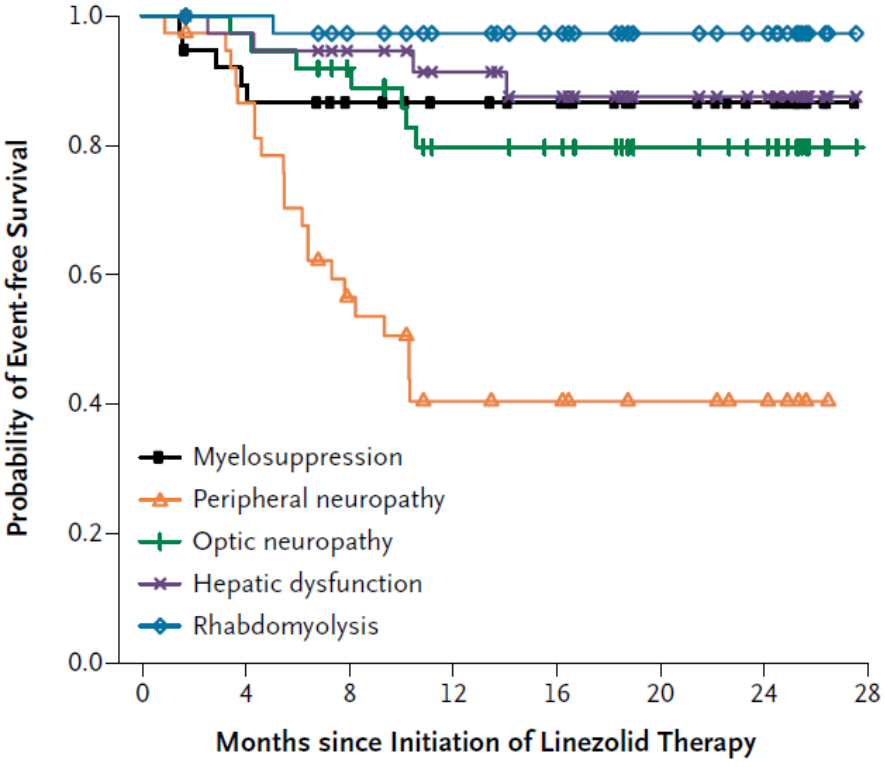
LZD was administrated as the **supplementary drug** when the patients were treated by HRZ/HRZE for more than 2 weeks but their fever and neural symptoms had no improvement.

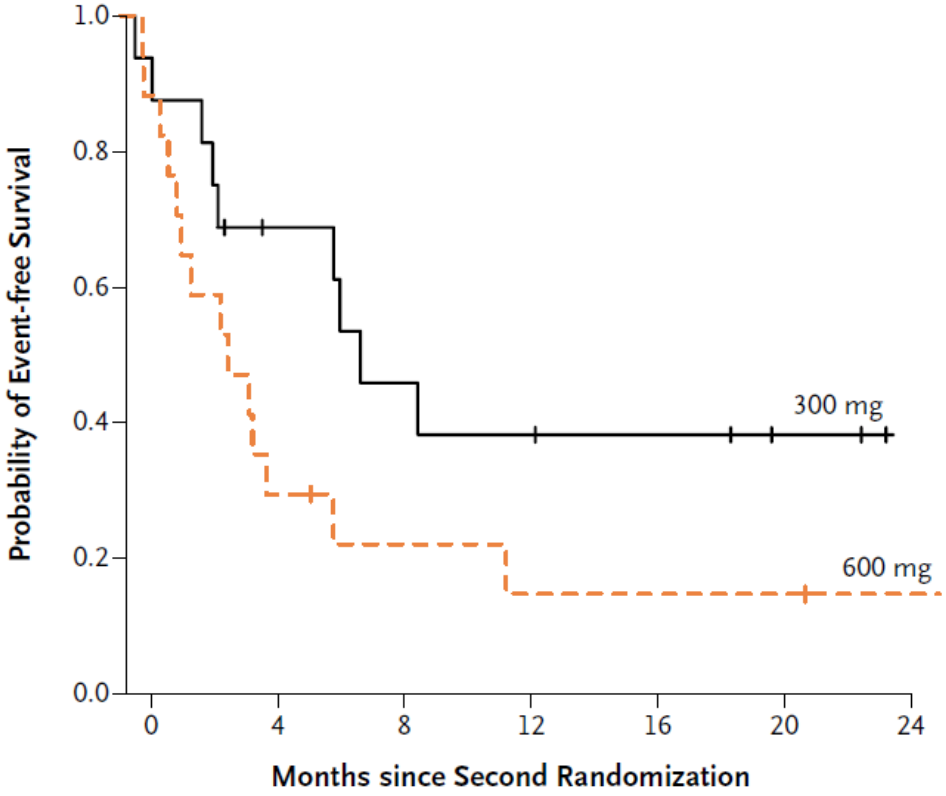
TABLE 3. Clinical Outcomes According to Different Treatment Regimens

Outcome and Group	Linezolid Group (n=36), No. (%)	Control Group (n=50), No. (%)	Relative Risk (95% Confidence Interval)	*P*
Outcome				
Favorable	32 (88.9)	35 (70.0)	1.00	—
Poor	4 (11.1)	15 (30.0)	3.43 (1.03–11.41)	0.037
Fever clearance time (wk)				
<1	18 (50.0)	6 (12.0)	1.00	—
1–4	12 (33.3)	18 (36.0)	4.50 (1.39–14.61)	0.010
>4	6 (16.7)	26 (52.0)	13.00 (3.61–46.82)	0.000
Duration time for hospital stays (mo)				
≤2	32 (88.9)	25 (50.0)	1.00	—
>2	4 (11.1)	25 (50.0)	8.00 (2.46–25.98)	0.000
Adverse event				
Yes	12 (33.3)	16 (32.0)	1.00	—
No	24 (66.7)	34 (68.0)	1.06 (0.43–2.65)	0.896

Li H, et al. The Pediatric infectious disease journal, 2016.

ADRs of LZD is depended on the dosage: 0.3 vs 0.6 qd





Lee, M., et al. New England Journal of Medicine, 2012. 367(16): p. 1508-1518.

ADRs of LZD 0.6 qd vs 0.6 bid

Migliori G B, et al. 2009

Retrospective cohort

195 MDR/XDR-TB patients

85 were treated with linezolid for a mean of 221 days.

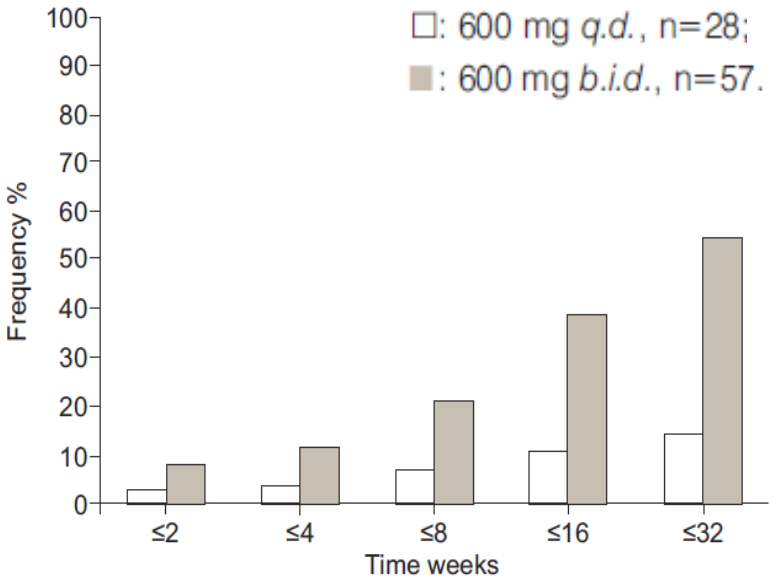


TABLE 1 Safety and tolerability of linezolid in patients treated for multidrug-resistant/extensively drug-resistant tuberculosis in Belarus, Germany, Italy and Switzerland, 2001–2007

	Total	600 mg *q.d.*	600 mg *b.i.d.*	p-value#
Patients				
Total n	85	28	57	
No adverse event	50 (58.8)	24 (85.7)	26 (45.6)	0.0004
Any adverse event	35 (41.2)	4 (14.3)	31 (54.4)	0.0004
Minor	8 (9.4)	0	8 (14)	
Major	27 (31.8)	4 (14.3)	23 (40.4)	0.01
Episodes				
Total n	52	5	47	
Anaemia	23 (44.2)	3 (60)	20 (42.5)	0.44
Thrombocytopenia	7 (13.5)	0 (0)	7 (14.9)	
Nausea/vomiting	4 (7.7)	1 (20)	3 (6.4)	0.25
Polyneuropathy	3 (5.8)	1 (20)	2 (4.3)	0.13
Others	15 (28.8)	0 (0)	15 (31.9)	

Data are presented as n (%), unless otherwise stated. #: comparison between 600 mg *q.d.* group and 600 mg *b.i.d.* group.

Migliori G B, et al. European Respiratory Journal, 2009,34(2):387-393.

Adverse events of LZD is associated with duration and dosage

Haematologic toxicities

Thrombocytopenia
Anemia

Reversible with cessation of drug or with lowering the dose of drug

Optic neuropathy
Lactic acidosis

Medical emergency

Reversible with cessation

Peripheral neuropathy

May or may not improve with cessation of drug.

In ~1/3 of TBM patients using LZD at 600mg bid for more than 2 month.

May or may not >90% of them did not resolve after at least 1 year of cessation

LZD for TBM: future treatment options

LZD

Solid effect against Mtb

Good CSF penetration

Dramatic therapeutic effect in severe cases

ADRs relates to dosage and duration

Indications

MRC grade II/III
No responding to traditional treatment

Dosing

600mg bid or 600mg qd

Duration of treatment

< 2 months

Acknowledgement

華山感染