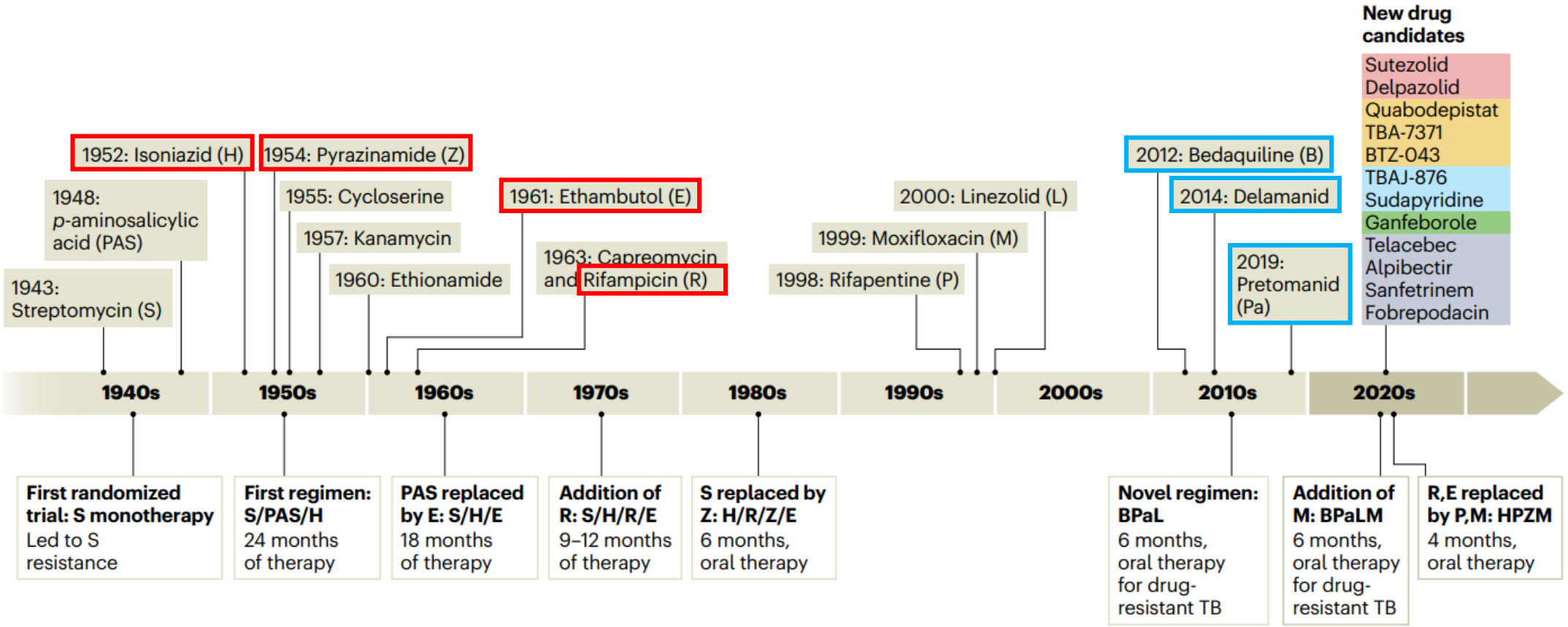
Management of adverse events in TB treatment

2025.3.27

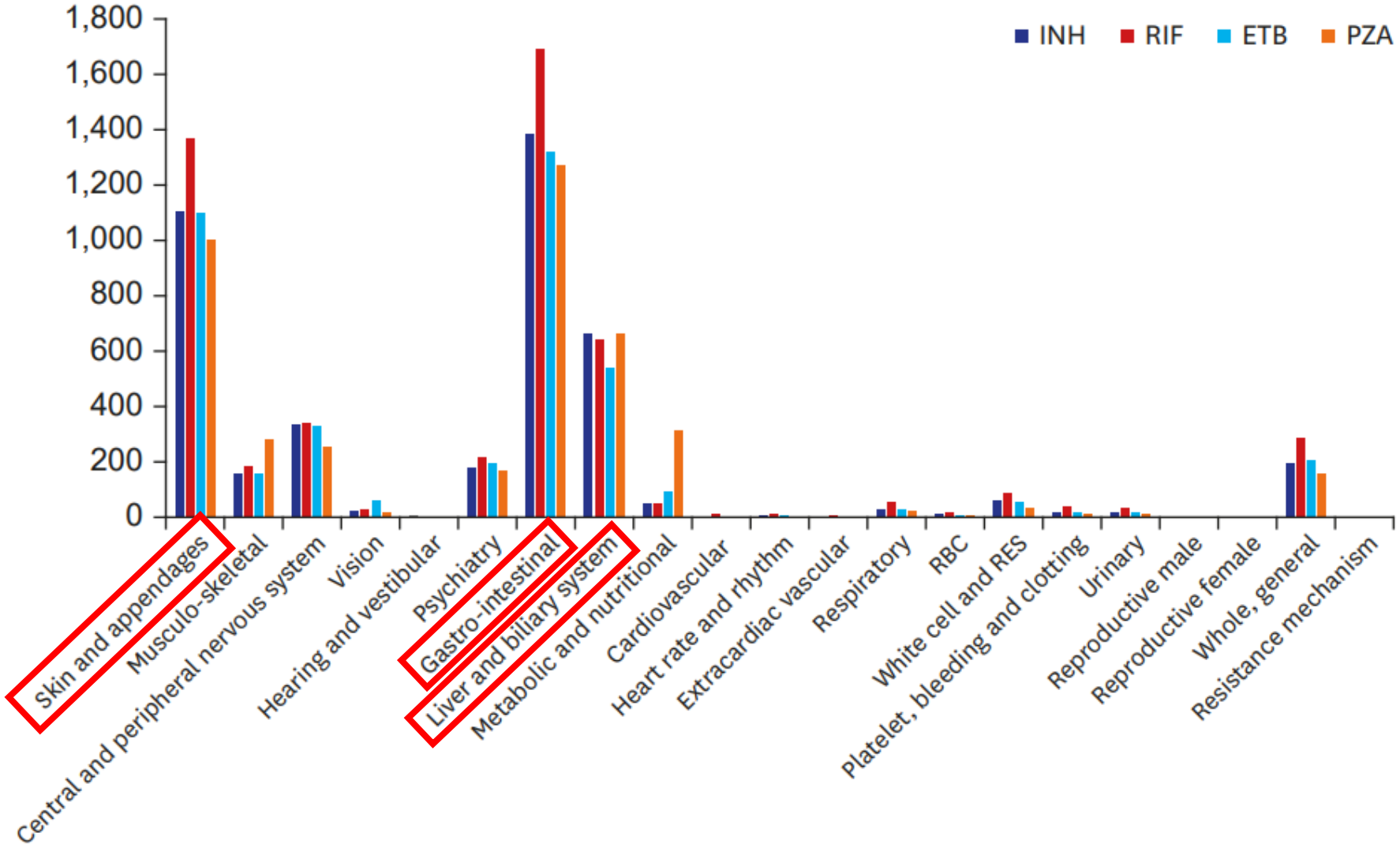
부산대학교병원 김새롬



EL Nuermberger et al. Nat Med. 2024 Mar;30(3):642-643.

DS-TB medication adverse reactions

Chung SJ et al. J Korean Med Sci. 2022 Apr 25;37(16):e128



Chung SJ et al. J Korean Med Sci. 2022 Apr 25;37(16):e128

Isoniazid

- 간독성
- 말초 신경염 : 신경전달물질 합성의 보조인자인 피리독신과 경쟁적으로 작용
- Drug-induced lupus erythematosus

Rifampin

- 간에서 대사, 담즙으로 배설 : 초기 일시적인 혈중 빌리루빈 증가
- 위장장애, 발열, 발진
- 혈소판 감소성 자반증, 급성 신부전, 급성 용혈성 빈혈, 무과립구증 (재투여 금기)

Variables	Overall N = 114	Favorable response n = 92	Unfavorable response n = 22	*P*
Adverse reactions to rifampicin				
Hepatotoxicity	68 (59.6)	55 (59.8)	13 (59.1)	> 0.999
Skin rash/Pruritus	62 (54.4)	51 (55.4)	11 (50.0)	0.825
Gastrointestinal discomfort	58 (50.9)	45 (48.9)	13 (59.1)	0.535
Fever	33 (28.9)	29 (31.5)	4 (18.2)	0.328
Blood cell count abnormality	17 (14.9)	14 (15.2)	3 (13.6)	> 0.999
Headache/Dizziness	15 (13.2)	13 (14.1)	2 (9.1)	0.782
General weakness	11 (9.6)	8 (8.7)	3 (13.6)	0.762
Renal injury	4 (3.5)	4 (4.3)	0 (0.0)	0.726

Kim HJ et al. Sci Rep. 2023 Jul 12;13:11275

Supplementary Table 3. The detailed representative treatment regimen for the intensive phase

Variables	Overall N = 114	Favorable response n = 92	Unfavorable response n = 22
HEZQ	25 (21.9)	23 (25.0)	2 (9.1)
HEQ	22 (19.3)	18 (19.6)	4 (18.2)

- The median duration of treatment : 10.2 months (four-drug or three-drug regimen)
- The recurrence rate : 2.2% with a median follow-up of 3.4 years.

Kim HJ et al. Sci Rep. 2023 Jul 12;13:11275

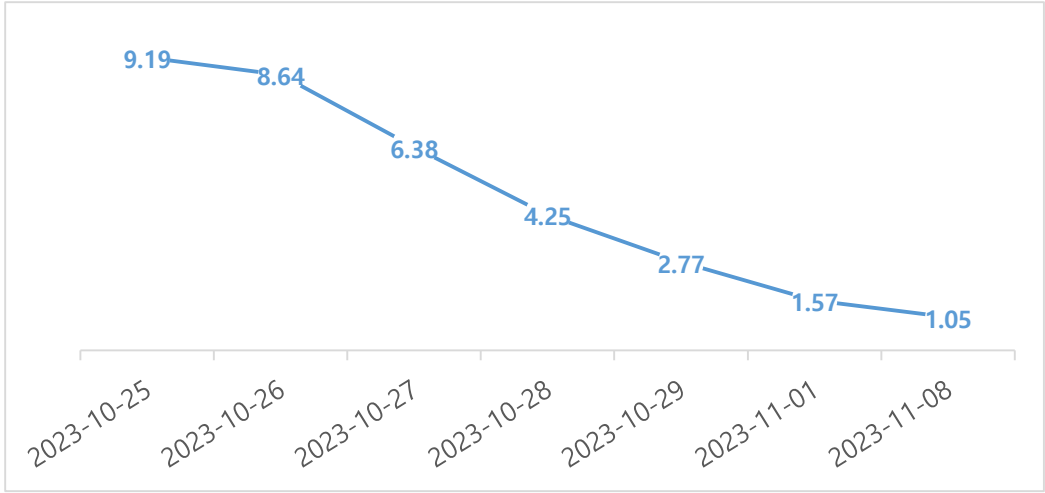
M/80

AFB stain (+), x-pert(+) 로 내원 → 2023-09-14 HREZ

2023-09-14 (치료 시작 전)	
BUN	11.2 mg/dL
Creatinine	1.14 mg/dL
GFR	62 mL/min/1.73m^2

2023-10-12 (치료 1개월 후)	
BUN	13.2 mg/dL
Creatinine	1.17 mg/dL
GFR	60.1 mL/min/1.73m^2

2023-10-24 (ER 내원)	
BUN	57.8 mg/dL
Creatinine	9.49 g/dL
GFR	5.4 mL/min/1.73m^2



진료일자 : 2023/10/24

진 료 과 : 응급의학과

[주호소]

1. general weakness
2. vomitting
3. diarrhea

[현병력]

현병력 : 상기환자 분 DM, MI, Tb 병력 있고 본원 호흡기내과에서 결핵약 복용 중인 분으로 20일부터 구토, 물설사 지속되며 식이가 잘 안되어 어제부터 general weakness 보여 본원 응급실로 내원함. 결핵약 복용하면서 오심, 구토 증상 지속됨. 구토는 한차례, 물설사는 하루 3차례 정도 봤다고 함.

Ethambutol

- 신장 배설
- 시신경염(optic neuropathy)

  : 2개월 이후 발생, 드물게 초기 발생 가능
- 말초 신경병증
- 간독성
- Drug eruption
- Psychosis

Table 2. Estimated prevalence of ethambutol-induced optic neuropathy at various doses

Ethambutol dose (mg/kg per day)	Estimated prevalence (%)
≤15	Less than 1 [9▪▪]
20	3 [9▪▪,14]
25	5–6 [9▪▪,13]
>35	18–33 [12,14]

Curr Opin Ophthalmol 2017 Nov;28(6):545-551.

Ethambutol

Table 3. Adjusted ORs for EON in relation to hypertension, diabetes, and renal diseases

Hypertension	Diabetes	Renal diseases	Controls (n = 11,485)	EON cases (n = 2,703)	Adjusted OR[a] (95% CI)	*P* value
-	-	-	5,962	1,227	Ref (1.00)	
-	-	+	18	9	2.44 (1.09–5.44)	0.030
-	+	-	1,068	288	1.3 (1.12–1.50)	< 0.001***
-	+	+	23	6	1.27 (0.52–3.12)	0.605
+	-	-	1,911	458	1.17 (1.04–1.32)	0.012*
+	-	+	73	26	1.73 (1.10–2.72)	0.017*
+	+	-	2,185	556	1.24 (1.11–1.38)	< 0.001***
+	+	+	245	133	2.63 (2.11–3.27)	< 0.001***

OR = odds ratio, EON = ethambutol-induced optic neuropathy, CI = confidence interval.

[a]Adjusted for age and sex.

*$P < 0.05$, ***$P < 0.001$.

J Korean Med Sci. 2025 Jun 2;40(21):e65

Pyrazinamide

- 간 대사, 대사 산물은 신장으로 배설
- 간독성
- 관절통 (요산 농도와 관계없이 발생 가능)
  - 비스테로이드계 소염제 등으로 증상 조절
  - 무증상 요산 농도 증가시 요산 저해제 사용 필요하지 않으나, 통풍 발생시 중단
- Hyperuricemia
- Flushing, photosensitivity
- 위장장애

Table 2. Types and onset time of severe adverse events due to PZA.

Variables	No. patients (%)	Time of onset (days, IQR)
Total	227 (100.0)	22.0 (14.0–42.0)
Hepatotoxicity	101 (44.5)	27.0 (14.0–47.5)
GI intolerance	54 (23.8)	18.0 (11.8–33.8)
Cutaneous adverse reactions	36 (15.9)	19.5 (12.0–37.3)
Arthropathy	27 (11.9)	42.0 (21.0–59.0)
Others[†]	9 (4.0)	15.0 (12.5–18.5)

Kwon BS, et al. PLoS One. 2020. Jul 21;15(7):e0236109

Table 3. Risk factors for the occurrence of severe adverse events due to pyrazinamide.

Variables	Univariate			Multivariate		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age (year)	1.019	1.012–1.027	<0.001	1.013	1.004–1.023	0.007
Sex, Male (%)	0.910	0.693–1.196	0.500	1.245	0.881–1.760	0.214
Chronic liver disease	0.868	0.367–2.051	0.747	0.944	0.398–2.240	0.896
DM	1.450	0.963–2.182	0.075	1.039	0.628–1.719	0.883
Renal insufficiency	1.817	0.621–5.321	0.276			

Kwon BS, et al. PLoS One. 2020. Jul 21;15(7):e0236109

Variables	Total, n = 390	Without PZA, n = 34 (8.7%)	With PZA, n = 356 (91.3%)	*P* value
Age, years	75.49 ± 7.12	79.35 ± 7.18	75.13 ± 7.01	0.001

Variables	Total, n = 390	Without PZA, n = 34 (8.7%)	With PZA, n = 356 (91.3%)	*P* value
Treatment Success, n (%)	342 (87.7)	22 (64.7)	320 (89.9)	<0.001
PZA use time, median days (IQR)	61 (55–66)	0 (0–7)	62 (56–67)	<0.001
Treatment duration, median days (IQR)	190 (182–254)	272 (230–280)	189 (182–245)	<0.001
SAEs, n (%)	98 (25.1)	14 (41.2)	84 (23.6)	0.024
Time to first SAE, median days (IQR)	31 (14–74)	28 (21–52)	32 (14–85)	0.994

Yoon JY, et al. PLoS One 2024 Sep 26;19(9):e0309902.

DR-TB medication adverse reactions

약제내성 결핵 치료

퀴놀론 감수성 MDR/RR-TB

6개월 BPaLM 요법

or 9개월 MDR-END 요법

→ 18-20개월 장기요법

퀴놀론 내성 MDR/RR-TB → 6개월 BPaL 요법 → 18-20개월 장기요법

6개월 BPaL(M)

베다퀼린 (B)	첫 2주간 400mg 하루 한번 매일 복용 이후 나머지 전체 치료 기간 200mg 하루 한번 주 3회 복용
프레토마니드(Pa)	전체 치료 기간 200mg 하루 한번 매일 복용
리네졸리드(L)	전체 치료 기간 600mg 하루 한번 매일 복용
목시플록사신(M)	전체 치료 기간 400mg 하루 한번 매일 복용

- 총 치료기간 26주 (6개월)
- 전체 약제 1주 이상 복용하지 않은 경우, 해당 기간만큼 복용 보충 (단, 치료 연장 기간은 4주를 초과하지 않음)

9개월 MDR-END

레보플록사신	전체 치료 기간 750mg 하루 한번 매일 복용 (체중 50kg 이하) 전체 치료 기간 1,000mg 하루 한번 매일 복용 (체중 50kg 초과)
델라마니드	전체 치료 기간 100mg 하루 두 번 매일 복용 (총 용량 : 하루 200mg)
리네졸리드	첫 2개월간 600mg 하루 한번 매일 복용 이후 나머지 전체 치료 기간 300mg 하루 한번 매일 복용
피라진아미드	전체 치료 기간 1,000mg 하루 한번 매일 복용 (체중 50kg 미만) 전체 치료 기간 1,500mg 하루 한번 매일 복용 (체중 50-70kg) 전체 치료 기간 2,000mg 하루 한번 매일 복용 (체중 70kg 초과)

- 총 치료기간 40주 (9개월)
- 결핵균 배양음전이 치료 시작 후 3-6개월 사이에 이루어지는 경우, 전체 치료기간 3개월 연장 (총 52주)

Bedaquiline (베다퀼린,서튜러정)

- ATP synthase 억제
- 첫 2주간 400mg 하루 한번 매일 복용
  이후 나머지 전체 치료 기간 200mg 하루 한번 주 3회 복용
- Nausea, arthralgia (joint pain), headache (~10%)
- QTc prolongation
- Hyperuricaemia, phospholipidosis , elevated transaminase (early signal for risk of pancreatitis)

Adverse event occurring in ≥20% of patients — no. (%)	Bedaquiline (N=79)	Placebo (N=81)
Nausea	32 (41)	30 (37)
Arthralgia	29 (37)	22 (27)
Vomiting	23 (29)	22 (27)
Headache	23 (29)	18 (22)
Hyperuricemia	20 (25)	27 (33)
Hemoptysis	16 (20)	14 (17)

Diacon AH, et al. N Engl J Med 2014;371:723-732

Table S4. Grade 3 or 4 treatment-emergent laboratory abnormalities[6] in the overall treatment phase occurring in ≥5% of patients in either treatment group in the intent-to-treat population.

	Bedaquiline*	Placebo
Incidence – No. (%)	**(N=78†)**	**(N=81)**
Hyperuricemia	30 (38.5)	30 (37.0)
Increased white blood cell count	11 (14.1)	5 (6.2)
Increased aspartate aminotransferase	9 (11.5)	4 (4.9)
Increased gamma glutamyl transferase	7 (9.0)	3 (3.7)
Increased alanine aminotransferase	6 (7.7)	2 (2.5)
Increased plasma prothrombin time	5 (6.4)	5 (6.2)
Hyperglycemia	4 (5.1)	5 (6.2)
Increased pancreatic amylase	4 (5.1)	1 (1.2)

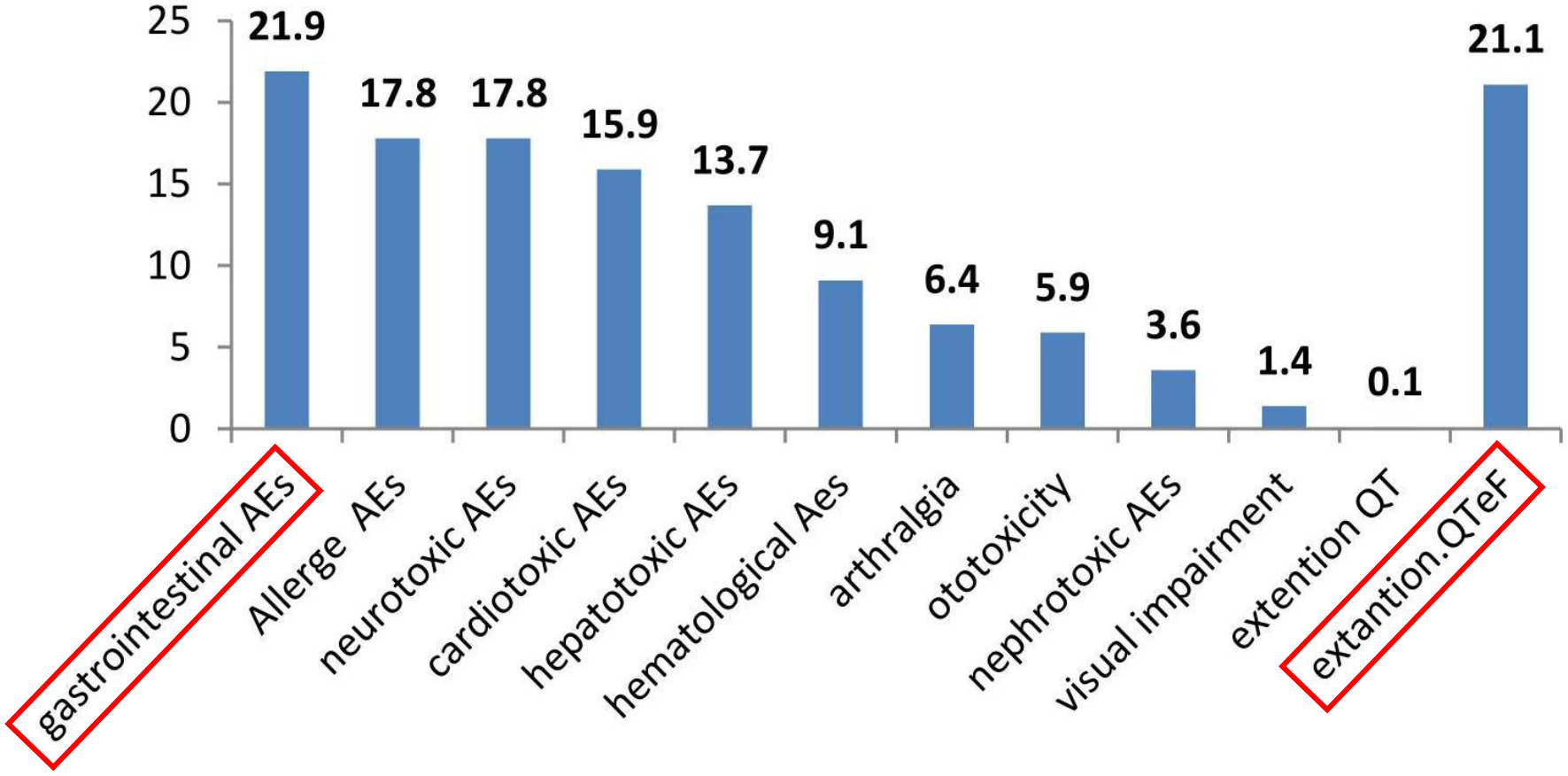
Diacon AH, et al. N Engl J Med 2014;371:723-732

- The mean change from baseline in the **QTcF**
  - increase of 15.4 msec in the **bedaquiline** group
  - increase of 3.3 msec in the placebo group (P<0.001)

- No direct relationship was seen between bedaquiline or the bedaquiline metabolite (M2) plasma level and corresponding absolute QTcF values or changes in the QTcF.

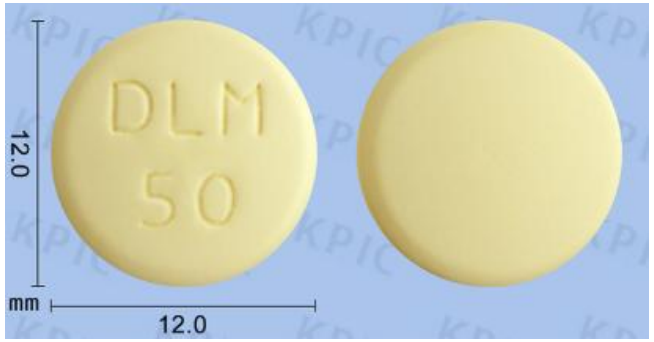
- No reports of clinically significant arrhythmia during the trial.

Diacon AH, et al. N Engl J Med 2014;371:723-732



Starshinova A, et al. Antibiotics (Basel). 2022 Nov 14;11(11):1622.

Delamanid (델라마니드,델티바정)



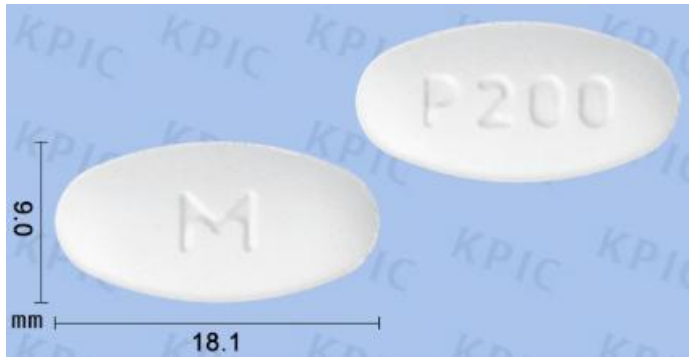
- Mycolic acid biogenesis inhibition
- 전체 치료 기간 100mg 하루 두 번 매일 복용
  (총 용량 : 하루 200mg)
- Contraindication : Albumin < 2.8 g/dL
- Nausea, vomiting, insomnia, anxiety
- QTc prolongation

Table 2. Incidence of Adverse Events (Occurring in ≥10% of Patients in Either Delamanid Group and with Greater Frequency Than in the Placebo Group).*

	Delamanid, 100 mg Twice Daily	Delamanid, 200 mg Twice Daily	Placebo
Gastrointestinal			
Nausea	58 (36.0)	65 (40.6)	53 (33.1)
Vomiting	48 (29.8)	58 (36.2)	44 (27.5)
Upper abdominal pain	41 (25.5)	36 (22.5)	38 (23.8)
Cardiovascular			
Palpitations	13 (8.1)	20 (12.5)	10 (6.2)
Prolonged QT interval on ECG	16 (9.9)	21 (13.1)	6 (3.8)
Hypokalemia	20 (12.4)	31 (19.4)	24 (15.0)

Gler MT, et al. N Engl J Med. 2012 Jun 7366(23):2151-60.

Pretomanid (프레토마니드, 도브프텔라정)



- 전체 치료 기간 200mg 하루 1회
- Headache, GI disorder (nausea), contact dermatitis, Hb level decreased, diarrhea, dizziness
- QTc prolongation, hepatotocixity, myelosuppression

Occhineri S, et al. Curr Res Pharmacol Drug Discov.2022:3:100128.
Nedelman JR, et al. Antimicrob Agents Chemother. 2020. Dec 16;65(1):e01121-20.

Nausea, vomiting

- Administer antibiotics with food
- At different time of day
- Antiemetics, acid-suppressing agents
- Mint, ginger candies

✓ Metoclopramide – administer 30 minutes before TB medications

✓ Ondansetron (or promethazine) – administer 30 minutes before TB medications and again 8 hours later

✓ Benzodiazepines (e.g. diazepam and lorazepam)

Johnson TM, et al. J Clin Tuberc Other Mycobact Dis. 2024 Jul 27:37:100470.

QTc prolongation

- QTcF >500ms, discontinue medication
- Minimization/avoidance of additional QT prolongation medications
- Correct electrolytes abnormalities (Ca, Mg, K)
- Correct underlying predisposing factors (hypothyroidism)

Johnson TM, et al. J Clin Tuberc Other Mycobact Dis. 2024 Jul 27:37:100470.

Linezolid (리네졸리드)

- 세포 내 미토콘드리아에서 단백질 합성을 방해
- Nausea, vomiting, diarrhea
- **Myelosuppression**
- **Optic nerve toxicity, peripheral neuropathy**
- Pseudomembranous colitis, vaginal candidiasis, hypoglycemia, serotonin syndrome, lactic acidosis, arrhythmia (tachycardia), transient ischemic attacks, pancreatitis, seizures

F/49

타원 TB-PCR (+) 으로 HREZ 치료 중 LPA: HR 내성

BPaLM 변경

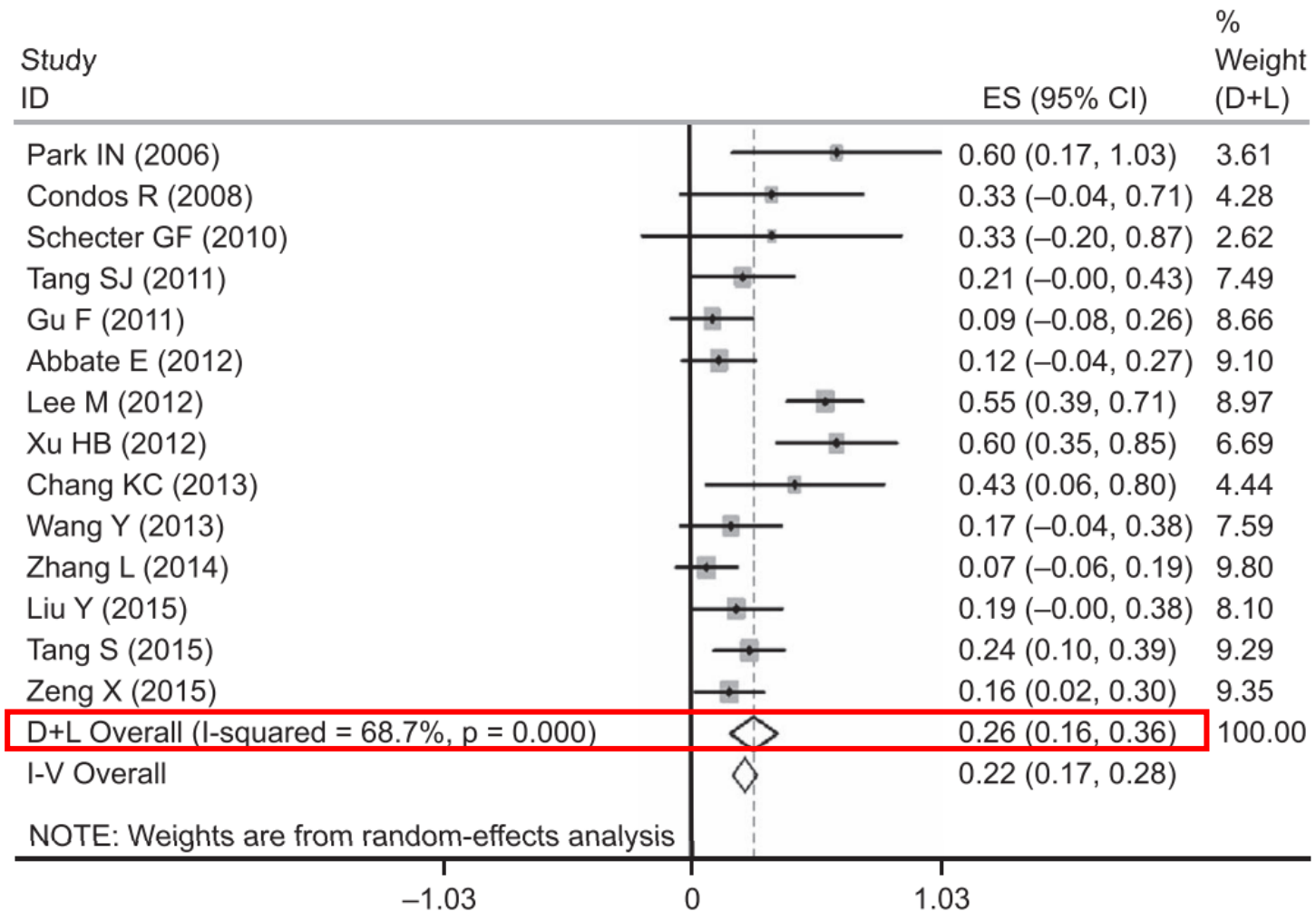
- 2주 후 nausea 호소 → prokinetics 추가
- 12주 후 "종아리 아래로 감각이 무뎌진 것 같아요", "찌릿한 느낌도 있어요 "

	BPaL(M)	MDR-END
권고 용법	• 전체 치료 기간 600mg 투여 – 용량 : 최소 첫 2개월은 600mg – 최소 누적 투약 기간: 4개월(18주)	• 첫 2개월간 600mg 투여 • 이후 나머지 치료 기간 300mg 투여
중단[#]	• 치료 시작 2개월(9주) 이내 영구 중단 허용 불가 • 전체 치료 기간 중 누적 8주를 초과하여 중단 허용 불가	• 치료 시작 2개월(9주) 이내 영구 중단 허용 불가
감량	• 치료 시작 2개월(9주) 이내 : 재심사 이후 감량 결정 • 치료 시작 2개월(9주) 이후 : 재심사 없이 감량 가능	• 치료 시점과 관계없이 감량 가능 (재심사 대상 아님)

Linezolid 300mg 으로 감량

4주 후 종아리 감각저하 진행, 발목 아래는 찌르는 느낌 → pregabalin 추가

증상 악화로 마지막 3주 linezolid 중단



Lifan Z et al. Int J Tuberc Lung Dis. 2019 Dec 1; 23(12):1293-1307

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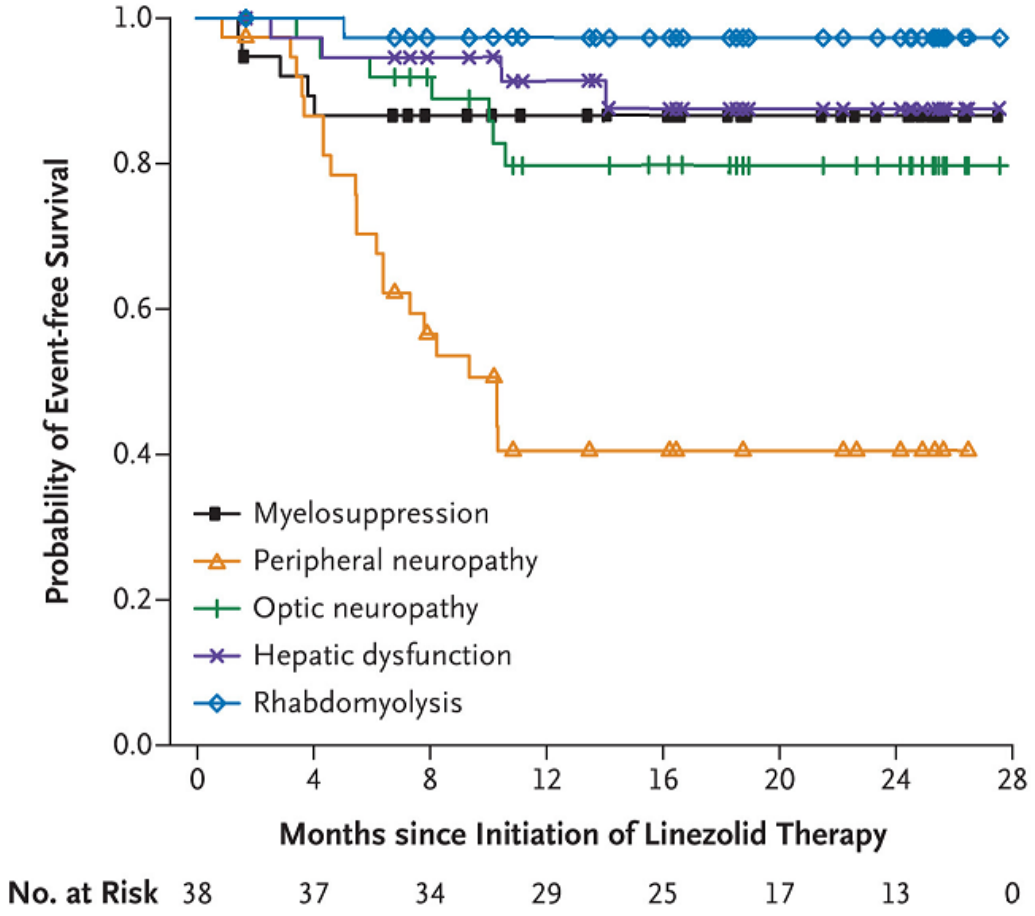
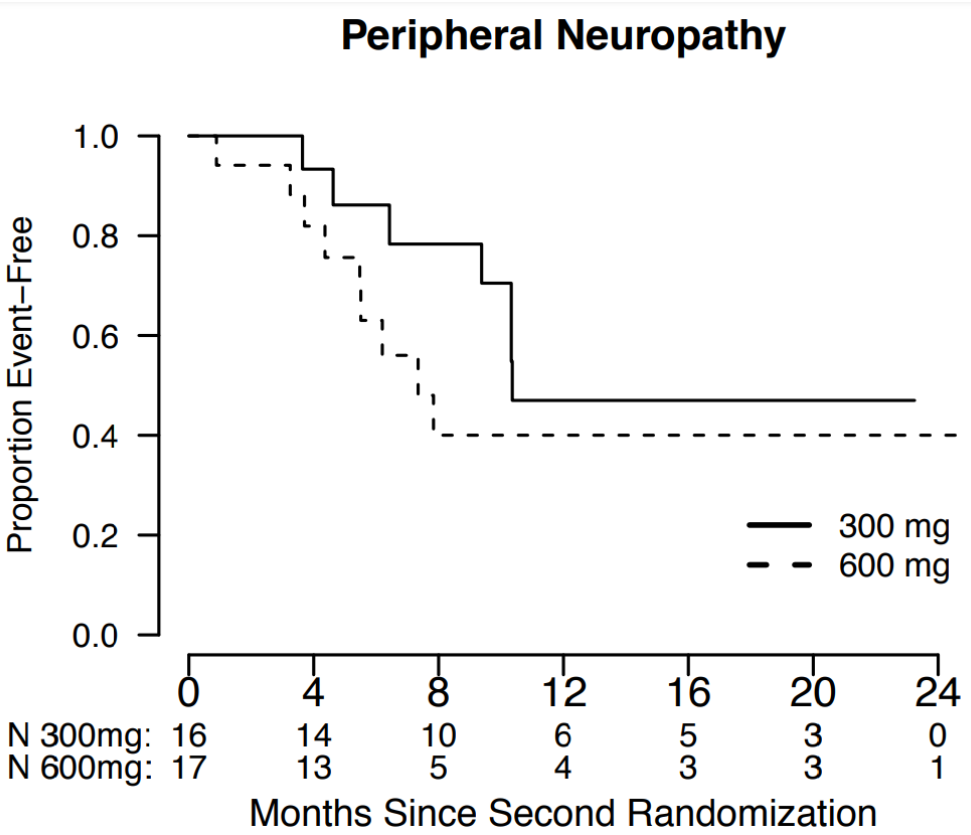




Lee M, et al. N Engl J Med. 2012 Oct18; 367(16):1508-18

Multivariable analysis of mean linezolid dose in mg/kg/d and time to peripheral neuropathy, anemia and leukopenia in participants treated for multidrug-resistant tuberculosis in Sweden 1992–2018. 35.6% 27.3% 22%

Variable	Peripheral neuropathy (n = 119)		Anemia (n = 130)		Leukopenia (n = 130)	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Female sex	-		1.96 (0.96–3.98)	0.063	2.53 (1.16–5.53)	0.020
Creatinine[a]	0.99 (0.65–1.48)	0.95	-		-	
Linezolid dose[b] (mg/kg/d)	1.0		1.0		1.0	
< 8 (ref)						
8 to <12[c]	1.44 (0.65–3.19)	0.37	1.33 (0.43–4.10)	0.62	1.82 (0.52–6.39)	0.35
≥ 12	2.89 (1.08–7.74)	0.035	6.62 (2.22–19.8)	0.001	5.23 (1.48–18.5)	0.010

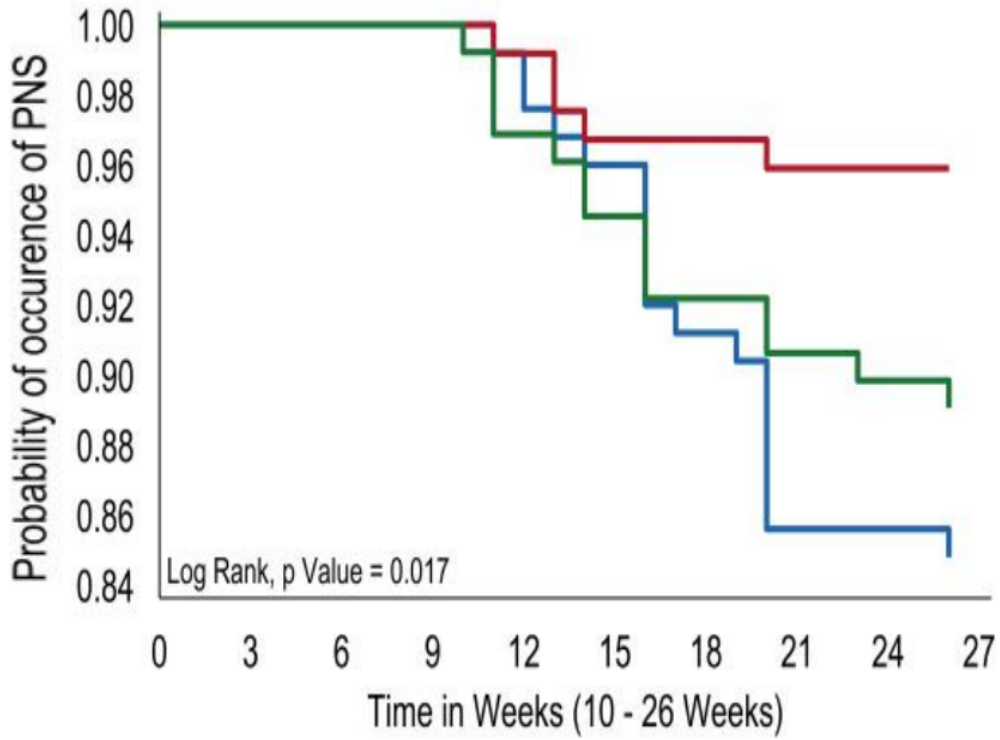
Kuhlin et al. Int J Antimicrob Agents 2024 Oct;64(4):107302

ARM - 1 : Lzd 600mg 26주

ARM - 2 : Lzd 600mg 9주 → 300mg 17주

ARM - 3 : Lzd 600mg 13주 → 300mg 13주

Population and Treatment Outcome	Participants, No. or No. (%)[a]			
	Arm 1 (n = 135)	Arm 2 (n = 135)	Arm 3 (n = 133)	Total (n = 403)
Cure at end of treatment	120 (93)	117 (94)	115 (93)	352 (93)



Padmapriyadarsini C, et al, Clin Infect Dis 2024 Dec 17;79(6):1375-1385.

Neuropathy phenotype	Toxic causes to consider
Sensory predominant	Commonly cause predominant sensory ataxia: Mercury, nitrous oxide, acrylamide Pyridoxine (vitamin B6), platinum compounds, brentuximab vedotin, amiodarone
	Other causes of sensory predominant neuropathy: Alcohol, cadmium, *n*-hexane/glue-sniffing, allyl chloride, carbon disulphide, ethylene oxide Taxanes, bortezomib, thalidomide, *BRAF*/MEK inhibitors, leflunomide, linezolid, metronidazole, calcineurin inhibitors, isoniazid, ethambutol, triazole antifungals, amiodarone, phenytoin, colchicine, chloroquine, levodopa/carbidopa intestinal gel, fluoroquinolones
Can involve significant distal motor weakness	Nitrous oxide, lead, arsenic, thallium, *n*-hexane/glue-sniffing, organophosphates Vinca alkaloids, *BRAF*/MEK inhibitors, dapsone, nitrofurantoin, disulfiram, amiodarone
Predominant neuropathic pain	Alcohol, mercury, thallium, ciguatoxin Taxanes, bortezomib, thalidomide, linezolid, metronidazole, nitrofurantoin, disulfiram, cotrimoxazole
Acute/subacute sensorimotor neuropathy ('GBS like')	Arsenic, thallium, seafood toxins (saxitoxin, tetradotoxin), diethylene glycol, *n*-hexane/glue-sniffing (if acute high doses) Immune checkpoint inhibitors, tumour necrosis factor inhibitors, *BRAF*/MEK inhibitors, calcineurin inhibitors, nitrofurantoin, bortezomib (rarely), amiodarone (rarely)
Optic neuropathy	Nitrous oxide, lead, mercury, thallium Vincristine, calcineurin inhibitors, linezolid, ethambutol, isoniazid, amiodarone, chloroquine, dapsone, disulfiram

Smyth D, et al. Pract Neurol. 2023 Apr;23(2):120-

Antibiotic	Incidence of PN	Risk Factors for PN	Pathogenesis	Type of Neuropathy
Isoniazid	2-44%	Alcohol dependence, malnutrition, diabetes, HIV, elderly and pregnant	Interference with vitamin B6 synthesis	Sensory peripheral neuropathy
Ethambutol	1-18%	increasing age, prolonged duration of EMB, a higher dose, hypertension, poor renal function, diabetes, and concurrent optic neuritis, related to tobacco and alcohol [4]	Zinc chelation affecting mitochondrial metal-containing enzymes and excitotoxic pathway	Optic neuropathy
Linezolid	13-20%	Prolonged treatment and increased doses	Unknown, could be related to protein inhibition and mitochondrial toxicity	Sensory peripheral neuropathy and optic neuropathy
Metronidazole	10-85%	Chronic treatment and increased dose	Axonal degeneration, shown to bind to neuronal RNA	Motor and Sensory peripheral neuropathy, optic and autonomic neuropathy

MR Jones, et al. Curr Clin Pharmacol. 2020;15(1):38-48.

- 가급적 원인 약제를 조기에 중단하거나 용량을 감량 (LZD TDM)
- 증상에 대한 지속적인 교육, 환기
- Gabapentin, pregabalin, duloxetine (아직 효과를 입증한 RCT 없음)

감사합니다.