Case Based Learning 2
Infection

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Case

- Patient
  - F/30
  - Known HBV carrier
- C.C: Fever, nausea, vomiting, headache (1WA)
- IMG opd (입원전일)
  - cPA, U/A: no abnormality
  - WBC: 2310, Hb: 11.7, ESR: 24 (0-20), CRP: 0.10 (0.01-0.3)
  - Impression: R/O Acute gastroenteritis

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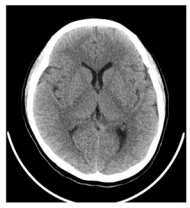
Case

- ER visit for HA, vomiting (입원전일)
  - Neck stiffness: none
  - Brain CT: WNL
  - WBC: 2940, Hb: 12.8, ESR: 15, CRP: 0.10
  - U/A: WBC ++
  - Influenza antigen test (A/B) negative



- Admission to IMG (HD #1)
  - Impression: R/O Acute gastroenteritis
  - Tx.: Hydration, antibiotics(Ceftriaxone 1g q 12hrs)

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HD #3

- Nausea, vomiting, headache 지속, fever 호전
- Lab: WBC: 9310, Hb: 12.7, ESR: 10, CRP: 0.14, Na/K/Cl 133/2.9/98
- NR consultation for altered consciousness
  - 새벽 2시에 갑자기 의식이 흐려지고 1분 이내로 왼손을 떨었다.
  - 새벽 4시에 화장실에 가려는데 왼발을 끌었음.
  - 눈이 자꾸 위로 올라가고 말이 어눌해짐.
  - 질문에 적절한 대답을 못하고 자꾸 살려달라고 함.
- N/Ex
  - Drowsiness, confusion
  - Neck stiffness: (+)
  - Left 6th N palsy
  - DTR: hyperreflexic for all extremities

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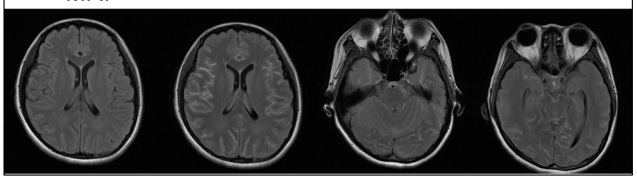
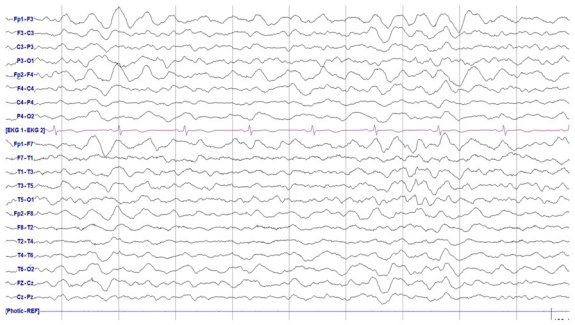
Laboratory findings

- CSF study
  - Pr: 56.5cmH_2O
  - WBC: 160 (lymphocyte; 69%, neutrophil; 21%, monocyte; 10%), RBC: 30
  - Protein: 375mg/dL, glucose 48mg/dL (serum: 132)
- MRI



EEG findings



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Diagnosis of Tb meningitis

- Early diagnosis is single the most important prognostic factor
- Classic clinical manifestation
  - Subacute meningitic illness
  - Neck stiffness is usually absent during early disease
  - In advanced stage, the diagnosis is usually apparent, but at a serious cost to the patient

	Symptoms	Clinical signs	CSF examination
Children	Early symptoms are non-specific and include cough, fever, vomiting (without diarrhoea), malaise, and weight faltering	Initial apathy or irritability that progresses to meningism, decreased level of consciousness, signs of raised intracranial pressure (often bulging anterior fontanelle and abducens nerve palsy), and focal neurological signs (most often hemiplegia)	Usually clear and colourless; raised numbers of white cells (0·05x10⁹–1·00x10⁹/L), with mixture of neutrophils and lymphocytes; raised protein (0·5–2·5 g/L); ratio of CSF to plasma glucose <0·5 in 95% of cases
Adults	Non-specific prodrome of malaise, weight loss, low-grade fever, and gradual onset of headache over 1–2 weeks; followed by worsening headache, vomiting, and confusion, leading to coma and death if untreated	Variable degrees of neck stiffness; cranial nerve palsies (VI>III-IV>VII) develop as disease progresses and confusion and coma deepen; monoplegia, hemiplegia, or paraplegia in about 20% of cases	High opening pressure (>25 cm H_2O) in 50% of cases; raised numbers of white cells (0·05x10⁹–1·00x10⁹/L), with mixture of neutrophils and lymphocytes; raised protein (0·5–2·5 g/L); ratio of CSF to plasma glucose <0·5 in 95% of cases

The Vietnam Diagnosis Rule

Entry criteria
- Adult (age >15 years) with meningitis and ratio of CSF to plasma glucose <0·5

Clinical features and scores
- Age ≥36 years (score +2)
- Age <36 years (score 0)
- Blood white cell count ≥15×10⁹/L (score +4)
- Blood white cell count <15×10⁹/L (score 0)
- History of illness ≥6 days (score −5)
- History of illness <6 days (score 0)
- CSF white cell count ≥0·75×10⁹/L (score +3)
- CSF white cell count <0·75×10⁹/L (score 0)
- CSF neutrophils ≥90% of total white cells (score +4)
- CSF neutrophils <90% of total white cells (score 0)

Interpretation
- Total score ≤4 = tuberculous meningitis
- Total score >4 = alternative diagnosis

Originally,
86% sensitive
79% specific for TB meningitis in adults

In F/U studies,
sensitivity: 96-98%
Specificity: 68-88%

Thwaites GE et al., Lancet, 2002

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In Our Case

Entry criteria
- Adult (age >15 years) with meningitis and ratio of CSF to plasma glucose <0·5

Clinical features and scores
- Age ≥36 years (score +2)
- Age <36 years (score 0)
- Blood white cell count ≥15×10⁹/L (score +4)
- Blood white cell count <15×10⁹/L (score 0)
- History of illness ≥6 days (score −5)
- History of illness <6 days (score 0)
- CSF white cell count ≥0·75×10⁹/L (score +3)
- CSF white cell count <0·75×10⁹/L (score 0)
- CSF neutrophils ≥90% of total white cells (score +4)
- CSF neutrophils <90% of total white cells (score 0)

Interpretation
- Total score ≤4 = tuberculous meningitis
- Total score >4 = alternative diagnosis

CSF glucose ratio:
<0.5(48/132)

F/30
WBC: 2310
History of illness: 7 days
CSF WBC: 160
CSF neutrophil: 21%

Total: -4

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Laboratory Diagnosis of TB Meningitis

- Microscopy
  - The diagnostic utility of CSF Ziehl-Neelsen staining for acid-fast bacilli is often very poor
  - Large CSF volume improves sensitivity, but it rarely exceeds 60%
  - Several modification to the Ziehl-Neelsen stain
- Nuclear acid amplification technique
  - Real-time PCR
- Interferon-gamma release assays

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Neuromaging

- Brain CT
- Brain MRI
  - Superior to CT especially when in the involvement of brainstem
  - DWI enhances the detection of early infarction and border-zone encephalitis
  - Gadolinium-enhanced MRI allows visualization of leptomenigeal tubercles.

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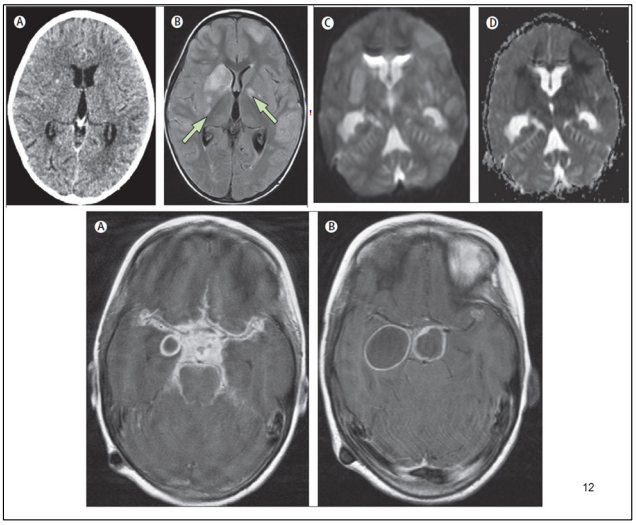

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Initiation of Treatment

- Treatment
  - TB medications (INH, RMP, EMB, PZA, pyridoxine, streptomycin)
  - Dexamethasone 10mg bolus, 4mg q 4hrs
  - AED: Levetiracetam 1000mg BID

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History of Chemotherapy

- Streptomycin (1946) : low in CSF, severe toxicity
- Para-amino salicylic acid (PAS): low in CSF
- INH (1952): high in CSF, 90% recovered with triple therapy
- RFP (1970): high sterilization of TB lesion, low in CSF
- PZA (1970): high in CSF, 6 month treatment of pulmonary TB with RFP
- But the effects of INH+RFP+PZA on TB meningitis was not different from that of triple therapy

Donald PR. Tuberculosis, 2010 [14]

CSF Penetration of Individual 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	..

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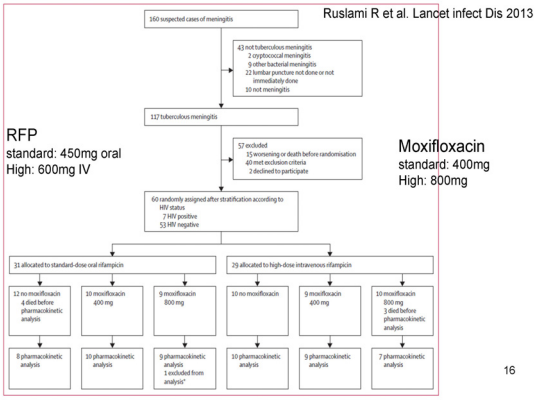
Levofloxacin in Tuberculous Meningitis



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Levofloxacin in Tuberculous Meningitis

	600 mg, intravenous (n=26)	450 mg, oral (n=26)	Ratio of intravenous to oral	p value
Plasma				
AUC_{0-8} (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*

	800 mg (n=16)	400 mg (n=19)	Ratio of 800 mg to 400 mg	p value
Plasma				
AUC_{0-8} (mg.h/L)*	60·4 (45·4–80·3)	28·6 (24·2–33·8)	2·1 (1·6–2·9)	<0·0001†
AUC_{0-8} (mg.h/L)	31·5 (24·1–41·1)	15·1 (12·8–17·7)	2·1 (1·5–2·8)	<0·0001†
C_{max} (mg/L)	7·4 (5·6–9·6)	3·9 (3·2–4·8)	1·9 (1·4–2·6)	<0·0001†
T_{max} (h; median, range)	2 (1–6)	2 (1–6)	..	0·301‡
CSF			..	
C_{max} (mg/L)§	2·43 (1·81–3·27)	1·52 (1·28–1·82)	1·60 (0·34–2·20)	0·006†

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Are We Using the Right Drugs and Doses?

	WHO[78,80] and UK[12] recommendations			
	Daily dose in children	Daily dose in adults	Route of administration	Duration
Antituberculosis drugs				
Isoniazid	10–20 mg/kg (maximum 500 mg)	300 mg	Oral	12 months
Rifampicin	10–20 mg/kg (maximum 600 mg)	450 mg (weight <50 kg) or 600 mg (weight ≥50 kg)	Oral	12 months
Pyrazinamide	15–30 mg/kg (maximum 2 g)	1·5 g (weight <50 kg) or 2·0 g (weight ≥50 kg)	Oral	2 months
Ethambutol	15–20 mg/kg (maximum 1 g)	15 mg/kg	Oral	2 months
Ethionamide	Not recommended	..		
Adjunctive corticosteroids				
Prednisolone	4 mg/kg*	2·5 mg/kg*	Intravenous initially, then switch to oral when safe to do so	4 weeks then reduce to stop over 4 weeks
Dexamethasone	0·6 mg/kg*	0·4 mg/kg*	Intravenous initially, then switch to oral when safe to do so	Reducing each week to stop over 6–8 weeks

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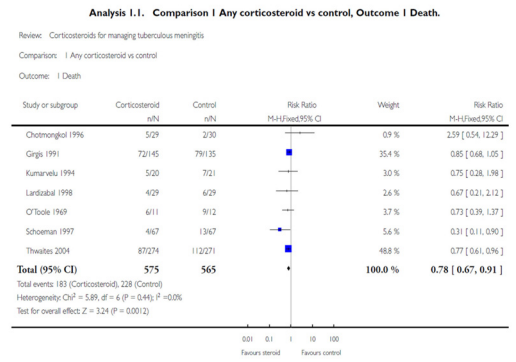
Steroid in Tuberculous Meningitis



Singh PK, Cochrane review 2008[19]

Prevention of TB Meningitis

- 7 YO daughter
- BCG vaccination
- Prophylactic anti-TB medication?

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Prevention of TB Meningitis

- Vaccination of TB meningitis
  - BCG vaccination is for the protection against disseminated forms of childhood tuberculosis, especially meningitis by BCG-primed T cell response
  - While successful prevention of pyogenic bacterial meningitis, the benefits of BCG vaccination is not satisfactory
  - Several new tuberculosis vaccines in clinical trials
- Isoniazid prophylaxis is highly effective for the prevention in young children exposed to household contacts

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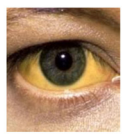
Two Months Later,

- The patient visit the outpatient clinic for excessive fatigue
- On physical examination, sclera icterus was noted



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Medication-induced Hepatotoxicity

- Incidence: 2-39% (usually around 10%)
  - Transient changes in ALT and bilirubin levels are relatively common and do not signify true hepatotoxicity
- Potency
  - High: INH, RFP, PZA
  - Less: Streptomycin, Ethambutol

Table 1 Suggestions on managing drug-induced hepatitis in tuberculosis

Authority	Monitoring in presence of risk factors† (especially liver diseases)	Stopping drugs if clinical or symptomatic hepatitis	Cut-off levels for stopping drugs (even when asymptomatic) ALT	Bilirubin
ATS	Yes	Yes	5×‡	↑
BTS	Yes	Yes	5×	↑
ERS	—	Yes	5×	↑
HKTBS	Yes	Yes	3×§	2×¶

Yew WW and Leung CC, Respirology, 2006

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Recommendation

Box 2: National recommendations for managing ATT induced hepatotoxicity and restarting the therapy

- If a drug induced hepatitis is diagnosed, ATT drugs are to be stopped
- Wait until the jaundice resolves (A severely ill patient may die without TB drugs)
- It is strange but fortunate that in most cases the patient can restart the same drugs without hepatitis returning.
- If jaundice returns, and the patient has not completed the intensive phase, give him two months of Streptomycin, INH and Ethambutol followed by 10 months of INH and Ethambutol.
- If the patient has completed the intensive phase, give him INH and Ethambutol until he has had a total of 8 months treatment for Short Course Chemotherapy (SCC) or 12 months for standard regimen.

Box 3: BTS recommendations for restarting the therapy in patients developing hepatotoxicity

- INH should be introduced initially at a dose of 50 mg/day, increasing sequentially to 300 mg/day after 2–3 days if no reaction occurs, and then continued.
- After a further 2–3 days without reaction to INH, rifampicin at a dose of 75 mg/day can be added, increasing to 300 mg after 2–3 days, and then to 450 mg (<50 kg) or 600 mg (>50 kg) as appropriate for the patient's weight after a further 2–3 days without reaction, and then continued.
- Finally, pyrazinamide can be added at a dose of 250 mg/day, increasing to 1.0 g after 2–3 days and then to 1.5 g (<50 kg) or 2 g (>50 kg).

Kishore et al., 2007, Kathmandu University Medical Journal

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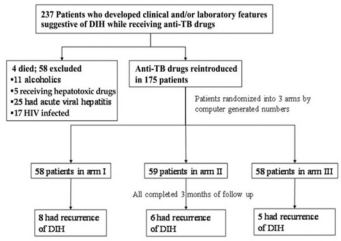
Reintroduction Methods

Table 1. Three Different Regimens for Reintroduction of Anti-Tuberculosis Drugs

Study arm	Regimen
Arm I	H, R, and Z at maximum dosages from day 1
Arm II	R at maximum dosage from day 1, H at maximum dosage from day 8, and Z at maximum dosage from day 15
Arm III	H at dosage of 100 mg/day from day 1, maximum dosage from day 4; R at dosage of 150 mg/day from day 8, maximum dosage from day 11; and Z at dosage of 500 mg/day from day 15, maximum dosage from day 18



Sharma SK, et al., Clinical Infectious Diseases, 2010

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Resistance or Intolerance

	Regimens	Comments
Isoniazid resistance (with or without streptomycin resistance)	2REZFq followed by 10REZ, or 2REZ followed by 10RE	Studies[40] suggest that isoniazid resistance has little effect on outcome as long as pyrazinamide is used for 6 months; fluoroquinolones (either moxifloxacin or levofloxacin) might improve outcome in meningitis
Rifampicin monoresistance	2HZEFq followed by 10HZE, or 2HZEIa followed by 10HZE	An injectable drug (eg, streptomycin or amikacin) or a fluoroquinolone for the first 2 months might improve outcomes in severe disease; if possible, serum concentrations of aminoglycosides (streptomycin and amikacin) should be monitored, and hearing loss should be checked for by audiology if treatment is used long term (>1 month)
Resistance to isoniazid and rifampicin (multidrug resistance)	6ZE*FqIaX followed by 18ZEFq	Regimens should be tailored to individual susceptibility patterns when possible; a 6-month intensive phase with an injectable drug, a fluoroquinolone, and at least three other active drugs, followed by a continuation phase of 12–18 months with at least three active drugs (one of them a fluoroquinolone) is suggested by WHO[39]

Numbers in the regimen abbreviations indicate the number of months of treatment with the specified drug combination. R=rifampicin. Z=pyrazinamide. E=ethambutol. Fq=fluoroquinolone. H=isoniazid. Ia=injectable agent. X=another drug (eg, ethionamide, cycloserine, or linezolid). *Use both Z and E if susceptible; replace either with other drugs (eg, ethionamide, cycloserine, linezolid,) if not susceptible to make a total of at least five active drugs in the initial phase of treatment.

Yew WW and Leung CC, Respirology, 2006

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Summary

- Diagnosis
  - Neck stiffness is frequently absent
  - Vietnam diagnosis rule
  - Large CSF volume improve the sensitivity
- Treatment
  - Sufficient dosage, CSF concentration
  - Quinolone can be a good alternative drug
  - Use of steroid in selected patients can be beneficial
  - Hepatotoxicity is common, but it is frequently self-limiting or not recur with the same regimen

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