Case presentation

95/10/04

Intern 林麗慧

Supervisor 李彥憲主任

Basic data

- Name:楊x樹
- ID: Q101293521
- Gender: male
- Age: 82 y/o
- Admission date:95/09/16

- Chief complaint:
  - Oral discomfort with mild trismus for several days

Present illness

- Mr. Yang had complained oral discomfort with mild trismus (jaw closure) for several days.
- A traffic accident was happened for 3 weeks ago

  the wound over right foot was found
- Cough with sputum - for 6 days
- Progressive trismus with intraoral pain had developed.
- He visited DaLin TzuChi OPD on 9/16.

Social History

- Smoking:(+) quit
- Drinking:(+) sociality
- Betel nut chewing: (-)

Past History

- denied DM, HTN, heart disease, and other systemic disease
- 91/06: Rt leg DVT s/p insertion of Greenfield filter
- 95/03~: diffuse large B-cell lymphoma, Stage IIIa, s/p biopsy and 6th course of C/T with R-COP

Physical Examination

- General appearance: acute ill looking
- Consciousness: alert, GCS: E4V5M6
- Vital signs: T/P/R 36/68/18, bp 131/76mmHg
- HEENT:
  Pale conjunctiva(-), Icteric sclera(-)
  trismus (+)
  Stiff neck?
  Dysphagia?
- Chest:
  Symmetric expansion (+)
  Breath sound: Moist rales(-), Wheezing(-)
- Heart: regular rhythm, no murmur
- Abdomen: soft, flat, no tenderness, rigidity?
- Extremities: wound over right foot, size? muscle power?

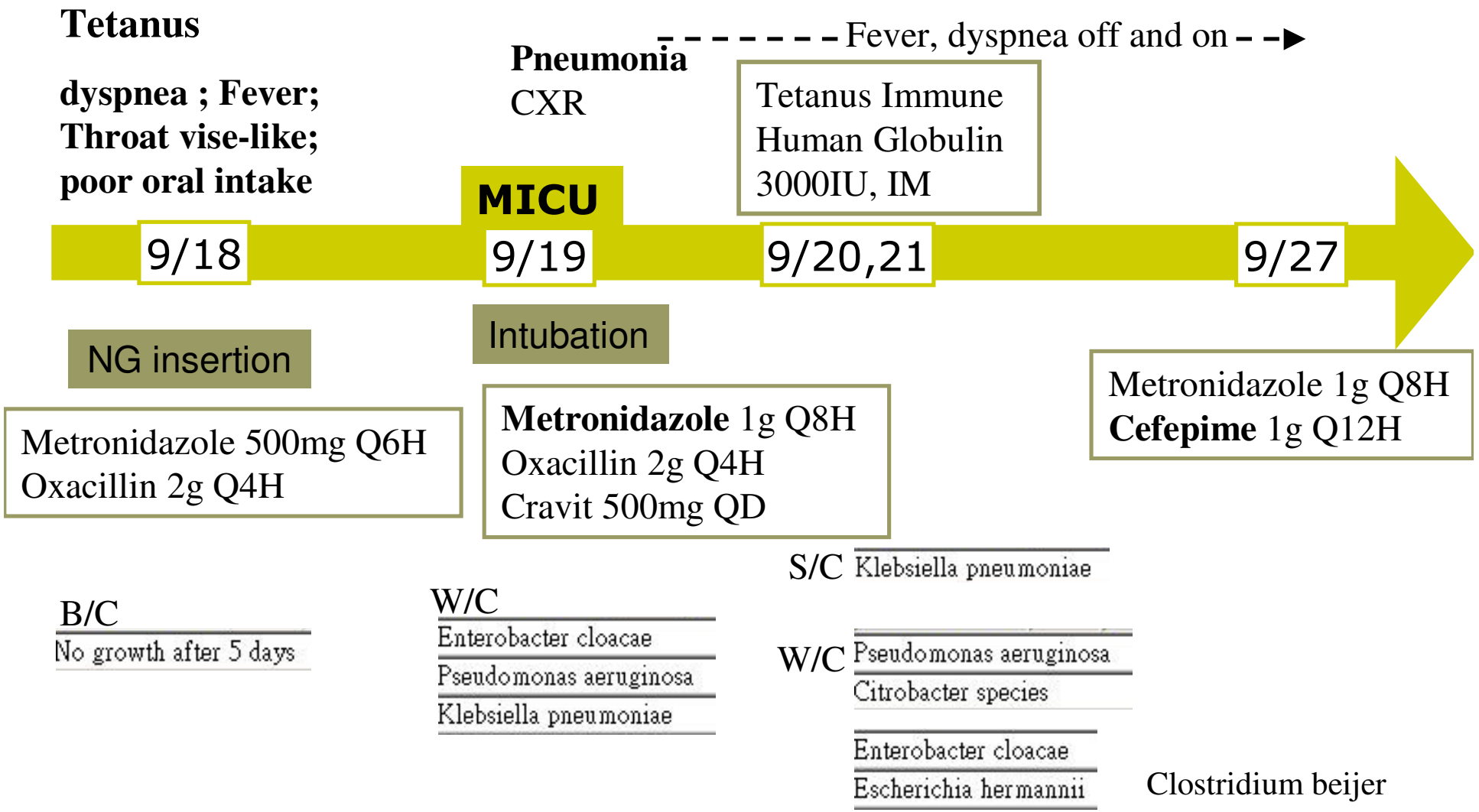
Lab data- CBC & BCS

0950916	WBC	8.88	*10^3/u
	RBC	4.95	*10^6/u
	Hb	10.4	g/dl
	Ht	33.0	%
	MCV	66.7	fl
	MCH	21.0	pg
	MCHC	31.5	%
	PL	231	*10^3/u
	RDW-CV	17.6	%
	PDW		fl
	MPV		fl
	P-LCR		%

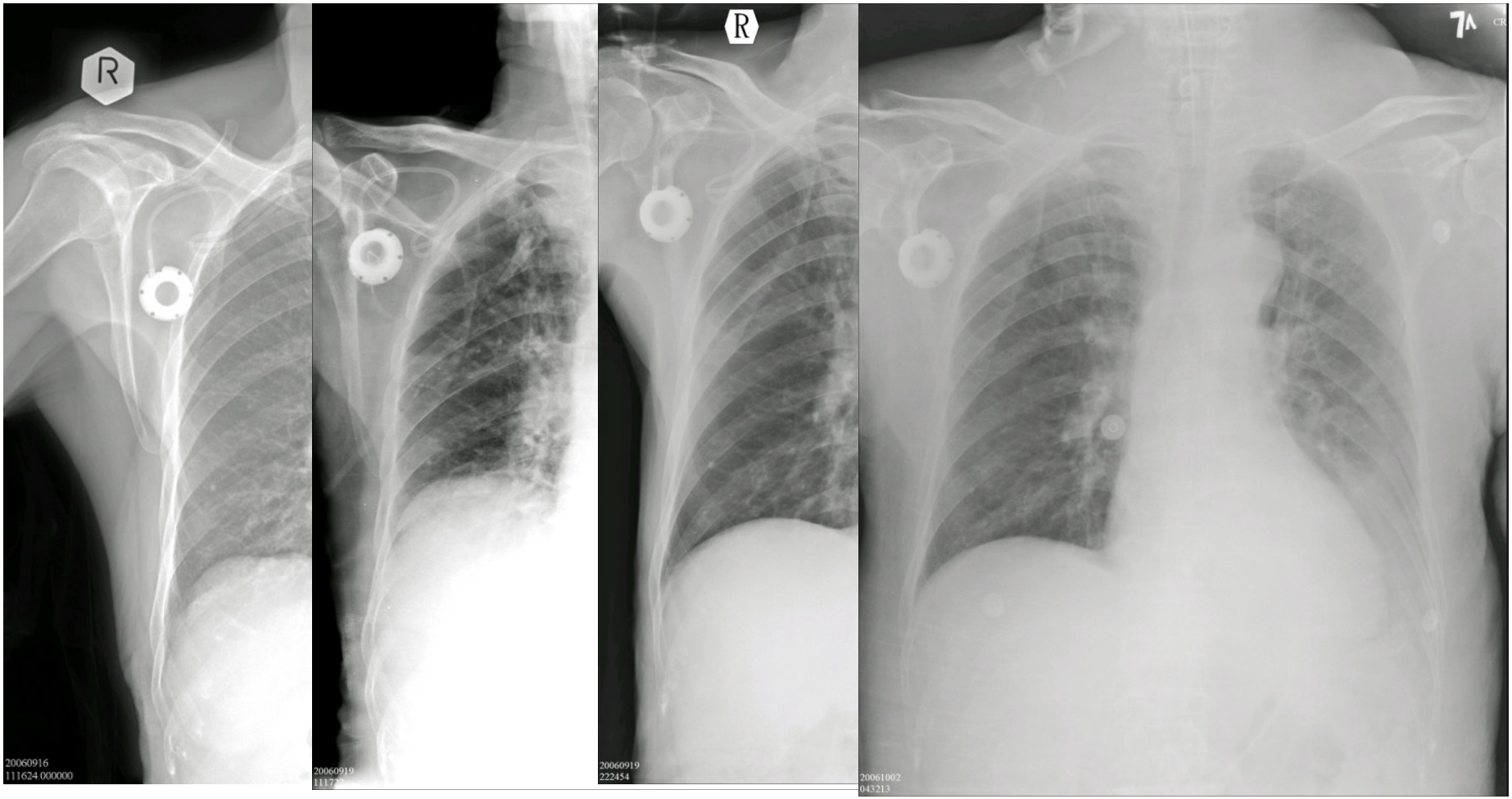
0950916	GOT/AST	28	IU/L
	GPT/ALT	19	IU/L
	TBI	0.4	mg/dl
	DBI	0.0	mg/dl
	LDH	424	IU/L
	T P	7.0	g/dl
	ALB	3.5	g/dl
	GLO	3.5	g/dl
	BUN	16	mg/dl
	CRE	0.8	mg/dl
	GLU-AC	88	mg/dl
	Na	135	mmol/L
	K	4.43	mmol/L

Within normal range

Clinical course



CXR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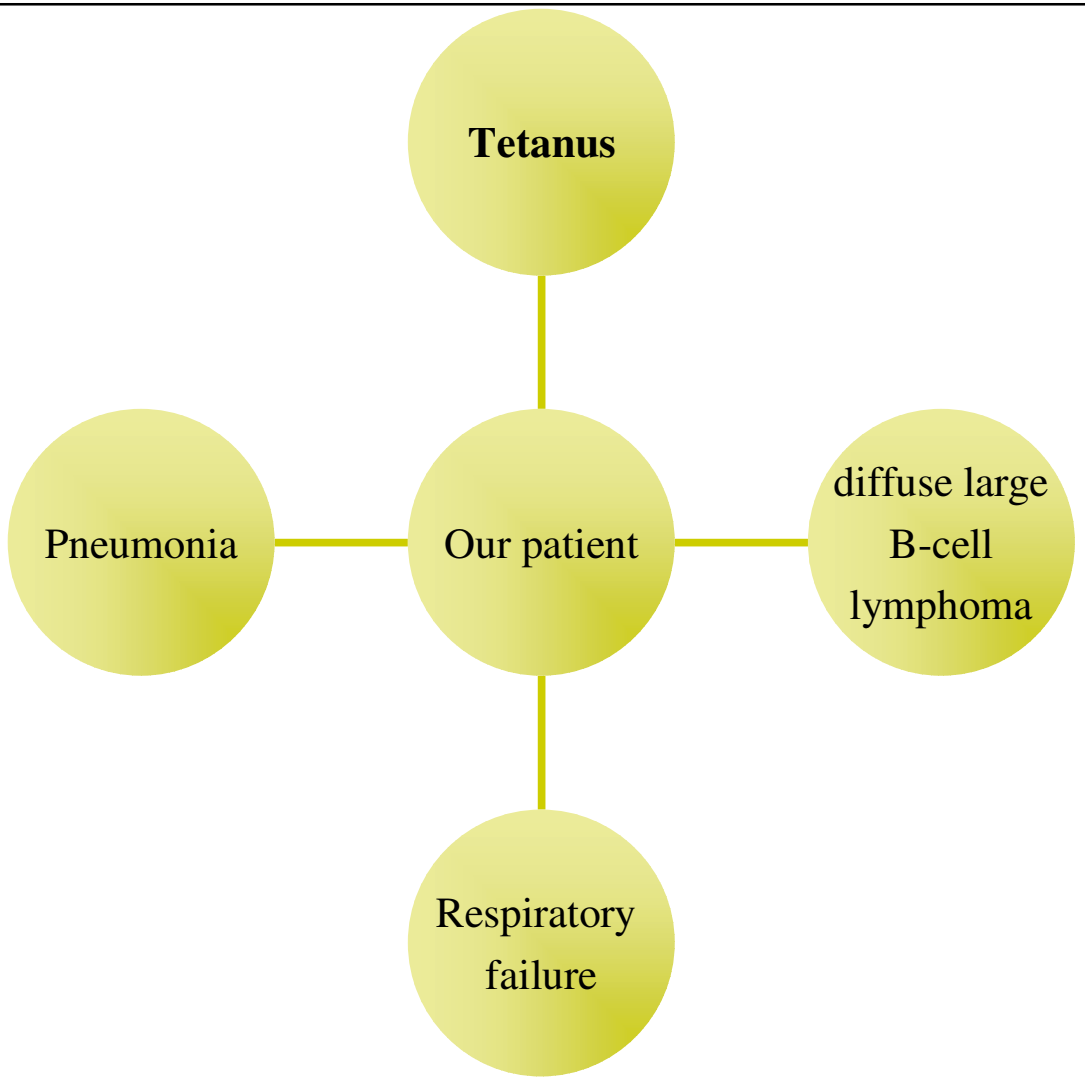
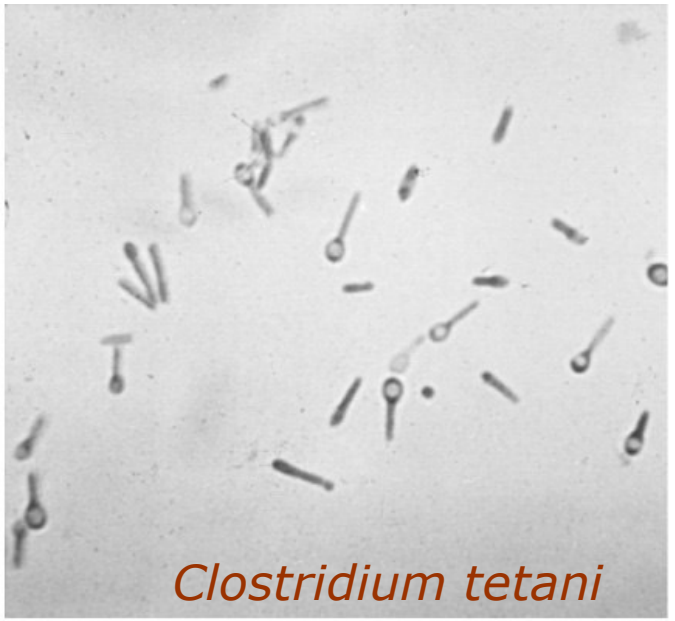
Summary


Tetanus
Pneumonia
Our patient
diffuse large B-cell lymphoma
Respiratory failure

Discussion



1. Differential Diagnosis of Trismus
2. Pathophysiology of Tetanus
3. Treatment of Tetanus
   — Antitoxin therapy

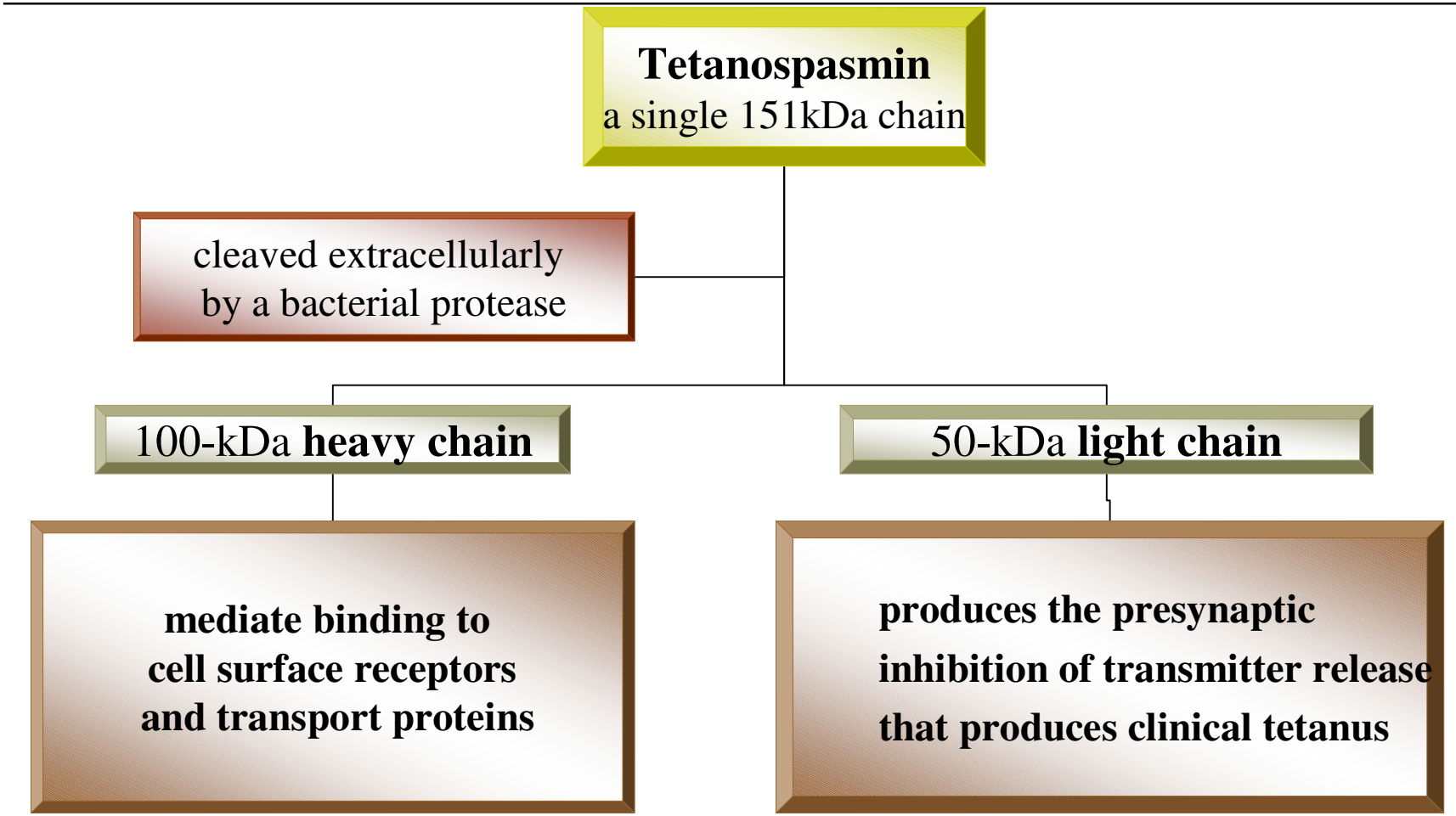
Etiology & DDx of Trismus

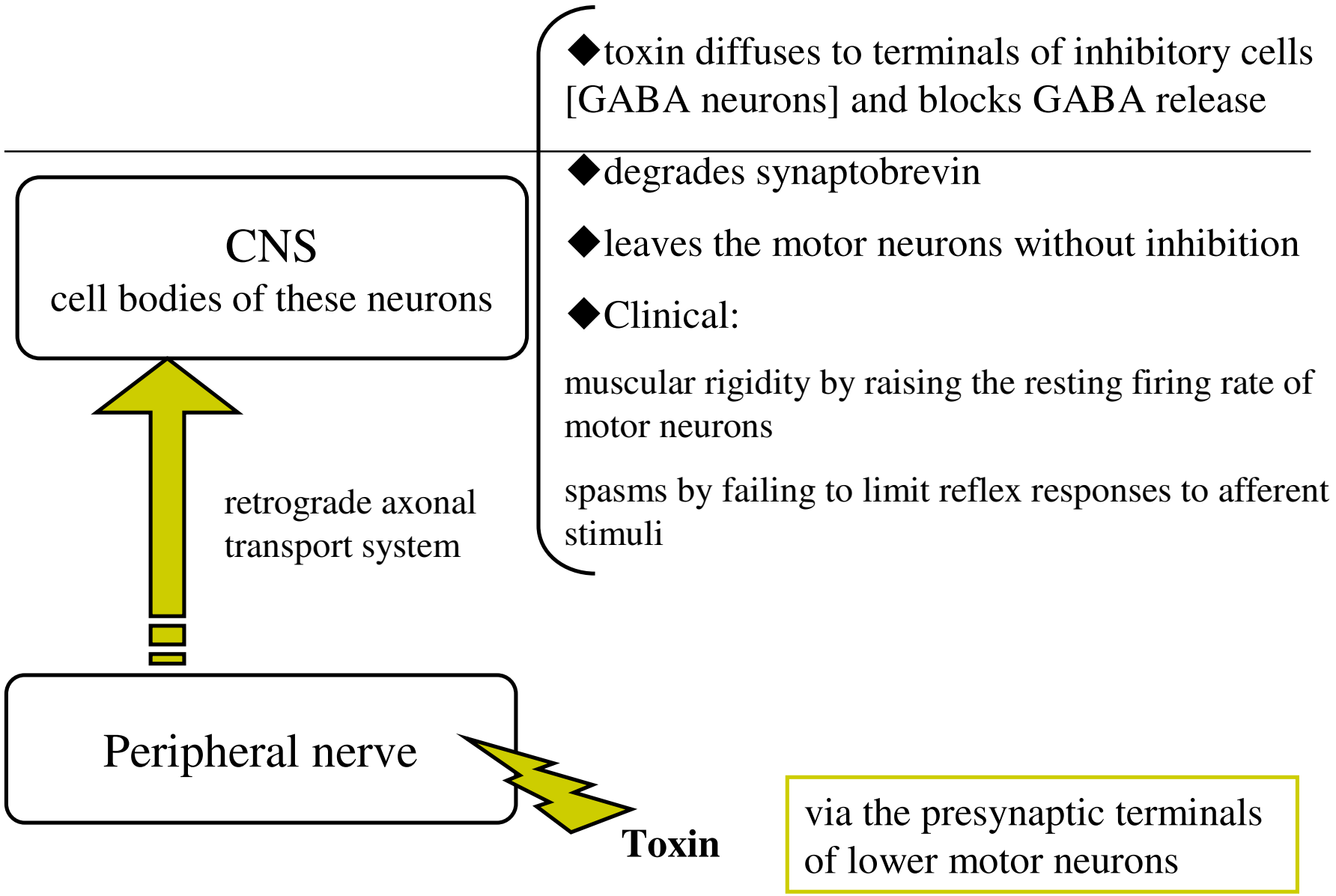
Infection/odontogenic	pulpal, periodontal, pericoronal
Nonodontogenic	peritonsillar/brain/parotid abscess, **tetanus**, meningitis, pharyngeal diphtheria, Mumps
Trauma	fracture mandible/zygomatic arch, foreign bodies
Iatrogenic	postextraction, local anesthetic injection
TMD	trauma, myofascial muscle spasm, internal derangement
Tumors and oral care	tumors of epipharyngeal and parotid region, TMJ, submucus fibrosis
Drugs	phenothiazine, succinyl choline, tricyclic antidepressant, **metaclopramide**, halothane
Radiotherapy	postradiation fibrosis, osteoradionecrosis
Congenital	hypertrophy of coronoid, trismus pseudocamptodactyly syndrome
Miscellaneous	hysteria, lupus erythematosus

Tetanus

- Organism： *Clostridium tetani*
- Neurotoxin：Tetanospasmin [tetanus toxin]
- Diagnosed purely by clinical observation

Pathogenesis



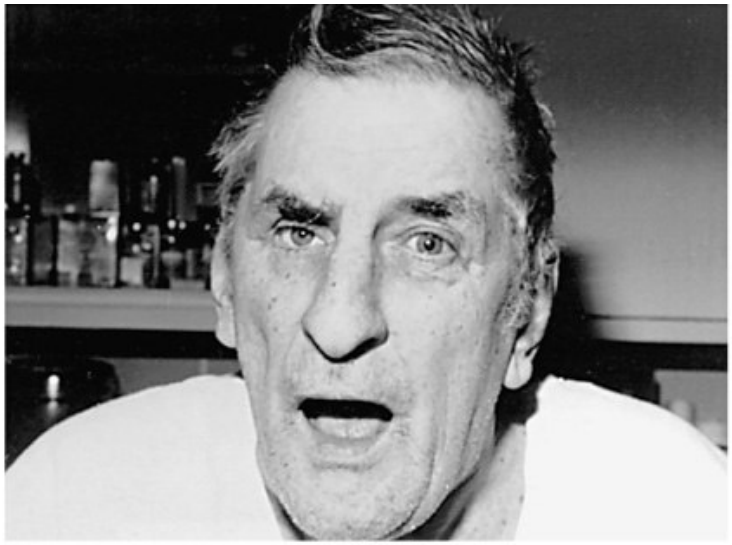

◆toxin diffuses to terminals of inhibitory cells [GABA neurons] and blocks GABA release
◆degrades synaptobrevin
◆leaves the motor neurons without inhibition
◆Clinical:
muscular rigidity by raising the resting firing rate of motor neurons
spasms by failing to limit reflex responses to afferent stimuli
CNS
cell bodies of these neurons
retrograde axonal transport system
Peripheral nerve
Toxin
via the presynaptic terminals of lower motor neurons

Four clinical types of tetanus

- Generalized –
  - trismus
  - risus sardonicus
- Local
- Cephalic
- Neonatal

Common clinical manifestations

trismus lockjaw, masseter rigidity	A board-like **rigid abdomen**
risus sardonicus bitter laugh, sneering grin, increased tone in the orbicularis oris	Periods of **apnea** due to vise-like contraction of the thoracic muscles and/or glottal or pharyngeal muscle contraction
Stiff neck	**Dysphagia**
Opisthotonus	symptoms of autonomic overactivity



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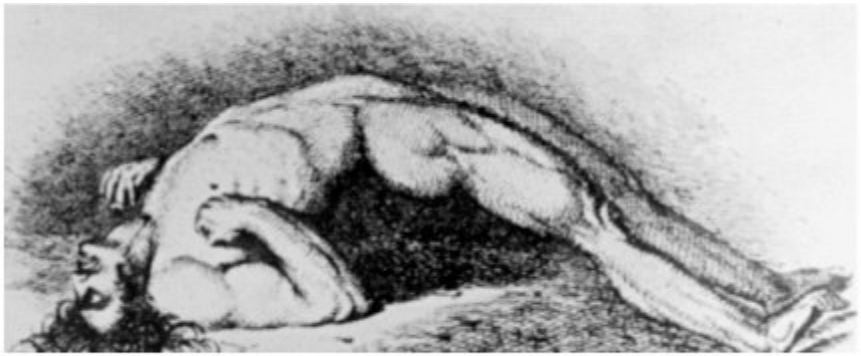

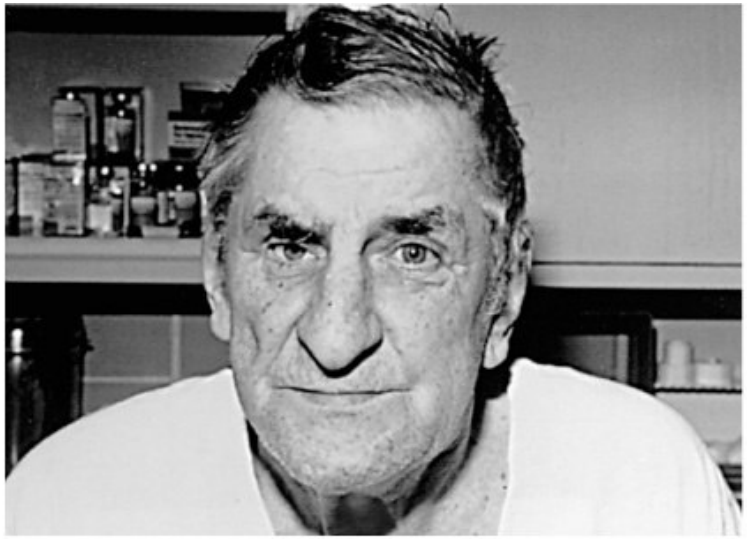

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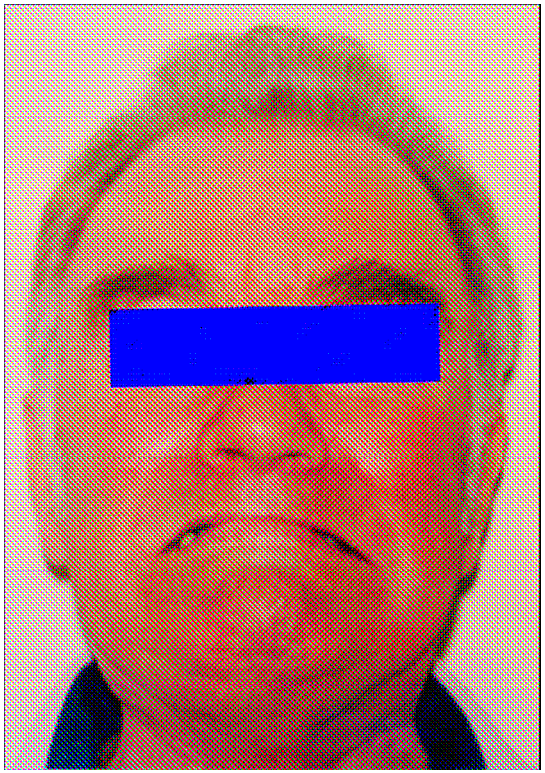


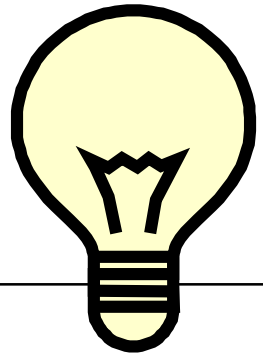
Treatment— Antitoxin therapy

- Neutralization of unbound toxin
- Passive immunization with HTIG shortens the course of tetanus and may lessen its severity.

- Our patient:

  HTIG 3000IU, intramuscular administration
- May emphasize HTIG in the nervous system

Question-



Population- adult with tetanus

Intervention- intrathecal TIG plus

Comparison- intramuscular TIG alone, no IT TIG

Outcome- Mortality

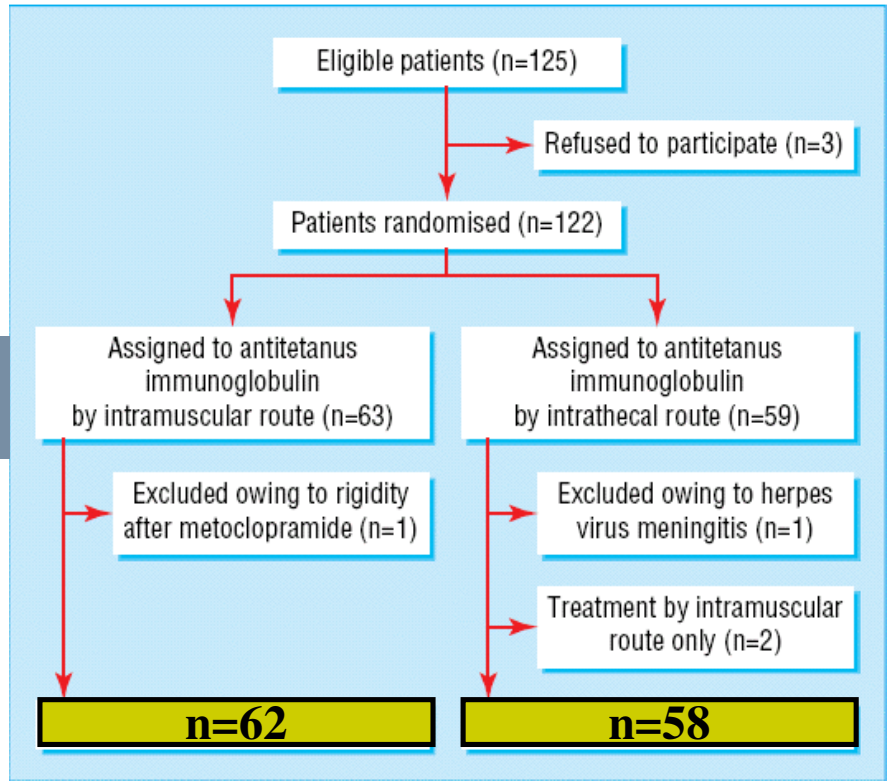
Search methods

- Database：PubMed
- Keywords
  - Tetanus[MeSH]
  - Immunoglobulins[MeSH]
  - Intrathecal, intramuscular therapy
- Limits: All Adult: 19+ years, Humans

Randomised controlled trial of tetanus treatment with antitetanus immunoglobulin by the intrathecal or intramuscular route

Intramuscular route (control group)

3000IU TIG, IM



Intrathecal and intramuscular routes (treatment group)

3000IU TIG, IM

1000IU TIG, IT

BMJ. 2004 Mar 13;328(7440):615

Clinical progression

Table 2 Clinical progression of patients treated for tetanus by the intramuscular route (control group) or intrathecal route

Clinical progression	No (%) in control group (n=60)	No (%) in study (n=58)	P value*
Improvement	10 (17)	21 (36)	χ^2=7.752;0.005
Stabilisation and improvement	13 (22)	15 (26)	
Deterioration†	37 (62)	22 (38)	

Small risk of deterioration or death within first 10 days
RR=0.6 95%CI 0.4-0.9

Severity

Classified tetanus	
grade 1	trismus, dysphagia, and generalised rigidity with no spasms
grade 2	mild and occasional spasms
grade 3	severe and recurrent spasms —usually triggered by minor or imperceptible stimuli
grade 4	features of grade 3 & overactivity of the sympathetic nervous system

Table 3 Severity of tetanus within 10 days of admission. Values are numbers (percentages) of patients

Days after admission	Grade of tetanus			
	I	II	III	IV
Day 2:				
Control	15 (27)	13 (24)	19 (35)	8 (15)
Study	20 (36)	22 (39)	13 (23)	1 (2)
Day 4:				
Control	10 (19)	13 (25)	20 (38)	10 (19)
Study	19 (36)	23 (43)	9 (17)	2 (4)
Day 6:				
Control	11 (21)	12 (23)	17 (33)	12 (23)
Study	18 (39)	21 (46)	7 (15)	—
Day 8:				
Control	9 (18)	16 (31)	17 (33)	9 (18)
Study	23 (52)	16 (36)	05 (11)	—
Day 10:				
Control	9 (21)	11 (26)	17 (40)	6 (14)
Study	22 (56)	10 (26)	5 (13)	2 (5)

82 patients were evaluated on day 10, 20 had been discharged, seven had died, and 11 missed appointments.

- most patients in the treatment group had grade I or II disease
- most patients in the control group had grade III or IV disease

Mortality

Table 5 Complications and mortality in patients treated for tetanus by the intramuscular route (control group) or intrathecal route

Outcome	Control group (n=62)	Study group (n=58)	Relative risk (95% CI)	P value
Complications	46 (74)	33 (57)	1.30 (1.00 to 1.70)	0.071
No complications	16 (26)	25 (43)		
Respiratory infection	42 (68)	29 (50)	1.35 (0.99 to 1.85)	0.073
No respiratory infection	20 (32)	29 (50)		
Respiratory failure or mechanical ventilation	34 (55)	22 (38)	1.45 (0.97 to 2.16)	0.094
No respiratory failure or mechanical ventilation	28 (45)	36 (62)		
Died	10 (16)	4 (7)	2.34 (0.78 to 7.05)	0.197
Did not die	52 (84)	54 (93)		

outcome	control	treatment	RR	P value
Died [14]	10 (16)	4 (7)	2.34 [0.78-7.05]	0.197
Did not die	52 (54)	54 (93)		

Sample size was too small

ICU was created, mortality from tetanus was decreased(35%->12%)

Intrathecal vs. **intramuscular administration of human antitetanus immunoglobulin** or **equine tetanus antitoxin** in the **treatment of tetanus : a meta-analysis**

- Search:
  the Medline database
  the Cochrane library
  the Current contents
  other electronic data
- keywords:
  - intrathecal tetanus antitoxin
  - intramuscular tetanus antitoxin
  - tetanus immunoglobulin (TIG)
- only randomized trials focusing the comparison of intrathecal vs. intramuscular routes
- End Point :

  the evaluation of the efficacy of ITS vs. IMS by calculating the mortality rate within the two groups

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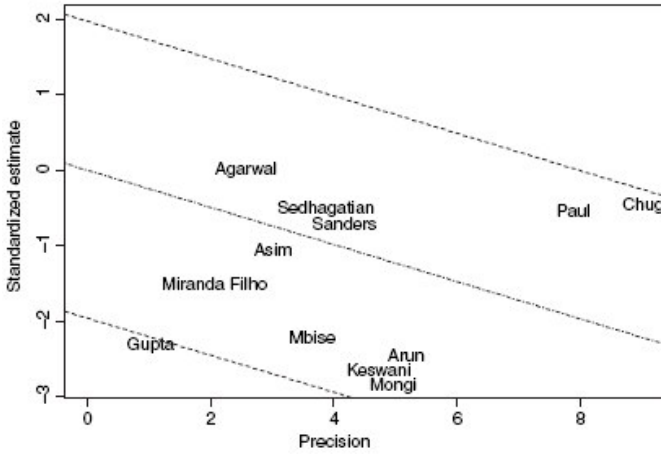
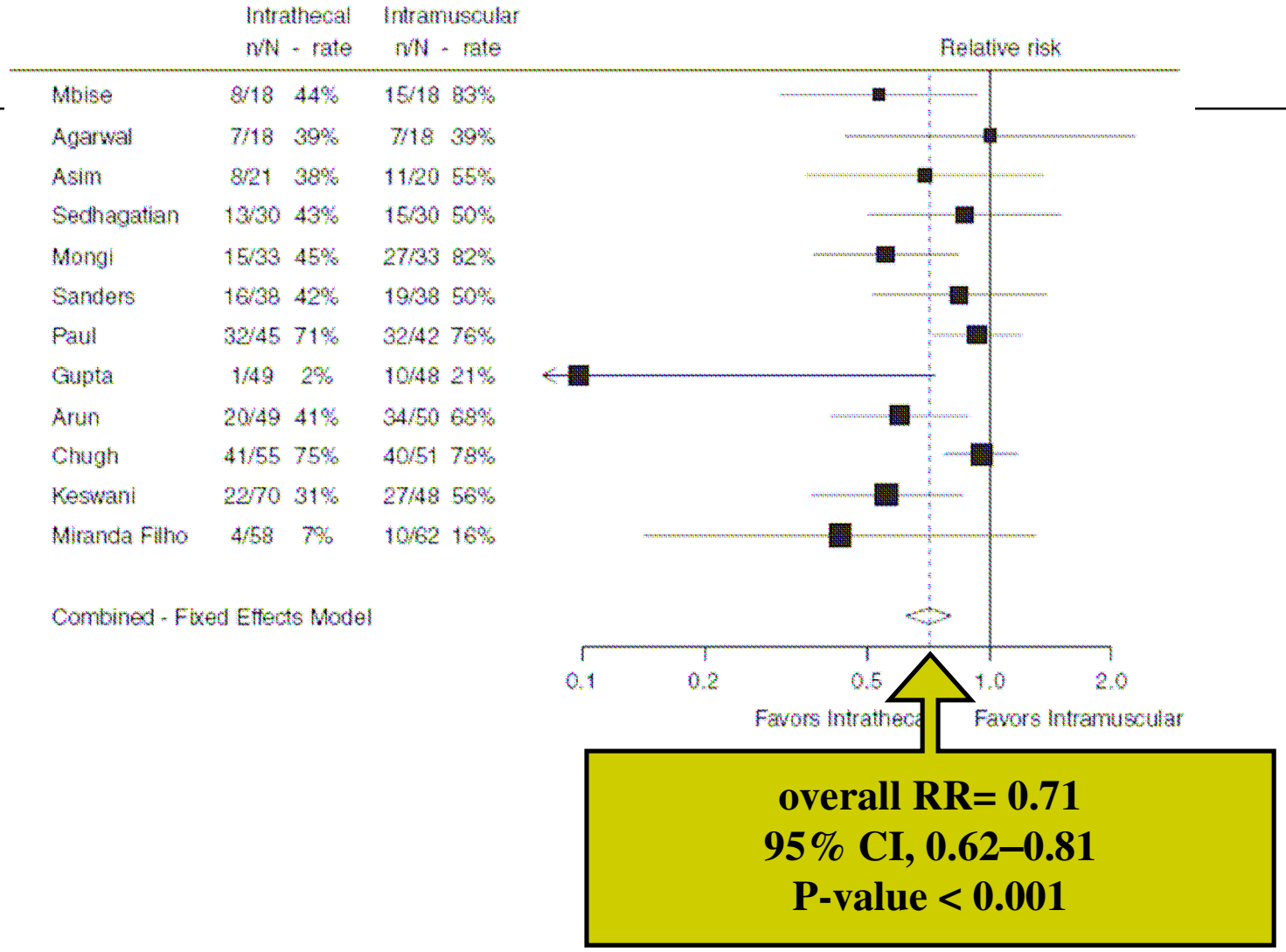
Table 1 Study characteristics of randomized trials comparing intrathecal with intramuscular administration of human immunoglobulin or equine antitoxin in the treatment of tetanus

							Mortality/sample size			Dose		Methods
Authors	Country	Year	Age	Score	Serum	Steroids	Total	ITS	IMS	ITS	IMS	Study type
Agarwal	India	1998	Adults	1,3	Human	No	14/36	7/18	7/18	250	750	SRDB
Gupta	India	1980	Adults	1,2,3	Human	No	32/97	1/49	10/48	250	1000	RT
Keswani	India	1980	Adults	1,2,3	Equine	No	49/118	22/70	27/48	200	10 000	RT
Mbise	Tanzania	1984	Adults	1,2,3	Equine	No	23/36	8/18	15/18	1500	10 000	RT
Miranda Filho	Brazil	2004	Adults	1.2.3	Human	No	14/120	4/58	10/62	1000	3000	RT
Sanders	England	1977	Adults	1,2,3	Equine	Yes	35/76	16/38	19/38	200	1500	RT

- 12 clinical trials; 942 patients
  - 6 trials: involved adult subjects (483 pt)
  - The other 6: conducted in neonates (459 pt)
- Galbraith plot: within 95% boundaries: homogeneity



mortality



the mortality rate : significantly lower for the intrathecal treatment

the mortality rate in subcategories:

Age adult vs. neonates

Dose low doses vs. high doses

Serum type serum (horse) vs. human TIG

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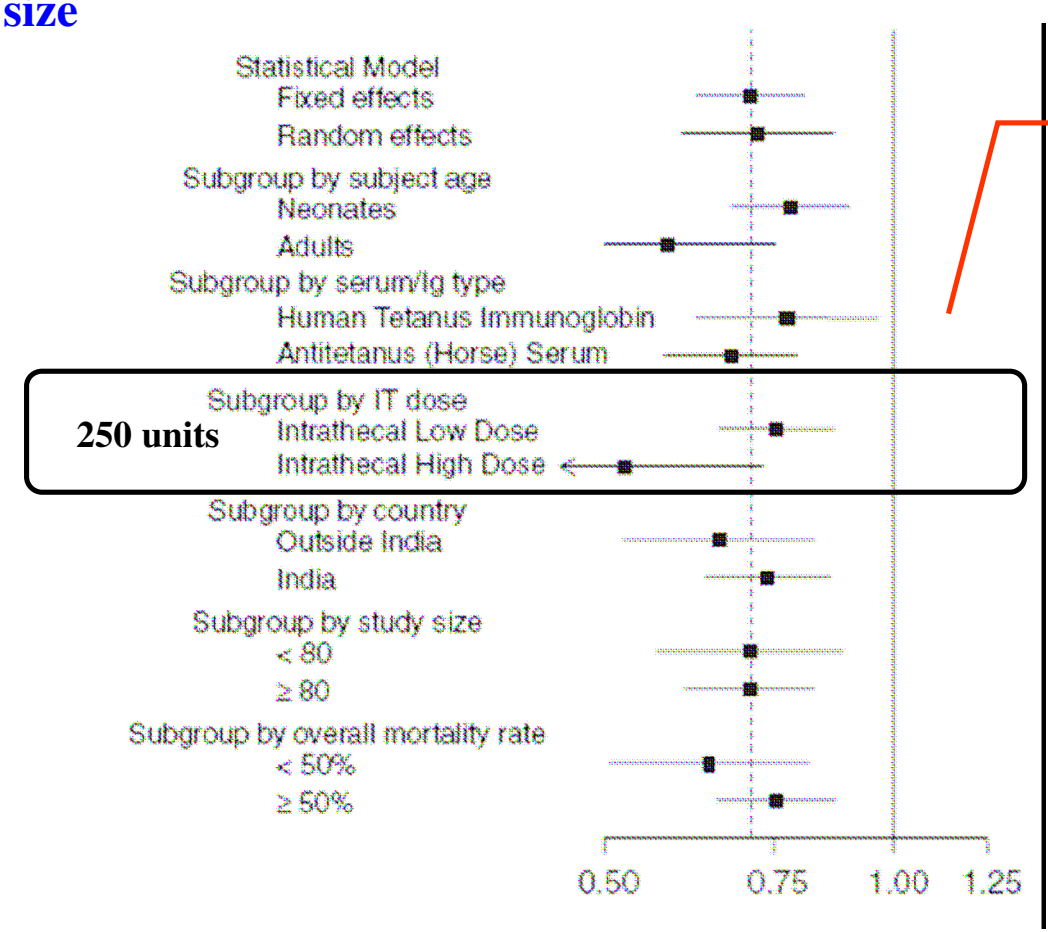
geographical location

study size



a significantly higher reduction in mortality

P =0.037

Conclusion

- Intrathecal TIG therapy compared with intramuscular TIG alone therapy has lower mortality rate.
- For our patient:
  - TIG 3000IU, intramuscular administration
  - intrathecal High dose TIG added

References

- Principles and Practice of Infectious Diseases
- Harrison's principles of internal medicine
- UpToDate: tetanus
- Trismus: Or is it tetanus? A report of a case
  Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;101:437-41
- Randomised controlled trial of tetanus treatment with antitetanus immunoglobulin by the intrathecal or intramuscular route
  BMJ. 2004 Mar 13;328(7440):615.
- Intrathecal vs. intramuscular administration of human antitetanus immunoglobulin or equine tetanus antitoxin in the treatment of tetanus: a meta-analysis
  Tropical Medicine and International Health july 2006
- A randomized double-blind sham-controlled study of intrathecal human anti-tetanus immunoglobulin in the management of tetanus
  Natl Med J India. 1998 Sep-Oct
- Prince Leopold Institute of Tropical Medicine-www.itg.be

Thanks for your attention!

Comment

- 此篇RCT的sample size訂定方式是否有註明,
- 一篇好的RCT應該要說明trial如何取多少sample
- Meta-analysis 如何去選擇,將所要的papers included進來

TABLE 242-1 Suggested Management Protocol for Generalized Tetanus

I. Diagnosis and Stabilization: First Hour After Presentation

A. Assess airway and ventilation. If necessary, perform endotracheal intubation using benzodiazepine sedation and neuromuscular blockade (e.g., vecuronium 0.1 mg/kg).
B. Obtain samples for antitoxin level, strychnine and dopamine antagonist assays, electrolytes, blood urea nitrogen, creatinine, creatine kinase, and urinary myoglobin determination.
C. Determine the portal of entry, incubation period, period of onset, and immunization history.
D. Administer benztropine (1 to 2 mg, intravenously) or diphenhydramine (50 mg, intravenously) to rule out a dystonic reaction to a dopamine blocking agent.
E. Administer a benzodiazepine intravenously (diazepam in 5-mg increments, or lorazepam in 2-mg increments) to control spasm and decrease rigidity. Initially, employ a dose that is adequate to produce sedation and minimize reflex spasms. If this dose compromises the airway or ventilation, intubate using a short-acting neuromuscular blocking agent. Transfer the patient to a quiet, darkened area of the intensive care unit.

II. Early Management Phase: First 24 Hours

A. Administer human tetanus immunoglobulin (HTIG), 500 units, intramuscularly; as an alternative, consider intravenous pooled immune globulin (see text).
B. At a different site, administer adsorbed tetanus toxoid such as tetanus-diphtheria vaccine (0.5 mL) or diphtheria-pertussis-tetanus vaccine (0.5 mL), as appropriate for age, intramuscularly. Adsorbed tetanus toxoid without diphtheria toxoid is available for patients with a history of reaction to diphtheria toxoid; otherwise, the correct combination for the patient's age should be employed.
C. Begin metronidazole 500 mg, intravenously, every 6 hr, for 7-10 days.
D. Perform a tracheostomy after placement of an endotracheal tube and under neuromuscular blockade if spasms produce any degree of airway compromise.
E. Débride any wounds as indicated for their own management.
F. Place a soft, small-bore nasal feeding tube or a central venous hyperalimentation catheter, and begin feeding. Patients receiving total parental nutrition should also be given parenteral H_2 blockade or other gastric protection.
G. Administer benzodiazepines as required to control spasms and produce sedation. If adequate control is not achieved, institute long-term neuromuscular blockade (e.g., vecuronium 6-8 mg/hr); continue benzodiazepines for sedation with intermittent electroencephalographic monitoring to ensure somnolence. Neuromuscular junction blockade should be discontinued daily to assess the patient's physical examination and to decrease the possibility of excessive accumulation of the blocking agent.

III. Intermediate Management Phase: The Next 2-3 Weeks

A. Treat sympathetic hyperactivity with labetalol (0.25-1.0 mg/min as needed for blood pressure control) or morphine (0.5-1.0 mg/kg/hr by continuous infusion; see text for other recommendations). Consider epidural blockade with a local anesthetic. Avoid diuretics for blood pressure control, because volume depletion will worsen autonomic instability.
B. If hypotension is present, initiate saline resuscitation. Place a pulmonary artery catheter and an arterial line, and administer fluids, dopamine, or norepinephrine as indicated.
C. Sustained bradycardia usually requires a pacemaker. Atropine or isoproterenol may be useful during pacemaker placement.
D. Begin prophylactic heparin.
E. Use a flotation bed, if possible, to prevent skin breakdown and peroneal nerve palsies. Otherwise, ensure frequent turning and employ antirotation boots.
F. Maintain benzodiazepines until neuromuscular blockade, if employed, has been terminated, and the severity of spasms has diminished substantially. Then taper the benzodiazepine dose over 14-21 days.
G. Begin rehabilitation planning.

IV. Convalescent Stage: 2-6 Weeks

A. When spasms are no longer present, begin physical therapy. Many patients require supportive psychotherapy.
B. Before discharge, administer another dose of tetanus-diphtheria vaccine or diphtheria-pertussis-tetanus vaccine.
C. Schedule a third dose of toxoid to be given 4 weeks after the second.

Adapted from Bleck TP. Tetanus. In: Scheld WM, Whitley RJ, Durack DT, eds. Infections of the Central Nervous System. New York: Raven Press; 1991:603-624.