

Delirium in a Returning Traveller

Canadian Society of Internal Medicine

Ted Giles Clinical Vignettes

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PGY4 General Internal Medicine

Consult

- ▶ 58 yrs hypertensive, afebrile male is admitted to the internal medicine service with 24-hours of non-fluctuating confusion
 - ▶ Carphologia*
 - ▶ Failure to follow commands
 - ▶ Outbursts of incomprehensible speech

*Carphologia: Picking type behaviours in delirious/confusional states.
From Greek: "to collect straw"

Past Medical and Social History

- ▶ Born in Punjab, India
 - ▶ Lived in Calgary for thirty years
- ▶ No home medications
 - ▶ No herbal preparations or supplements
 - ▶ Never smoker, no alcohol, no illicit drugs
- ▶ Works as an office cleaner
- ▶ Lives with his wife
 - ▶ Has three healthy sons



Travel History

May

S	M	T	W	T	F	S
26	27	28	29	30	1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31	1	2	3	4	5	6

June

S	M	T	W	T	F	S
31	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	1	2	3	4

July

S	M	T	W	T	F	S
28	29	30	1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	1

August

S	M	T	W	T	F	S
26	27	28	29	30	31	1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31	1	2	3	4	5

Visiting friends and family in the Punjab region of India

September

S	M	T	W	T	F	S
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	1	2	3	4	5	6

Visiting friends and family in the Punjab region of India

October

S	M	T	W	T	F	S
27	28	29	30	31	1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31	1	2	3	4	5	6

November

S	M	T	W	T	F	S
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	1	2	3	4	5

December

S	M	T	W	T	F	S
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31	1	2	3	4

Presentation to hospital

Interim History

November

December

Returns from the Punjab

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Delirium onset

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Presents to ED

BCx: *Salmonella paratyphi* B

Develops fever and chills

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Presentation to hospital

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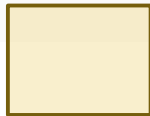
31

1

2



Ceftriaxone



TMP SMX

Physical Exam

- ▶ Tachycardia, hypertension
- ▶ Afebrile
- ▶ No focal neurologic finding or meningismus
 - ▶ Responded to questions with incomprehensible sounds
 - ▶ Agitated, restless
- ▶ No rash, no GI symptoms

Investigations

Variable	Patient's result	Reference range
CBC		
HgB	127 g/L	137-180 g/L
Plt	435 x 10 ⁹ /L	150-400 x 10 ⁹ /L
WBC	5.5 x 10 ⁹ /L	4.0-11.0 x 10 ⁹ /L
Chemistry		
Cr	111 umol/L	50-120 umol/L
T Bili	8 umol/L	0-24 umol/L
ALP	123 U/L	30-145 U/L
LDH	245 U/L	100-235 U/L
GGT	54 U/L	11-63 U/L
ALT	86 U/L	1-60 U/L
Ammonia	92 umol/L	12-47 umol/L
CRP	74.5 mg/L	0-8 mg/L

Investigations

- ▶ Mild anemia
- ▶ Thrombocytosis
- ▶ Mild hepatitis
- ▶ Elevated CRP
- ▶ Normal MR brain

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Cerebrospinal Fluid

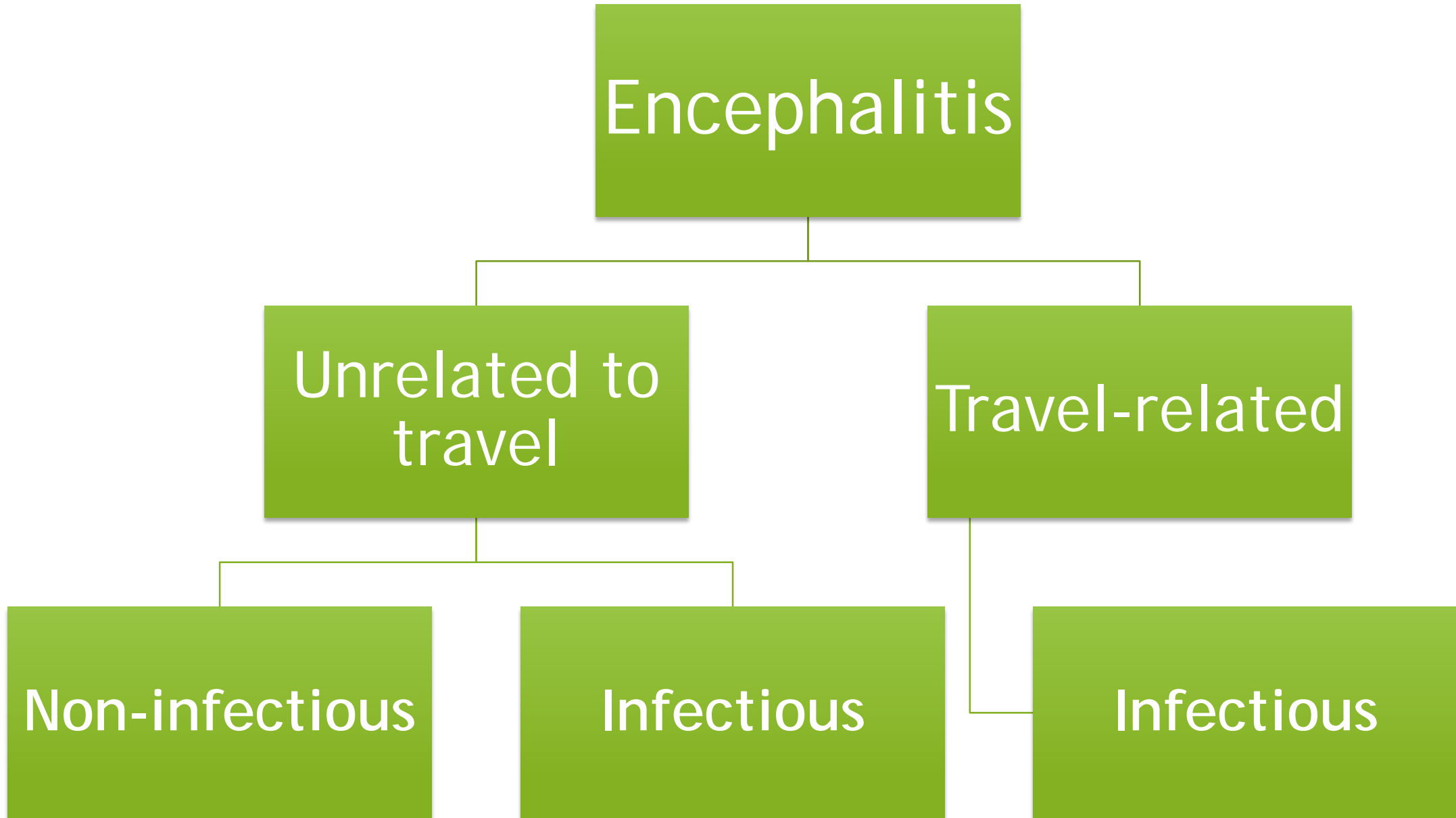
CSF	Patient values	Reference
Gram stain	No organisms	No organisms
Bacterial culture	No growth	No growth
Acid fast staining	Negative	Negative
RBC	7.8×10^6 /L	
WBC	5.0×10^6 /L	0-5.0 x10 ⁶ /L
Protein	0.50 g/L	0.15-0.45 g/L

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Protein	0.50 g/L	0.15-0.45 g/L

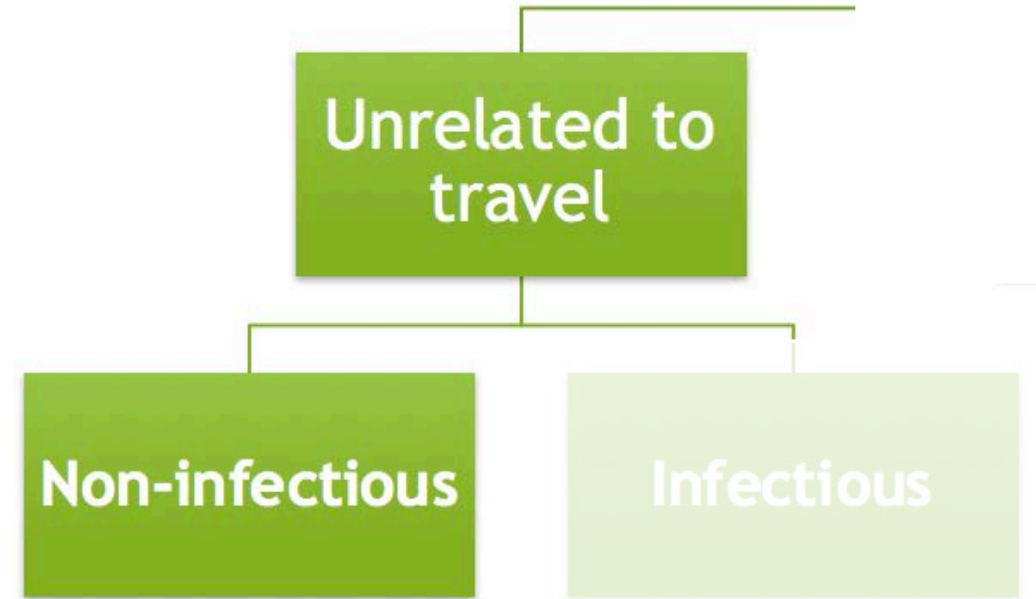
Diagnosis and Approach?

Encephalitis in a Returning Traveller



Encephalitis: Unrelated to travel

- No etiology identified 37%
- Acute immune-mediated 11%
- NMDA-receptor antibody 4%
- Systemic vasculitis 0.5%
- Multiple sclerosis 0.5%
- Paraneoplastic 0.5%



Case Patient Results: Non-infectious encephalitis

Potential Diagnosis	Variable	Patient's result
Non-infectious		
Acute immune-mediated	MRI brain	Normal
NMDA-R AB	NMDA receptor Ab	Negative
Systemic vasculitis	ANA	Positive, 1:80, homogenous
	ANCA	Negative
	Anti-dsDNA	10 IU/mL
	C3 complement	1.29 g/L
	C4 complement	0.38 g/L
Multiple sclerosis	MRI Brain	Normal
Paraneoplastic	Pan-imaging	None found

Encephalitis: Unrelated to travel



Herpes simplex viruses 19%

Varicella Zoster virus 5%

M tuberculosis 5%

Streptococci 2%

Enterovirus 1%

Influenza, Neisseria, toxoplasma,
Coxiella, EBV, Enterococcus,
HHV-6, HIV, JC, Listeria

Case Patient Results: Infectious encephalitis

*Blood test

Potential Diagnosis	Investigation CSF unless noted	Patients Result
HSV/VZV	Alphaherpes virus PCR	Negative
<i>M tuberculosis</i>	Acid fast stain	No organisms
Bacterial meningitis	Gram stain & Culture	No organisms
Enterovirus	Enterovirus RNA PCR	Negative
Parechovirus	Parechovirus RNA PCR	Negative
Influenza	Influenza A & B RNA PCR	Negative
HIV	HIV Antibody*	Negative
Syphilis	VDRL	Non-reactive

Infections in travellers returning from India

Hepatitis A

Hepatitis B

Typhoid fever

Malaria

Japanese encephalitis

Chikungunya fever



Dengue fever

Brucellosis

Poliomyelitis

HIV

Scrub typhus

Rabies

Encephalitis as a feature of travel-related disease

Disease	Associated with encephalitis?	Prominent features
Typhoid fever	4-11%	Fever, diarrhea
Rabies	Yes, >80%	Hydrophobia
Malaria	Yes, cerebral malaria	Fever
Japanese encephalitis	<1% infections	Parkinsonism
Chikungunya	<1% infections	Fever, polyarthrititis
Dengue	Exceptionally rarely	Severe arthralgia and myalgia
Brucellosis	2-7%	Fever & night sweats
Poliomyelitis	Yes	Flaccid paralysis
Zika	Unknown	Teratogenicity
Scrub typhus	No	
Hepatitis A	No	Jaundice
Hepatitis B	No	Non-specific

Case Patient Results

*Blood test

Potential Diagnosis	Investigation CSF unless noted	Patients Result
HSV/VZV	Alpha herpes virus PCR	Negative
<i>M tuberculosis</i>	Acid fast stain	No organisms
Bacterial meningitis	Gram stain & Culture	No organisms
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Parechovirus	Parechovirus RNA PCR	Negative
Influenza	Influenza A & B RNA PCR	Negative
HIV	HIV Antibody*	Negative
Syphilis	VDRL	Non-reactive
Rabies	Clinical	Survived
Malaria	Malaria blood smear*	Negative
Japanese encephalitis	IgG/IgM	Negative
Chikungunya	IgG/IgM	Negative
Dengue	Dengue PCR (CSF)	Negative
Brucellosis	Blood cultures*	Negative
Poliomyelitis	Clinical	No flaccid paralysis

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Scrub typhus	No	
Hepatitis A	No	Jaundice
Hepatitis B	No	Non-specific

Final diagnosis: *Salmonella* encephalitis
also known as “typhoid state” or “typhoid toxinemia”

A brief history of the “typhoid state”

It is, as a rule, a quiet delirium, though there are cases in which the patient is very noisy and constantly tries to get out of bed, and, unless carefully watched, may escape. The patient does not often become maniacal. . . . The eyes may be open, but he is oblivious to all surrounding circumstances and neither knows nor can indicate his wants. The urine and faeces are passed involuntarily. In this pseudo-wakeful state, or coma vigil as it is called, the eyes are open and the patient is constantly muttering. The lips and tongue are tremulous; there is twitching of the fingers and wrists—*subsultus tendinum* and *carphologia*. He picks at the bedclothes or grasps at invisible objects. These are among the most serious symptoms of the disease, and always indicate danger.

Sir William Osler 1892

A brief history of the the “typhoid state”

It is, as a rule, a quiet delirium, though there are cases in which the patient is in a state of coma. . . . The eyes may be open, but he is oblivious to all surrounding circumstances and neither knows nor can indicate his wants. The urine and faeces are in a state, or coma vigilans, in which the patient is constantly muttering. The lips and tongue are tremulous; there is twitching of the fingers and wrists—subsultus tendinum and carphologia. He picks at the bedclothes or grasps at invisible objects. . . . These are serious symptoms of the disease, and always indicate danger.

Sir William Osler 1892

A brief history of the “typhoid state”

eventually recovered. Delirium was usually manifested by a low muttering, but mania, sometimes accompanied with delusions and periods of melancholia, was also seen. Seven of the group exhibited psychosis after all other evidence of disease had disappeared—an incidence of psychosis of 1.94 per cent. With some of them it was a month or more before sufficient improvement had taken place to warrant discharge from the hospital.

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Common Manifestations of Typhoid Fever

- ▶ Human reservoir
- ▶ Contaminated food or water
- ▶ Incubation period: 5-21 days
- ▶ **Week 1: Fever, bacteremia, bradycardia**
- ▶ **Week 2: Abdominal pain, rash**
- ▶ **Week 3: Hepatosplenomegaly, intestinal bleeding... encephalitis**
(peak complications)

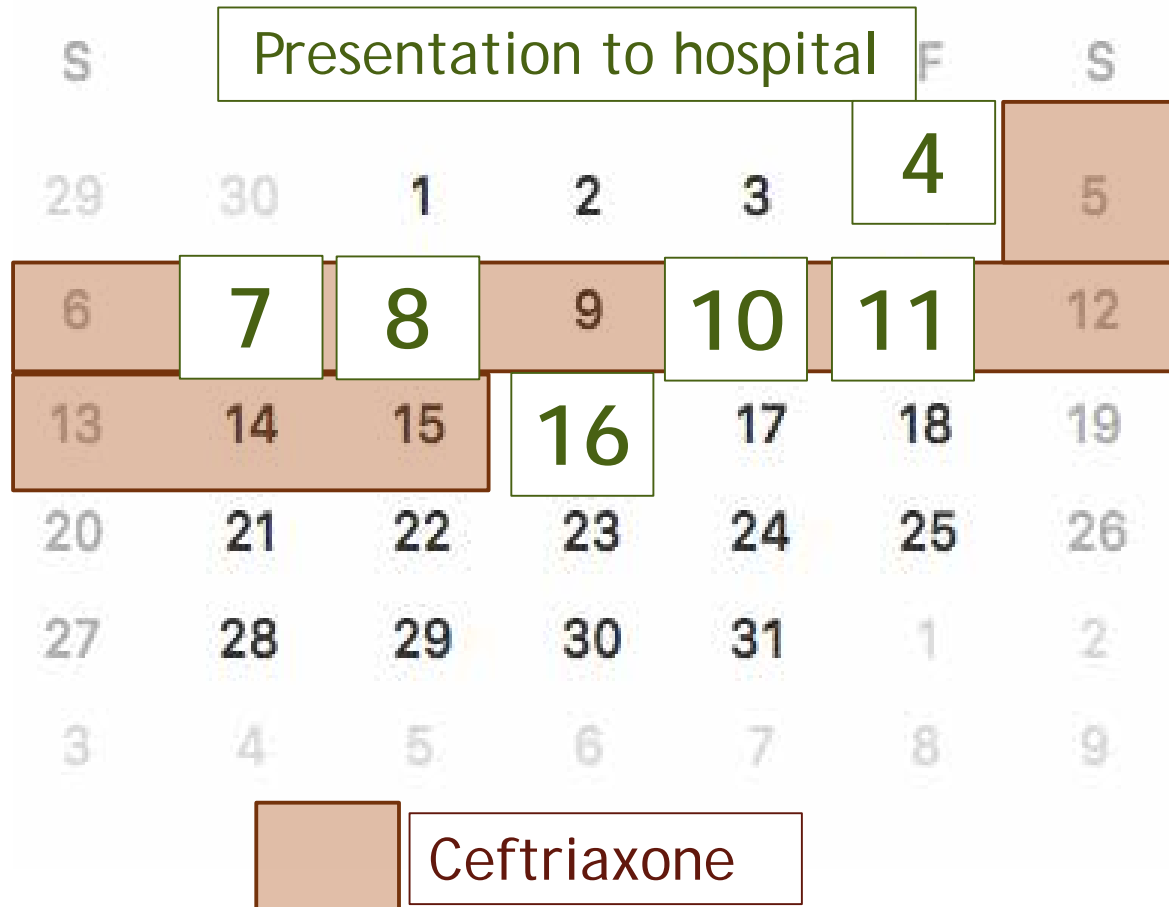
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28	29	30	1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	1

Management of *Salmonella* encephalitis

- ▶ Treat confirmed *Salmonella* infection as usual
 - ▶ 10-14 days of fluoroquinolones, cephalosporins
- ▶ Some poor quality evidence suggests that **severe typhoid** or **typhoid encephalitis** patients may benefit from dexamethasone
 - ▶ Retrospective case series demonstrate possible mortality benefit

Our Case revisited

December



- ▶ Received ten days of intravenous ceftriaxone
- ▶ Two days of vancomycin and acyclovir
- ▶ Begins yelling Punjabi words
- ▶ Begins yelling English words
- ▶ Answers appropriately in Punjabi
- ▶ Answers appropriately in English
- ▶ Discharged well

Conclusions

- ▶ Differential of encephalitis in a returning traveller includes infectious, non-infectious and travel-related infections
- ▶ Uncommon presentations of common travel-related illnesses may be unfamiliar to Western physicians
- ▶ Recognition of the “Typhoid State” or *Salmonella* encephalitis may prompt consideration of treatment with dexamethasone

Discussion and Questions

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References

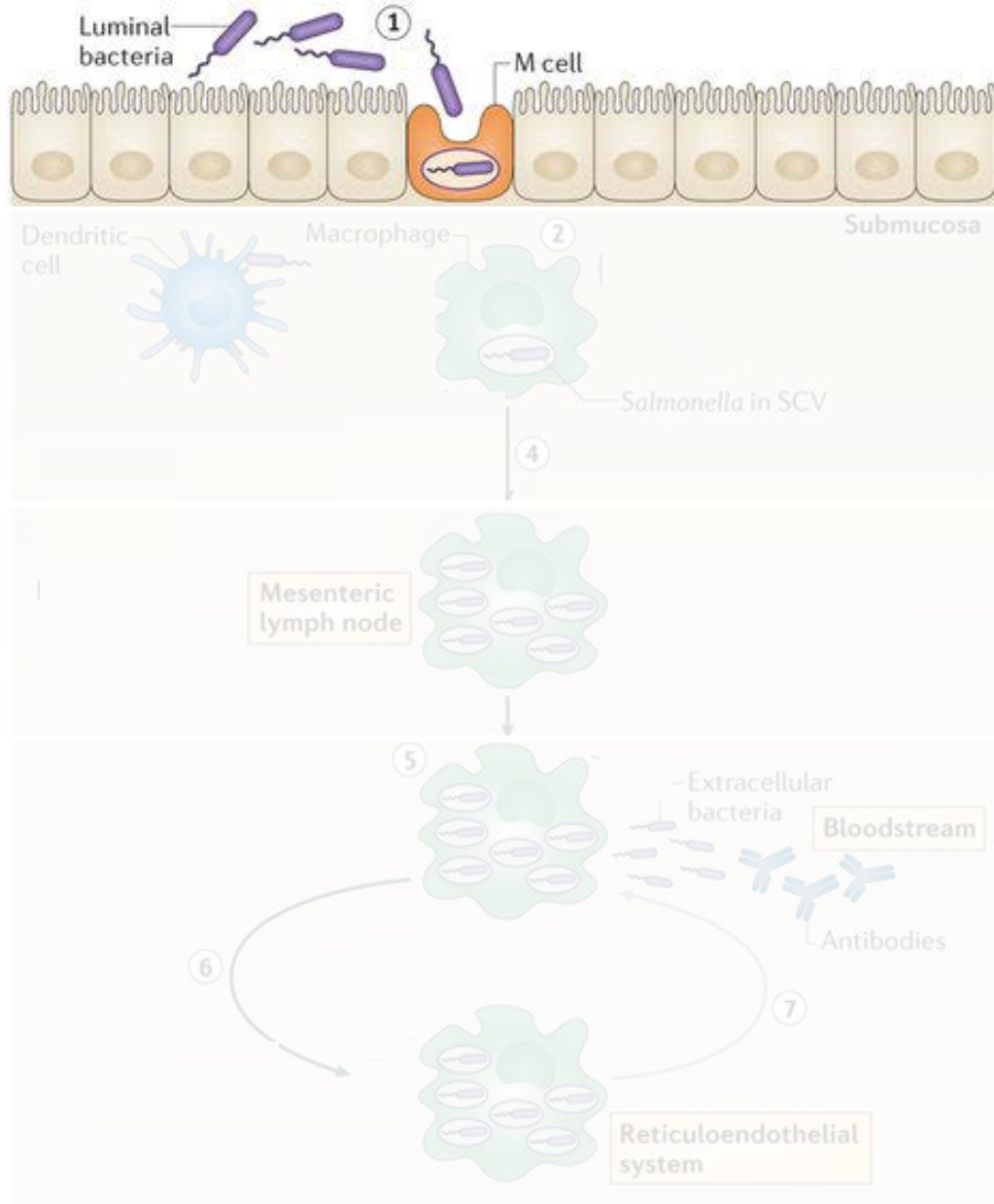
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How often do patients with typhoid fever develop neurologic manifestations?

BCx = Blood Culture

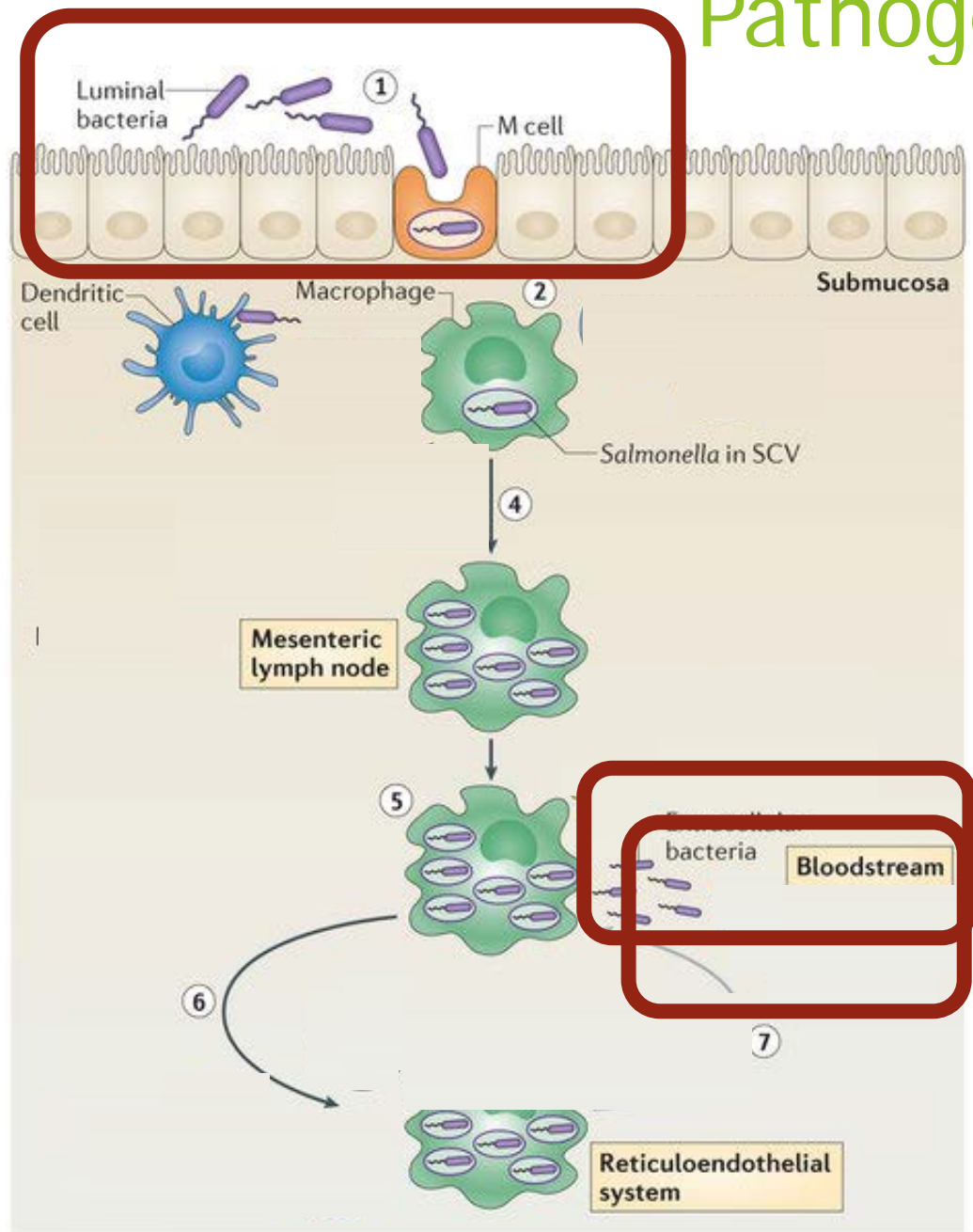
Author & year	Number Patients	Location	Diagnosis	Neuro Symptoms?	Encephalitis
Leung 2012	323	Bangladesh	BCx	21%	N/A
Lutterloh 2012	30	Malawi-Mozambique	Widal/BCx	13.2%	N/A
Lakhotia 2003	232	Jodhpur	Widal/BCx	27.1%	3.8%
Gazanfar 1997	791	Kashmir	Widal	73.3%	1.8%
Osuntokun 1972	959	Nigeria	BCx	57%	0.7%
Stuart 1946	360	Louisiana	BCx, Stool Cx, Widal	72.8%	1.94%

Salmonella infection in humans



- ▶ Bacteria invade intestinal M cells
- ▶ Macrophages and dendritic cells take up bacterium
- ▶ Infected cells migrate to lymph nodes
- ▶ Intra- and extra-cellular bacteria spread through bloodstream and reticuloendothelial system

Pathogenesis of *Salmonella* encephalitis



- ▶ Direct effect?
 - ▶ *Salmonella* is found in less than 2% of CSF cultures
- ▶ Effect of acute illness?
 - ▶ Unrelated to pyrexia and metabolic disturbances
- ▶ Cytokine mediated?
 - ▶ CSF cytokines elevated
- ▶ Immune mediated?
 - ▶ Occur in 3rd week of illness

Management of *Salmonella* Encephalitis

Study	Population	Methodology	Outcome
Christi 2009	23 with typhoid <u>encephalopathy</u>	Retrospective case study	20/20 survivors received dex, 0/3 fatalities did not
Rogerson 1990	99 with <u>severe</u> typhoid	Retrospective cohort of hydrocortisone	No difference in mortality
Punjabi 1988	30 children with <u>severe</u> typhoid	Randomized to dexamethasone or none	2/21 mortality in dex and 7/20 in antibiotic alone
Hoffman 1984	38 with <u>severe</u> typhoid	Randomized to dexamethasone or placebo	2/20 mortality in dex group vs 10/18 placebo

Salmonella encephalitis is a diagnosis of exclusion

- ▶ Dengue IgG and IgM were positive
 - ▶ Likely etiology behind mid-September febrile illness in India
 - ▶ Encephalitis reported in <1% dengue infections
 - ▶ Majority had neurologic manifestations during acute infection
 - ▶ One patient reported to have neurologic manifestations 2-weeks post infection
- ▶ West Nile and Chikungunya were not sent
 - ▶ Would require patient to have contracted **three** travel-related illness
- ▶ Japanese Encephalitis virus was not sent
 - ▶ Not described from the Punjab
 - ▶ Would require patient to have contracted **three** travel-related illness