

“In Sickness and in Health....”

Sushena Krishnaswamy

HOPC

- ◉ 38yo male
- ◉ Fevers 3 days after returning from wedding and honeymoon in Vietnam and Europe

PAST HISTORY

⦿ Chronic Hepatitis B

- Dx 2005 blood donation (sAg, cAb, eAb +ve)
- Regular follow up, no treatment
- Viral load 39IU/ml

⦿ Malaria

SOCIAL HISTORY

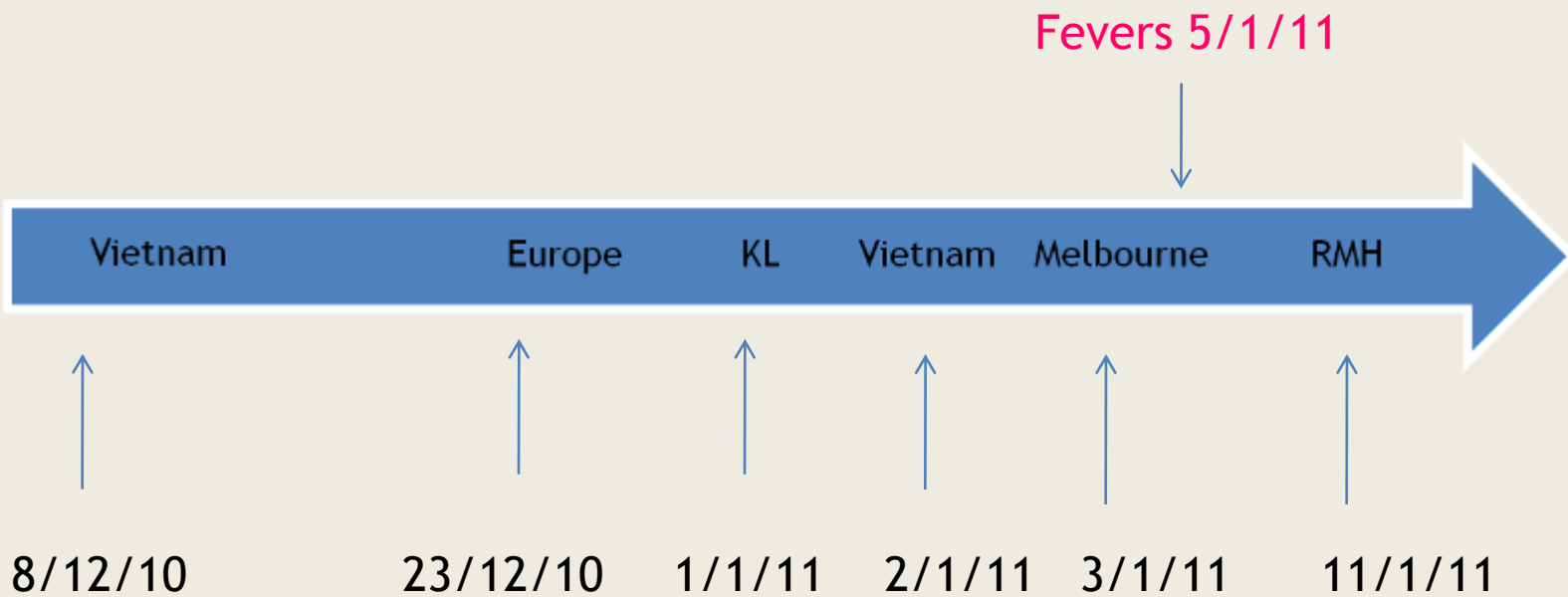
- ◉ Migrated from Vietnam aged 12
- ◉ Recently married
- ◉ Works as industrial chemist (pesticides)
- ◉ Non-smoker, Social ETOH, No IDU
- ◉ Childhood immunisations Vietnam

HOPC

- ⦿ Adm 11/1/11 (Day 7)

- 7 days fevers, headache, myalgia, anorexia
- 5 days rigors
- 2 days dark urine

- ⦿ No response to Augmentin DF, cefaclor by GP



INITIAL ASSESSMENT DAY 7

⦿ Emergency Department

- T39.3, HR 110, BP 116/67, RR 20, Sats 100%RA
- Admitted
- Symptomatic management

VIDS REVIEW DAY 8

- ◉ Afebrile
- ◉ Conjunctival suffusion
- ◉ Fine erythematous rash over torso
- ◉ Scattered petechiae legs and palate
- ◉ Microscopic haematuria



ADMISSION BLOODS

- ◉ Hb 151 MCV 76
- ◉ Wcc 3.2 Neut/Lymph 0.3/0.3
- ◉ Plts 43
- ◉ Blood Film- Toxic granulation, no fragments

- ◉ UEC - normal

- ◉ LFT - Alb 25, ALP 108, GGT 118, ALT 161, AST 264, Bili 18

- ◉ Thick and thin film, ICT - negative

- ◉ MSU - >1000rbc

EVENING OF DAY 8

- ⦿ MET call for hypotension- BP 80/40, Temp 40° C
- ⦿ Clinical volume overload
- ⦿ No urine output for 18 hours
- ⦿ Rash more diffuse
- ⦿ Glomerular rbc in urine

- ⦿ Ceftriaxone 2g d, Ciprofloxacin 500mg bd
- ⦿ Transferred to ICU

DAY 9

- ◉ Requiring CPAP
- ◉ Hypotensive despite 6.5L fluid resuscitation
- ◉ Noradrenaline up to 12mcg/min
- ◉ Minor oropharyngeal bleeding
- ◉ Rash almost resolved

- ◉ Switched to meropenem and doxycycline



RESULTS AT THIS POINT

- ⦿ Blood cultures -ve at 40 hours
- ⦿ HIV -ve, HCV -ve
- ⦿ ASOT, anti-DNAse B -ve
- ⦿ Rubella & measles PCR -ve
- ⦿ Urine Strep pneumo & Legionella Ag -ve
- ⦿ Mycoplasma IgG +ve

DAY 10

⦿ Renal RV

- DDx: Leptospirosis

IgA nephropathy unmasked by infection

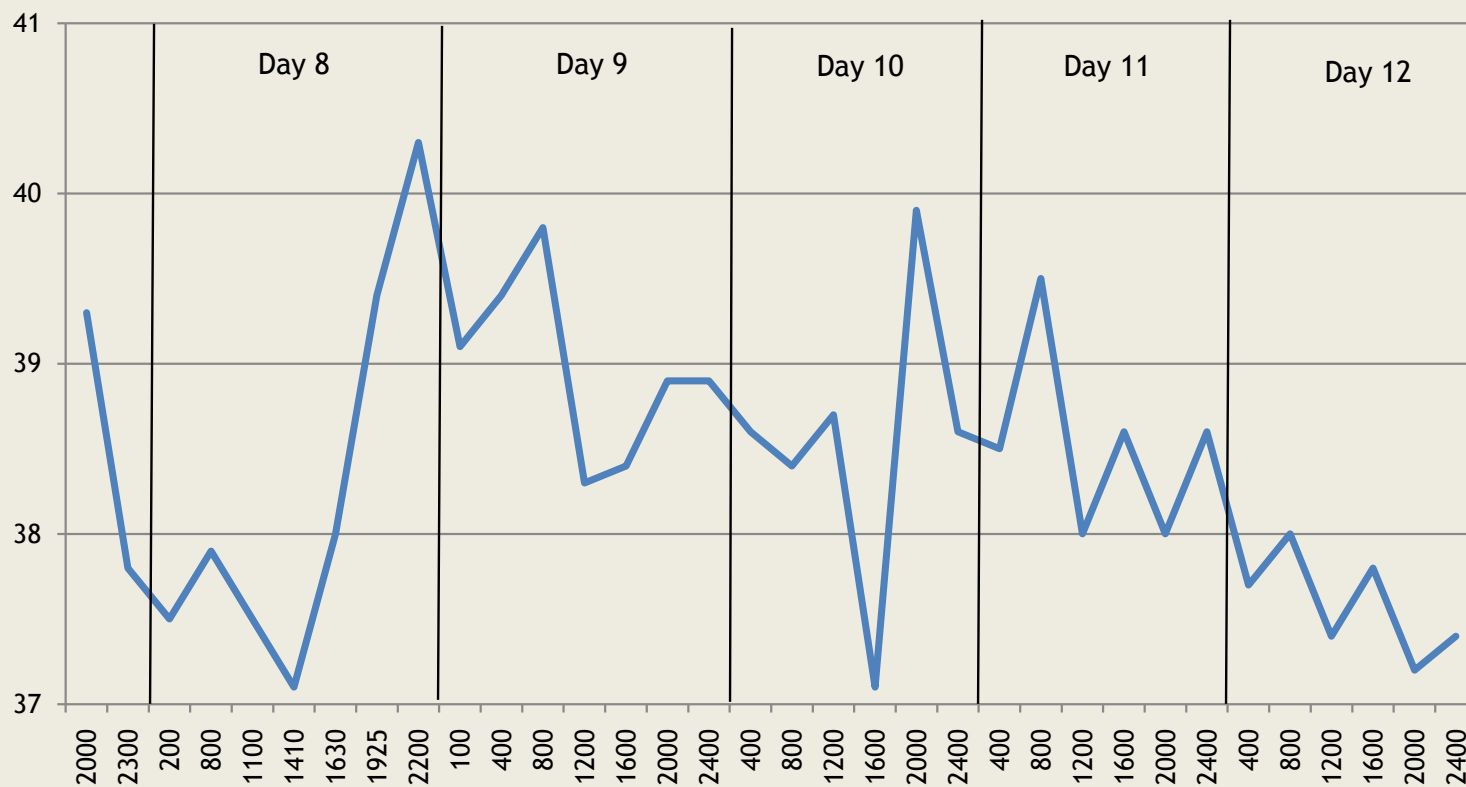
Post-infectious GN

Sepsis

⦿ CT chest/ abdo

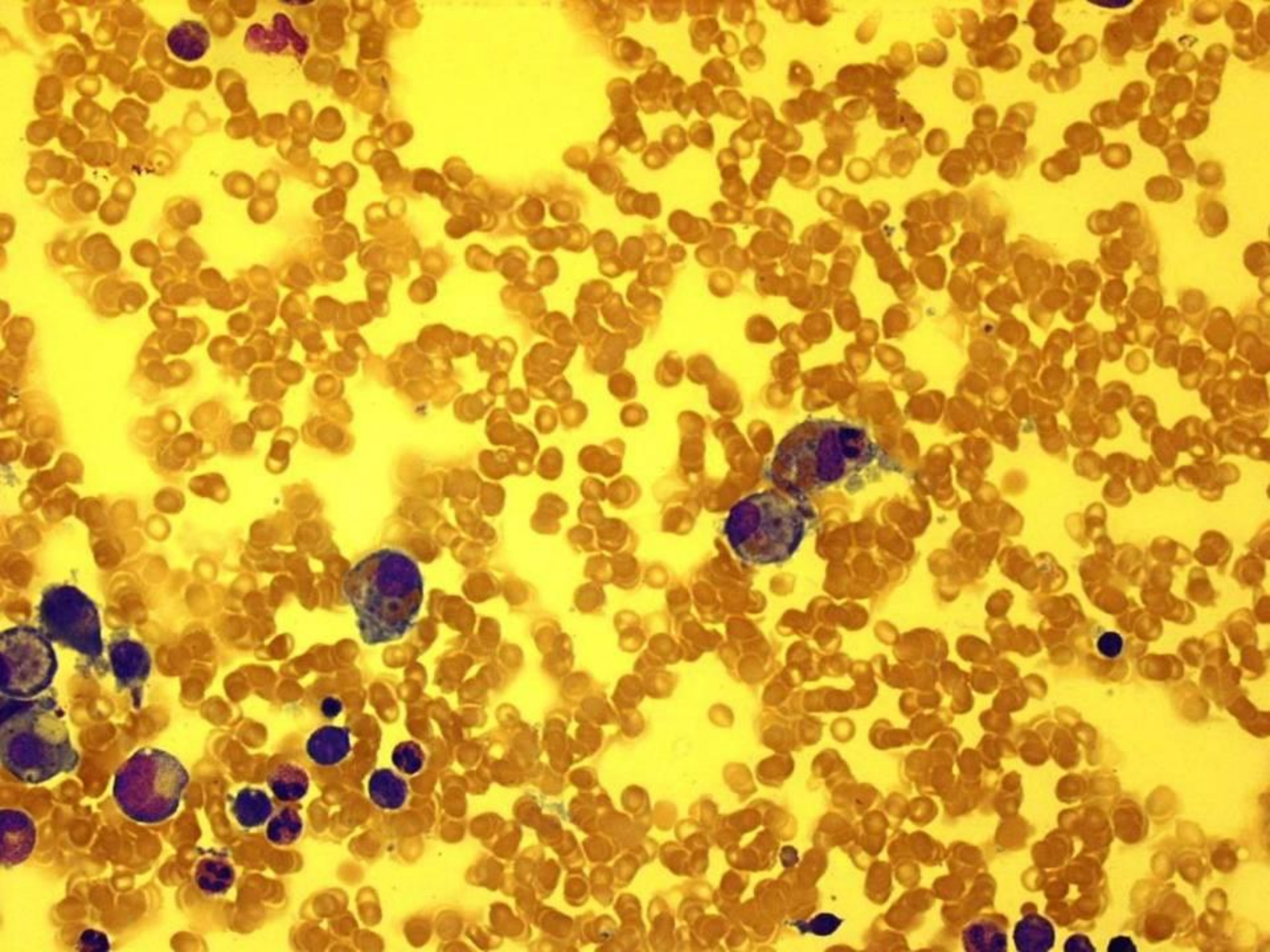


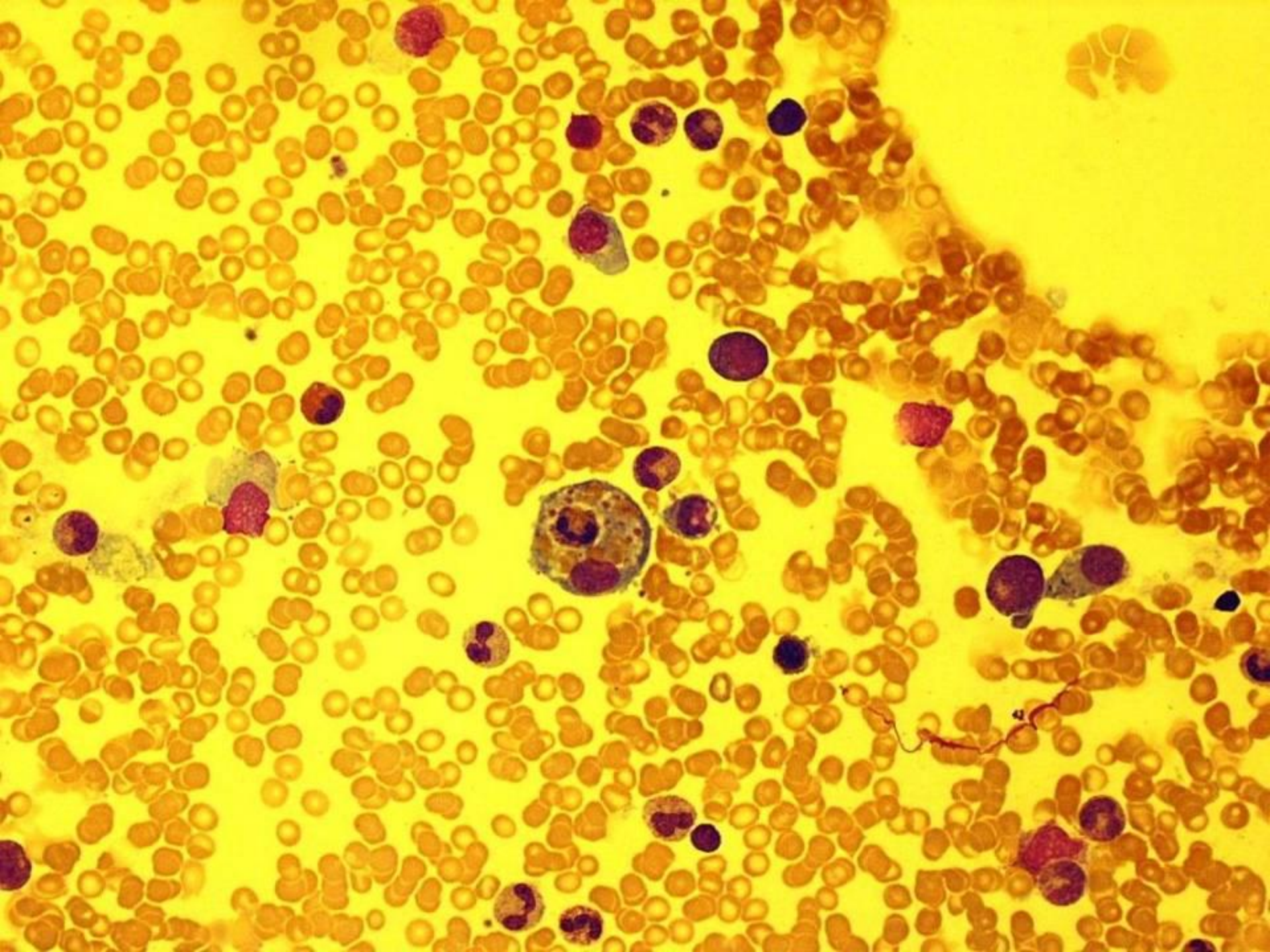
FEVER CHART



DAY 10

- ⦿ Inotropic & resp support slowly decreasing
- ⦿ Ferritin **7198**
 - Iron 1, Transferrin Sat 6%
- ⦿ BMAT





PROGRESS

◉ Day 11

- Bronchoscopy: inflamed airways
- Active diuresis
- Noradrenaline ceased

◉ Day 12 of illness

- Becomes afebrile

PROGRESS

◉ Day 13

- Discharged from ICU

◉ Day 16

- Discharged from hospital
 - ◉ Azithromycin
 - ◉ Doxycycline

RESULTS

ICU

BMAT

	7	8	9	10	13	16
Wcc	3.2	3.2	6.7	6.7	9.7	7.8
Neuts	0.3	0.3	3.7	3.7	171	3.4
Lymph	0.3	0.4	0.5	0.9	2.7	3.3
Platelets	43	29	34	35	171	367
ALP	108	108	92	96	206	166
GGT	118	111	93	102	242	207
ALT	161	161	189	296	255	179
AST	264	264	296	536	273	39
Bili	18	18	28	27	22	18
Ferritin				7198	3480	
CRP		158	119			17

RESULTS ON DISCHARGE

- ◉ All blood cultures -ve
- ◉ Dengue IgM & PCR -ve (day 7 & 12 of illness)
- ◉ Leptospirosis serology, urine & blood PCR -ve
- ◉ CMV IgM & IgG -ve
- ◉ EBV, Toxo IgG +ve
- ◉ WIDAL -ve
- ◉ Vasculitic screen NAD

RESULTS ON DISCHARGE

⊙ Hb electrophoresis

- Heterozygous HbE

⊙ Haemophagocytosis

- HSV, VZV, CMV PCR-ve
- EBV 7.5×10^5 cop/ml
- Quantiferon indeterminate
- HHV-8 PCR -ve
- Triglycerides 2.7
- Fibrinogen 2.9

⊙ Bronchoscopy

- +wbc, no orgs on gm
- K.pneumoniae, P.aeruginosa, Enterococcus
- Fungal culture -ve
- Legionella culture -ve
- PCP stain & PCR -ve
- Resp virus PCR -ve
- Herpes mutiplex PCR -ve
- AFB smear -ve
- Cytology NAD

OUTPATIENT REVIEW WEEK 1

- ⦿ Well
- ⦿ Back at work
- ⦿ Hepatitis almost resolved

ACUTE RICKETTSIAL SEROLOGY

SPOTTED FEVER GROUP RICKETTSIA

R.australis Total Antibody by IF : Positive (titre = 256) (Queensland tick typhus)
R.honei Total Antibody by IF : Positive (titre = 256) (Flinders Island spotted fever)
R.conorii Total Antibody by IF : Positive (titre = 256) (Mediterranean Spotted Fever)
R.sibirica Total Antibody by IF : Positive (titre = 256) (North Asian tick typhus)
R.rickettsii Total Antibody by IF: Positive (titre = 256) (Rocky mountain spotted fever)
R.akari Total Antibody by IF : Positive (titre = 256) (Rickettsial pox)

TYPHUS GROUP RICKETTSIA

R.prowazekii Total Antibody by IF: Positive (titre= 1024) (Epidemic typhus)
R.typhi Total Antibody by IF : Positive (titre= 1024) (Murine typhus)

SCRUB TYPHUS GROUP RICKETTSIA

O.tsutsugamushi Total Ab. serotype Gilliam by IF : Negative (titre <128)
O.tsutsugamushi Total Ab. serotype Karp by IF : Negative (titre <128)
O.tsutsugamushi Total Ab. serotype Kato by IF : Negative (titre <128)
O.tsutsugamushi Total Ab. serotype Litchfield by IF: Not available

CONVALESCENT SEROLOGY

SPOTTED FEVER GROUP RICKETTSIA

R.australis Total Antibody by IF : Positive (titre =4096) (Queensland tick typhus)
R.honei Total Antibody by IF : Positive (titre =4096) (Flinders Island spotted fever)
R.conorii Total Antibody by IF : Positive (titre =4096) (Mediterranean Spotted Fever)
R.sibirica Total Antibody by IF : Positive (titre =4096) (North Asian tick typhus)
R.rickettsii Total Antibody by IF: Positive (titre =4096) (Rocky mountain spotted fever)
R.akari Total Antibody by IF : Positive (titre =4096) (Rickettsial pox)

TYPHUS GROUP RICKETTSIA

R.prowazekii Total Antibody by IF: Positive (titre>=16384 (Epidemic typhus)
R.typhi Total Antibody by IF : Positive (titre>=16384 (Murine typhus)

SCRUB TYPHUS GROUP RICKETTSIA

O.tsutsugamushi Total Ab. serotype Gilliam by IF : Negative (titre <128)
O.tsutsugamushi Total Ab. serotype Karp by IF : Negative (titre <128)
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RICKETTSIAL PCR

RICKETTSIAL PCR

Spotted Fever / Typhus Group: DETECTED

Scrub Typhus Group: Not tested.

COMMENT: Evidence of rickettsial DNA in serum. This assay detects DNA from Rickettsia sp. It is reported as POSITIVE only when repeat testing of the patient specimen has confirmed the result was positive.

MURINE TYPHUS

EPIDEMIOLOGY

- ⦿ Documented on all continents

- No seasonal variation in tropics
- Northern hemisphere: hot/dry months
- NZ: April-October¹

- ⦿ Poor data on prevalence

- Serological survey 513 children (1-17yo) in Texas²
 - 13% IgG positive

¹ Gray E et al, J NZ Med Assoc 2007 (120) 1259

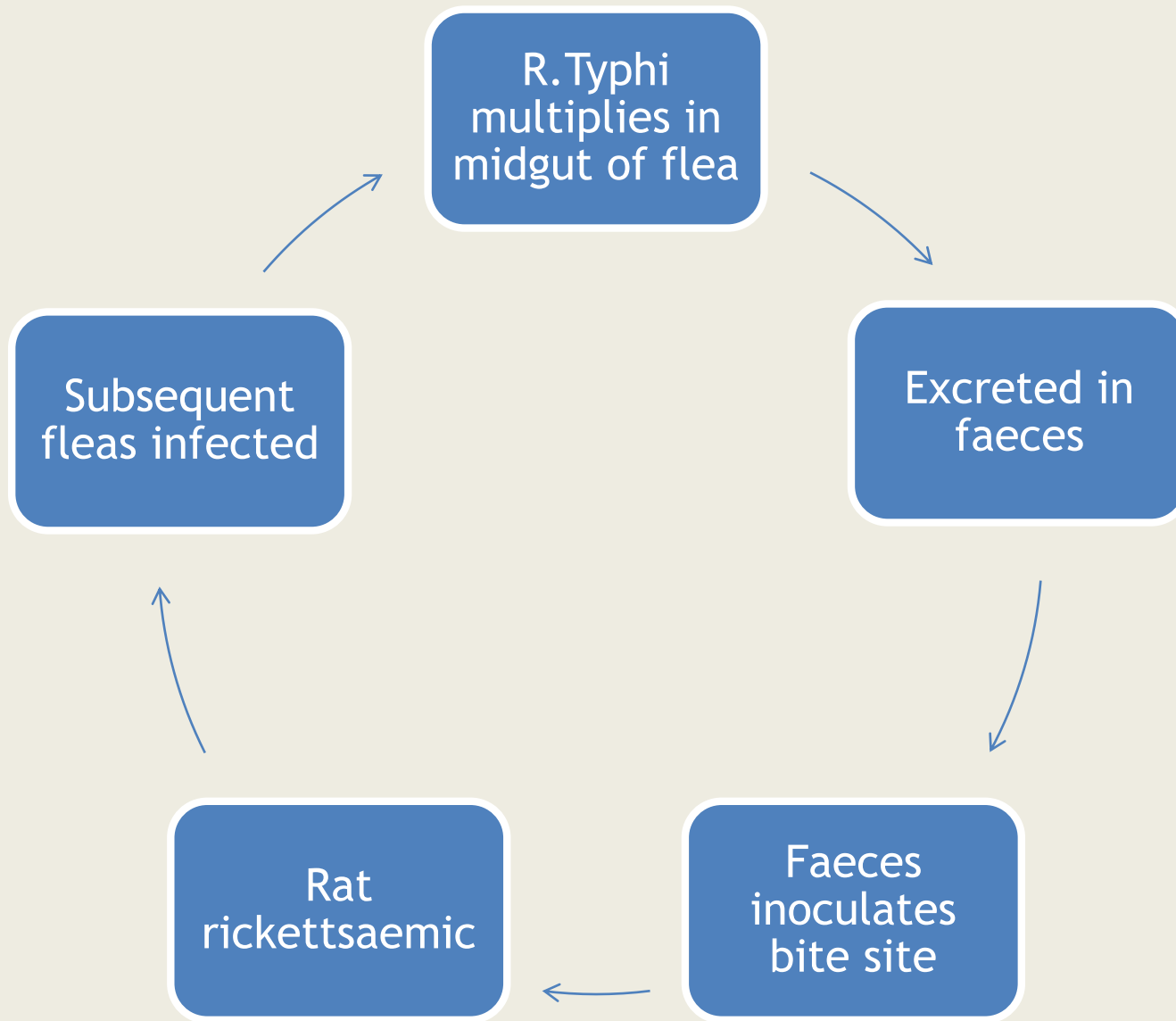
² UpToDate

AUSTRALIA

- Second rickettsial disease identified
- First published report in world in 1922
 - Association with rodents
 - Noted lower mortality
- Found Australia wide
 - First reported case from Victoria 2004²

TRANSMISSION

- R.typhi- obligate intracellular gram negative
- Rat flea - *Xenopsylla cheopis*
 - Rat- flea-rat cycle
- Less commonly
 - Cat flea - *Ctenocephalides felis*
 - Mouse flea - *Leptopsyllia segnis*



TRANSMISSION

- ◉ Neither rat fleas or rats develop disease

- ◉ Humans incidental hosts
 - ◉ Inhalation aerosolised infected flea faeces
 - ◉ Inoculation of faeces into fleabite

CLINICAL FEATURES

- ◉ Incubation period 8-16 days
- ◉ Classic triad- fever, headache, rash¹
- ◉ Rash day 6-7²
 - In <50% of cases
 - Trunk → peripheral, spares palms and soles
 - Petechial in <10%
 - Lasts 1-4 days

¹Parola et al. Emerg Inf Dis 2003;9:592-5

²Mouffok et al, - Emerg Inf Dis 2008;14:676

Table 1. Studies reporting clinical findings associated with murine typhus.

Clinical finding	Range of occurrence, %	References
Fever	98–100	[4, 13, 30–34]
Headache	41–90	[4, 13, 30–34]
Rash	20–80	[4, 13, 30–34]
Arthralgia	40–77	[4, 13, 30–34]
Hepatomegaly	24–29	[13, 30, 31, 33]
Cough	15–40	[4, 13, 30, 32–34]
Diarrhea	5–40	[4, 13, 30–34]
Splenomegaly	5–24	[13, 30, 31, 33]
Insect bite	0–39	[4, 30–34]
Nausea and/or vomiting	3–48	[4, 13, 30–34]
Abdominal pain	11–60	[4, 13, 30–32, 34]
Confusion	2–13	[4, 13, 30–34]

PREVALENCE IN AUF IN SE ASIA

	Murine Typhus	Leptospirosis
Semerang, Indonesia ¹	7%	10%
Rural Thailand ¹	2.8%	36.9%
Thai-Myanmar border ³	1.5%	17.5%
Vientiane, Laos ¹	9.6%	
Nepal ²	11%	

¹Gasem et al, Emerg Inf Dis 2009;15(6):975-7

²Zimmerman et al, Emerg Inf Dis 2008;14(10):1656-1659

³Ellis et al. Am J Trop Med Hyg 2006;74:108-13

COMPLICATIONS

⦿ Inflammatory Vasculitis

- Small-medium sized vessels
- Haemorrhage
- Increased vascular permeability → oedema
- Retinal haemorrhage, exudates, inflammation

⦿ Renal

- Pre-renal
- Interstitial nephritis

⦿ CNS

- Meningitis
- Nerve palsies
- Delirium

⦿ Respiratory

- Interstitial infiltrate

⦿ Splenic rupture

⦿ Up to 4% mortality¹

INVESTIGATIONS

- ⦿ Thrombocytopenia 48%
- ⦿ Hyponatremia 60%
- ⦿ LFT abnormalities 90%
- ⦿ Haematuria 28%

DIAGNOSIS

◉ Serology

- ◉ LPS in cell membrane cross-react other rickettsiae
- ◉ Epidemic typhus, Spotted fever Group
- Can DDX with
 - ◉ Western blot, Cross-adsorption studies

◉ PCR

◉ Culture

TREATMENT

- Spontaneous recovery within 2 weeks
- Tetracyclines
 - Hasten recovery & decrease complications
 - Defervescence usually within 48 hours
- No evidence in vivo for quinolones
 - Effective in vitro
- No RCT studying duration

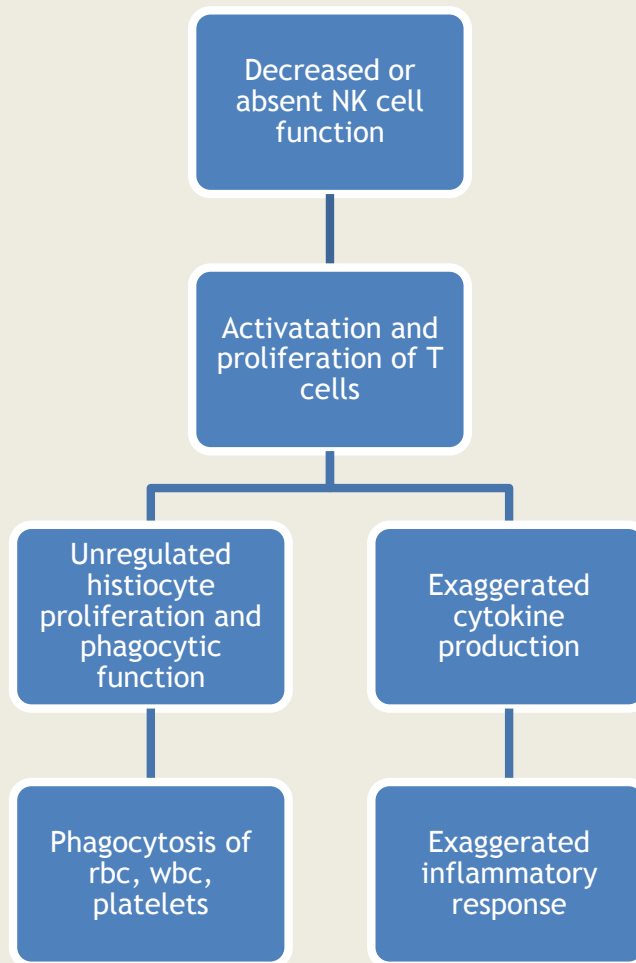
TREATMENT

⦿ Time to defervescence

- Doxycycline 2.9 days
- D + chloramphenicol 3.4 days
- Chloramphenicol 4.0 days
- D + ciprofloxacin 4.0 days
- Ciprofloxacin 4.2 days

RIKETTTSIAE AND HAEMOPHAGOCYTYC SYNDROME

PATHOPHYSIOLOGY OF HLH



DIAGNOSTIC CRITERIA 2007

- 1) Fever >38.5 for 7 or more days*
- 2) Splenomegaly $>3\text{cm}$ below costal margin
- 3) Cytopenia involving at least 2 cell lines*
- 4) Hypertriglyceridemia or hypofibrinogenemia*
- 5) Haemophagocytosis*
- 6) Hepatitis*
- 7) Low or absent NK cell activity
- 8) Ferritin $>500\text{mcg/L}$ (but >3000 more specific)*
- 9) Soluble CD25 $>2400\text{ U/ml}$

RICKETTSIAE AND HAEMOPHAGOCYTOSIS

○ 15 cases

- 5 Mediterranean Spotted Fever
- 7 scrub typhus
- 3 HME
- 13/15 adults
- Only 1 fulfilled updated HLH diagnostic criteria
- Steroids in 3, cyclosporin in 1

○ 2 papers of post-mortem findings of RMSF

- 8 children, 5 adults had HLH

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