Adult Cases

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BVIKM/SBMIC

Patient 1

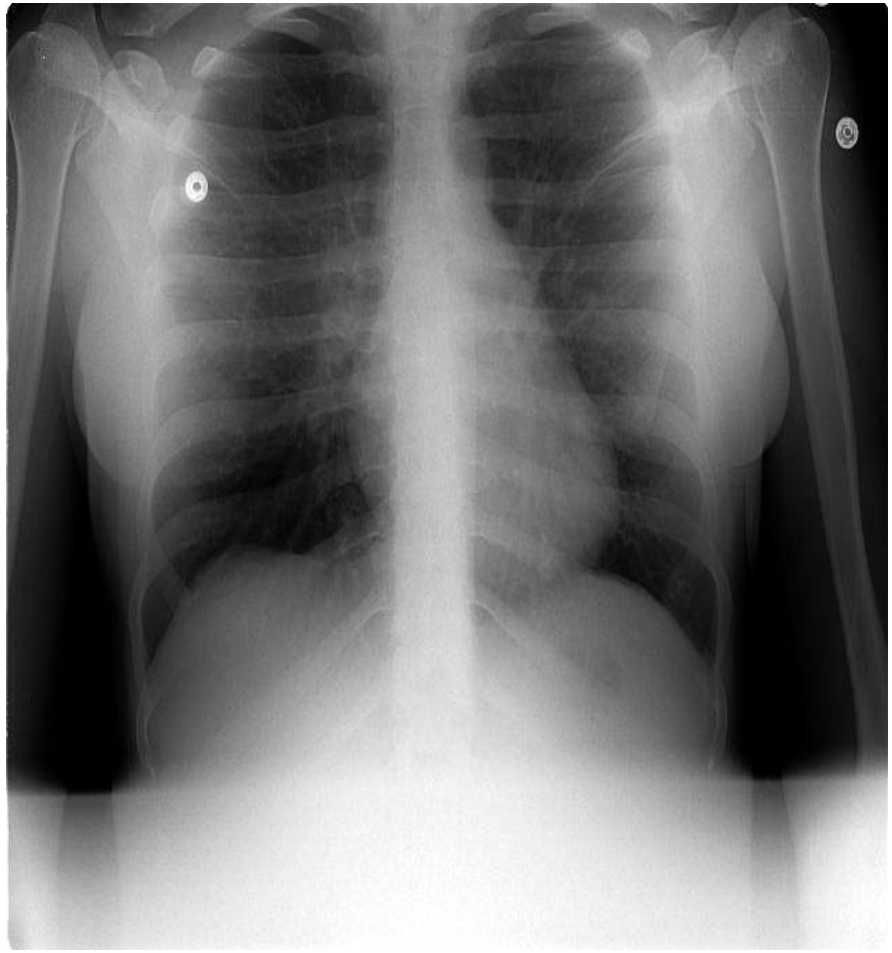
- A 26 year old woman presented to the emergency ward with fever, non productive cough and severe asthenia for two weeks
- 6 months history of Crohn disease
  treated with azathioprin (Imuran*) 150 mg qd
  and two months of methylprednisolone 16 mg qd
  stopped 2 weeks before hospitalisation
- No digestive disorder at the admission
- No rash
- No effect of 3 days of antibiotic therapy
  with oral amoxicilline-clavulanate
- Not sexually active

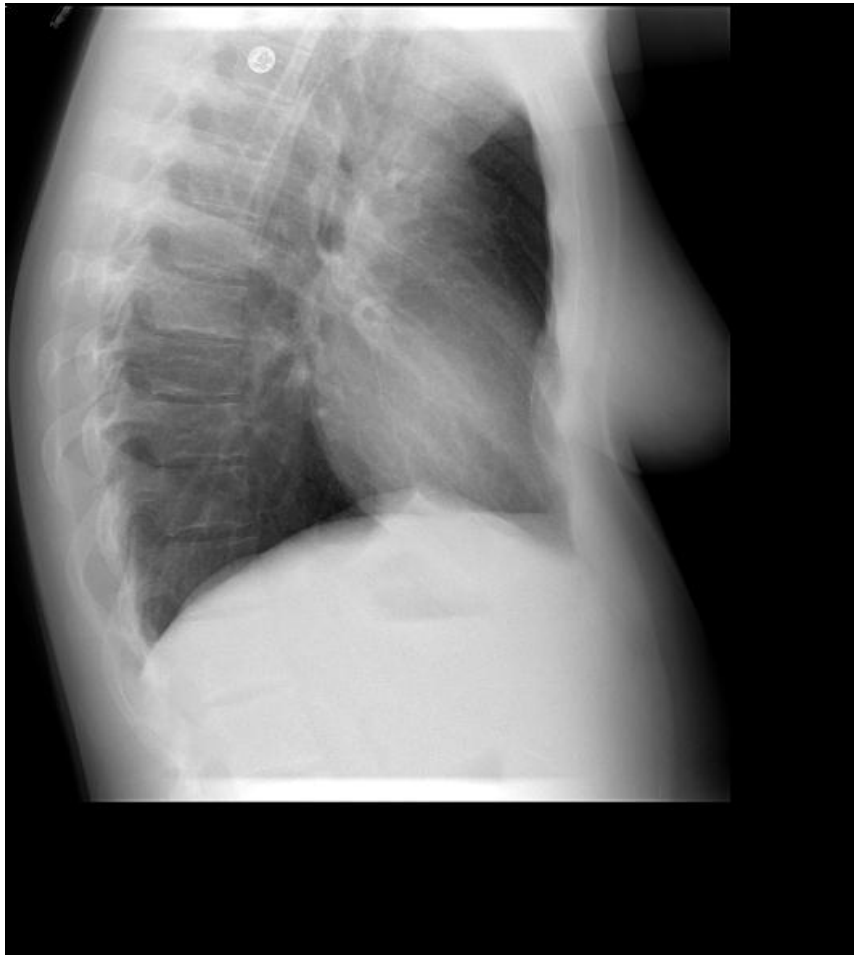
Clinical examination

- Fever up to 37°7 C, chills
- Blood pressure : 130/60
- Pulse rate : 92
- Respiratory Rate : 20
- The exam was unremarkable :
  no rash, no pharyngitis

	At admission (Saturday night fever)
White blood cell /mm3	4000 (PN 72 %, L19.1%)
Red blood cell g/dl	12.4
Platelets /mm3	107 000
CRP mg/dl (<0.5)	6.37
GOT UI/L (7-31)	72
GPT UI/L (7-31)	31
CPK UI/L (10-170)	69
LDH UI/L (125-250)	570
δ GT UI/L (5-36)	109
Ph alc UI/L (40-50)	117
Total Bili mg/dl (0.3-1.1)	1.5
Hep A IgG/IgM	+/-
Hep B AG HBs Ac anti-HBs, HBc	-
Hep C	-
EBV: Paul et Bunnel/ IgG/IgM/	IgG+
Mycoplasma pn. IgG (0-100) IgM (0-100)	 342 177
Chlamydia pn. IgG (0-100) IgA (0-100)	 127 > 1000

+ blood cultures
+ urinoculture





- **DD at the admission** :
  - Respiratory tract infection due to typical or « atypical » germs ? Chlamydia pneumoniae ?
  - Azathioprine haematologic and liver toxicity ?
  - Other

- **Treatment**
  - Hospitalisation
  - Intravenous infusion
  - Moxifloxacin 400 mg orally qd

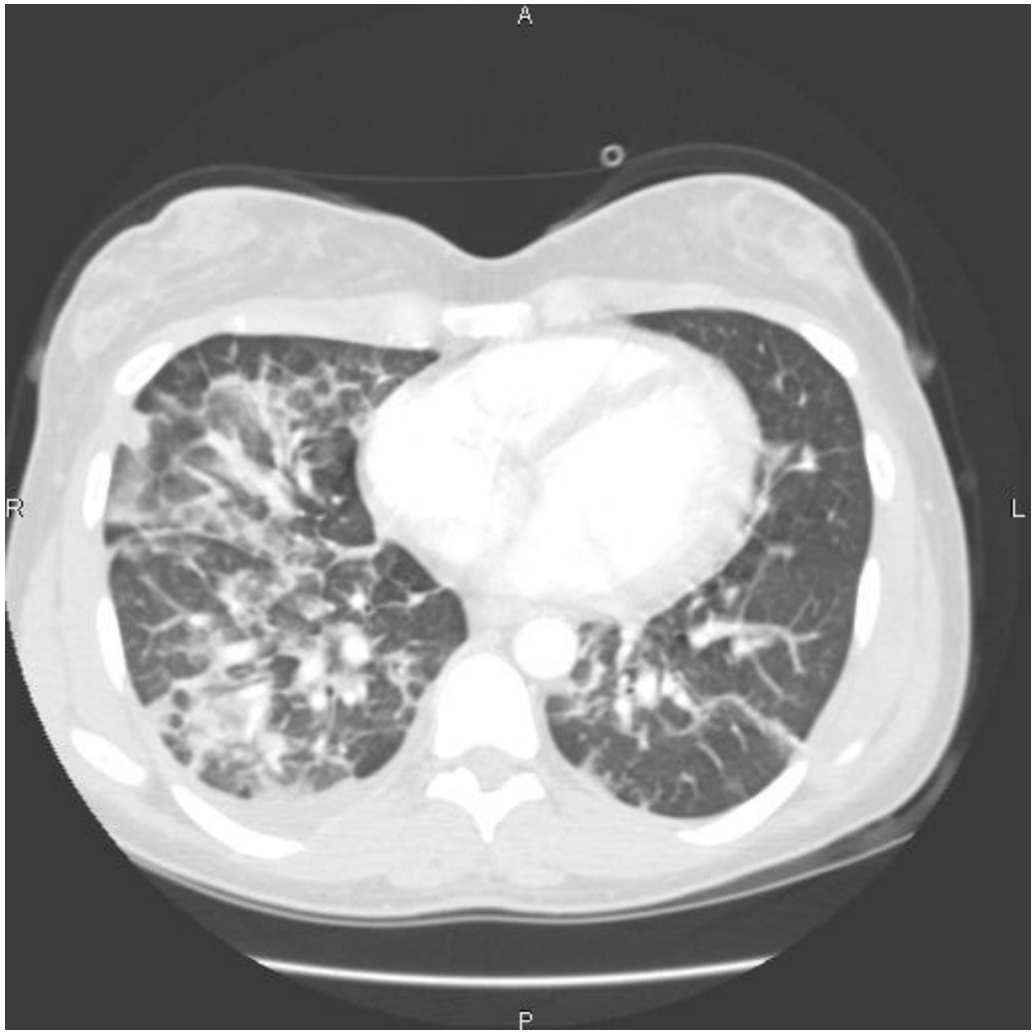
Evolution

- No improvement
- After 36 hours,
  - persistence of fever and chills,
  - increased respiratory impairment with polypnea

	Admission	+ 36 hours
White blood cell /mm³	4000 (PN 72 %, L19.1%)	**1900 (64%, L 30%)**
Red blood cell g/dl	12.4	**10.6**
Platelets /mm³	107 000	**105000**
CRP mg/dl (<0.5)	6.37	**4.64**
GOT UI/L (7-31)	72	**61**
GPT UI/L (7-31)	31	**34**
CPK UI/L (10-170)	69	**294**
LDH UI/L (125-250)	570	**511**
δ GT UI/L (5-36)	109	**102**
Ph alc UI/L (40-50)	117	**109**
Total Bili mg/dl (0.3-1.1)	1.5	**1.3**
D-dimères		**> 9000 microg/l**

- **+ 36 hours :**
  - **Legionella AC** neg
  - **Blood culture** neg
  - **Urine culture** neg
  - **Gazometry :**
    - pH 7.49
    - pCO_2 23.8
    - pO_2 49.4
    - BE -5.6
    - bicarbonate 18.5
    - sat O_2 90.8%

d3



Pulmonary Infiltrates :

right inferior and median lobe
+ left posterobasal lobe
+ bilateral diffuse interstitial

+ hepatomegaly

+ homogen splenomegaly

+ mediastinal adenopathies

NO pulmonary embolism

What is/are the possible diagnosis at this stage ? *(several answers possible)*

1. Azathioprin toxicity

25%

2. Bacterial pneumonia

25%

3. Viral primoinfection

25%

4. ‘Pneumocystis jiroveci’ pneumonia (PCP)

25%

1. Azathioprin – side effects

- Hematological
  Leucopenia >> Thrombopenia >> Anemia → Main side effect (with gastrointestinal), reversible
- Hypersensitivity, fever, rash, arthralgia, myalgia, hepatotoxicity, reversible interstitial pneumonia → Low frequency
- Viral infection in non transplanted patients → Low frequency

2. Atypical bacterial infection

- Pro :
  - Chlamydia serology : IgA +
- Contra :
  - No improvement < FQ treatment but immunosuppressed.

3. Viral primoinfection or reactivation

- Pro :
  - pancytopenia
  - CRP < 10 mg/dl at admission and not increased despite clinical impairment
  - Immunosuppressed with corticosteroid
  - Clinical presentation (2 weeks)
- Contra :
  - No severe immunosuppression
  - No rash

4. PCP

- Pro :
  - Severe hypoxia
  - LDH increased
  - Immunosuppressed with corticosteroid
- Contra :
  - Clinical presentation (2 weeks)
  - No severe immunosuppression
  - LDH didn’t increase between day1 and day3 despite no specific treatment

What investigation(s) do you perform at this stage ? (*several answers possible*)

1. Add HIV and CMV serologies

14%
2. Urinary legionella Ag

14%
3. Galactomanan determination (blood)

14%
4. Add toxoplasma, rubella and measles serologies

14%
5. Bronchoalveolar lavage + PCP/ PCR PCP + culture,…

14%
6. CD4 numeration

14%
7. Others

14%

Complementary diagnosis tests

- **HIV –**
- **CMV (EIA)**
  - IgG 44 UA/ml (0-7)
  - **IgM 1206 UA/ml (0-100)**
  - IgM (Sd ELISA) 244
  - IgG Avidity 6% **: recent infection**
- **Urine Legionella Ag : neg**
- **CD4 Lymphocytes : 284/mm³**
- **BAL :**
  - Direct exam : neg
  - Bacterial / fungal cultures : pending
  - CMV PCR : pending
  - *Jiroveci pneumocystis* (direct examen, PCR) : pending

In addition to supportive care, how do you adapt your treatment ?

1. Add broad spectrum antibiotic therapy to moxifloxacin + PCP empirical treatment + corticosteroid (severe hypoxia PCP and possible toxicity due azathioprine)

17%

2. 1 + stop azathioprine

17%

3. 1 + stop moxifloxacin

17%

4. 1 + gancyclovir

17%

5. Add gancyclovir to moxifloxacin

17%

6. Add gancyclovir and stop moxifloxacin

17%

Day 4

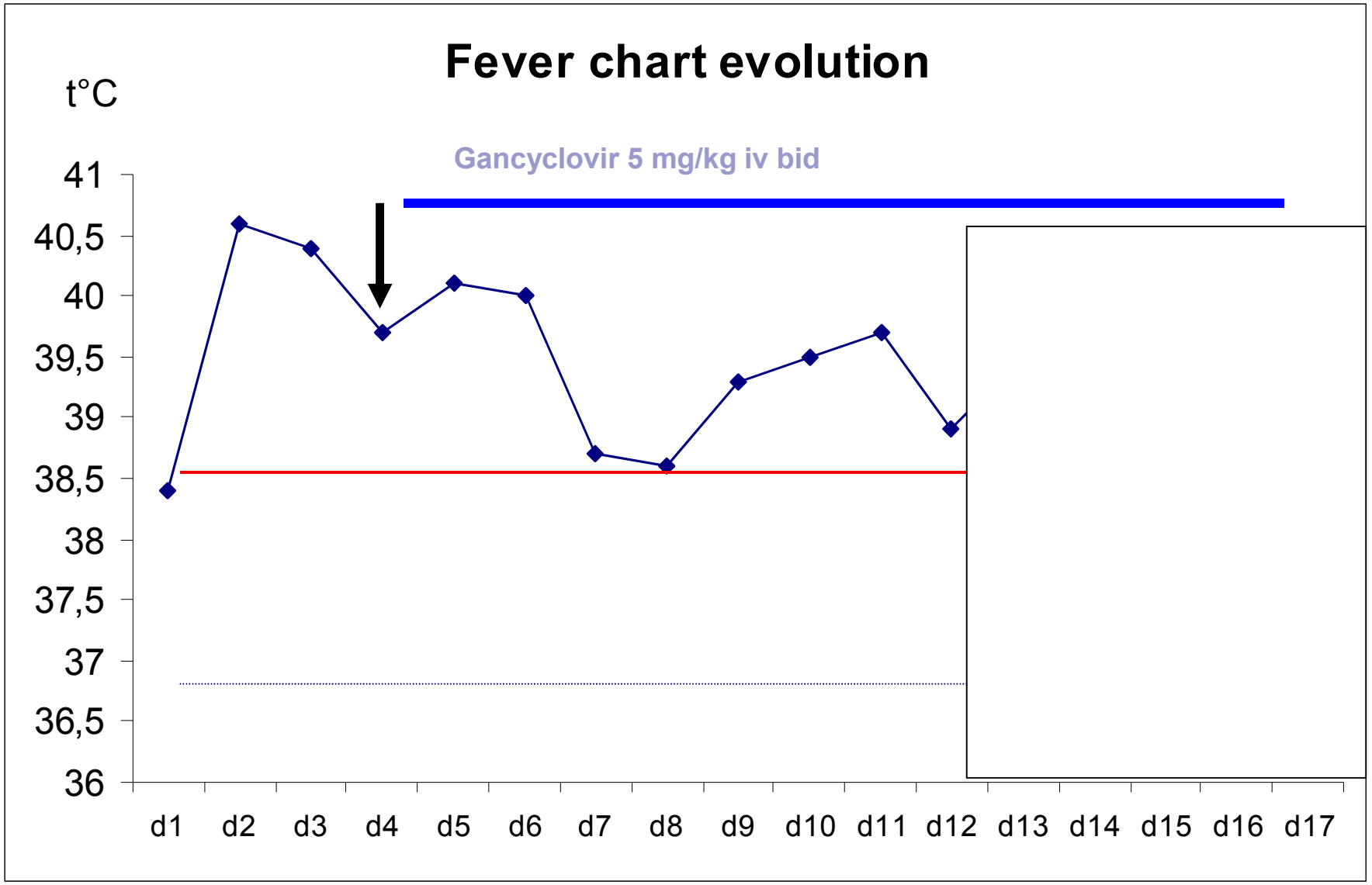
Chlamydia pn. IgG (EIA)	* 200 UA/ml		0 - 100
Chlamydia pn. IgA (EIA)	* 137 UA/ml		0 - 100
SEROLOGIE VIRALE			
EBV			
AC anti VCA IgG (EIA)	* 292 UA/ml		0 - 100
AC anti VCA IgM (EIA)	négatif		
AC anti EBNA (AC tardifs)	négatif		
Conclusion sérologie EBV:	Immunisation ancienne		
CMV			
CMV IgG (EIA)	< 6		
CMV IgM (EIA)	négatif		
Rougeole IgG (EIA)	* 4800 UI/ml		0 - 250
Rougeole IgM (EIA)	négatif		

- Confirmation of CMV primoinfection by testing previous (1 month before) blood sample
- CMV PCR on blood +
- CMV PCR on BAL +
- PCR and direct exam negative for PCP

→ **<u>Stop :</u> PCP treatment, corticosteroid, broad spectrum antibiotic therapy**

<u>Add :</u> gancyclovir

<u>Maintain :</u> moxifloxacin


Fever chart evolution
t°C
Gancyclovir 5 mg/kg iv bid
41
40,5
40
39,5
39
38,5
38
37,5
37
36,5
36
d1
d2
d3
d4
d5
d6
d7
d8
d9
d10
d11
d12
d13
d14
d15
d16
d17

After 8 days of gancyclovir

- Patient remain pyretic , > 38°5C, every day
- The respiratory function was improved but the patient remained depending of oxygen support!!
- Hematologic formula and hepatic enzymes were normal
- CRP stable, low
- Family and patient and doctors became nervous,…

What do you do now ?
(several answers possible)

1. You research another associate diagnosis or CMV localisation

17%
2. You control PCR CMV or CMV AGenemia

17%
3. You research presence of gancyclovir resistance

17%
4. You shift gancyclovir to foscarnet

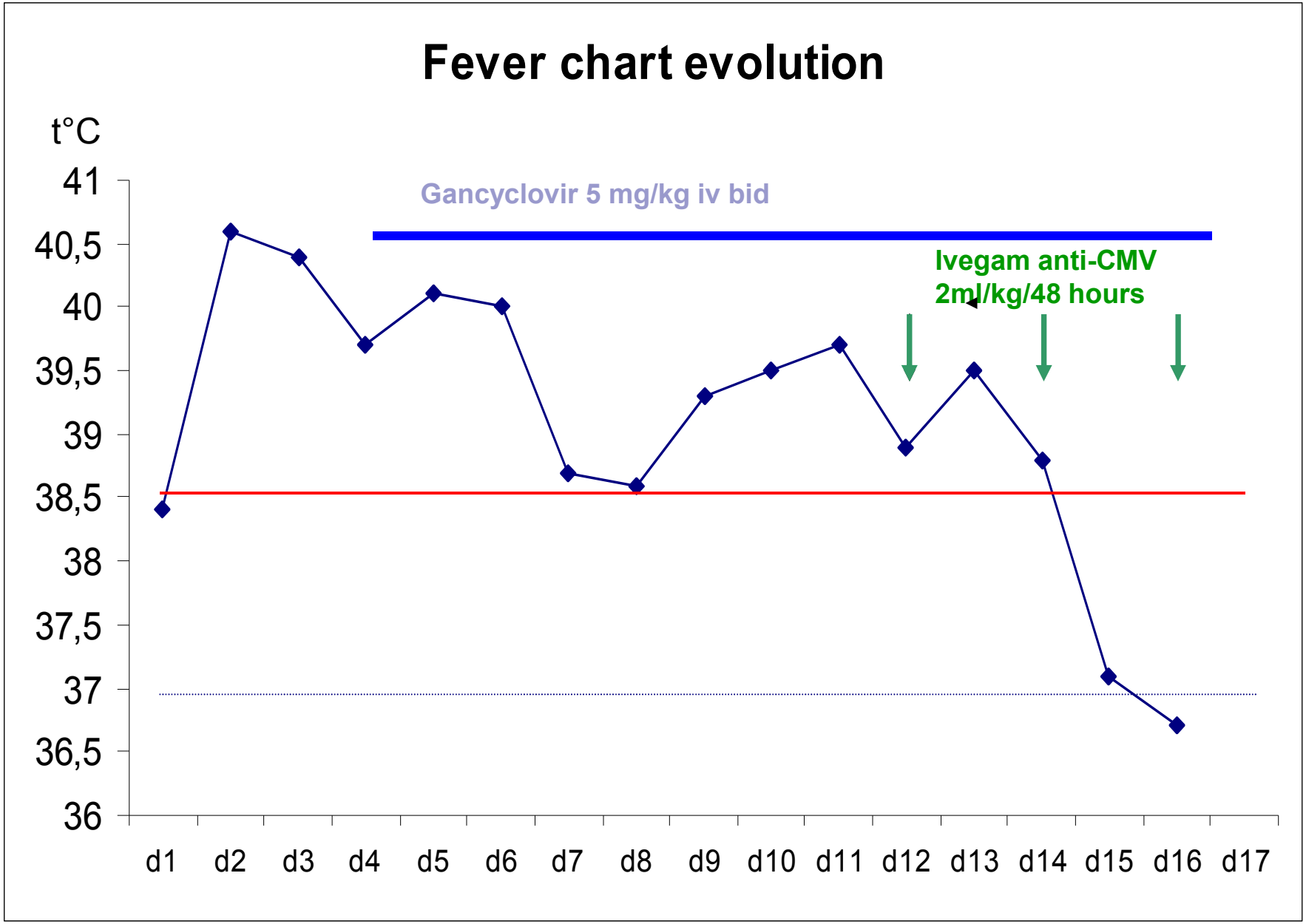
17%
5. You add specific immunoglobulin anti-CMV

17%
6. Other

17%

1. We research another viral associate diagnosis : measles,…
2. We control PCR CMV or CMV AGenemia : CMV PCR control remain + (less +)
3. We don’t research presence of gancyclovir resistance because patient didn’t received previous anti-CMV or anti-HSV/HZV treatment or prophylaxis

4. We don’t shift gancyclovir to foscarnet ?
5. We add specific immunoglobulin anti-CMV ?


Fever chart evolution
t°C
41
40,5
40
39,5
39
38,5
38
37,5
37
36,5
36
Gancyclovir 5 mg/kg iv bid
Ivegam anti-CMV
2ml/kg/48 hours
d1
d2
d3
d4
d5
d6
d7
d8
d9
d10
d11
d12
d13
d14
d15
d16
d17

Management of cytomegalovirus infections in patients treated with immunosuppressive drugs for chronic inflammatory diseases

Tnami and al.Revue de Medecine Interne 29 (2008) 305-310)

Types of patients

- **Review of 22 adult cases :**
  - 7 rheumatoid arthritis
  - 6 inflammatory bowel diseases
  - 6 connectivities
  - 2 systemic vascularitis
  - 1 still disease
- **Immunosuppressive therapy :**
  - 6 methotrexate
  - 7 azathioprin
  - 7 cyclophosphamid
  - 1 mycophenolate
  - 1 corticosteroid alone : high bolus doses /
  - 3 infliximab + other /
  - 19/22 corticosteroid associated to immunosuppressive therapy

- Visceral clinical presentation
  >>> 9/22 pulmonary
- Treatment
  - 14 gancyclovir iv or oral valganciclovir oral or foscarnet
  - 12 stop immunosuppressive therapy
  - 4 IgG
  - 1 GCSF
- Evolution
  - 5/22 deaths,
  - 3 < CMV pneumopathy with severe symptoms at the admission

Differencial diagnosis

- dd Pneumopathy due to methotrexate
- dd Primoinfection versus reactivation
- Effect of type of immunosuppressive therapy on the CMV ? Difference ? As in solid or bone marrow transplantation ?
- 21/22 cas have association immunosuppressive drug and corticosteroid
- AntiTNF-alpha (infliximab) :
  - **any evidence of direct association, the 3 patients receiving infliximag received also others immunosuppressive drugs**
  - **Torre-Cisnero and al (*Rheumatology 2005;44:1132-5*) showed that infliximab does not activate the replication of lymphotropic herpes virus in patients with refractory rheumatoid arthritis**.

Conclusions

- Evolution of symptomatic CMV infection is imprevisible and potentially severe in patients with CID
- Immunosuppressive therapy interruption :
  - **It's careful but not recommended in all cases (less severe cases).**
- Treatment :
  - **Valgancyclovir 900 mg bid oral if not threatening clinical situation, shift with gancyclovir 5 mg/kg bid iv if no amelioration**
  - **Gancyclovir 5 mg/kg bid iv**
  - **Foscavir**
  - **Cidofovir**
- No secondary prophylaxis recommanded/ follow PCR CMV or antigenemia and treat if reactivation.

Fever of unknown origin and CID

CMV antigenemia or quantitative CMV PCR +

Visceral localisation — **no visceral**

<u>What ?</u> **Valgancyclovir oral / gancyclovir iv**

<u>Duration ?</u> **Not defined, based on clinical evolution and virological evolution**

<u>Immunosuppressive therapy ?</u> **Maintain if necessary**

<u>Secondary prophylaxis ?</u> **No**

Patient 2

- A 66 year old man was admitted in emergency ward with abdominal pain, watery diarrhea, nausea, fever, fatigue and weight loss for 3 weeks
- Antibiotic therapy was prescribed during these 3 weeks (macrolide, amoxi-clav) without effect.
- Two days before admission, he presented inferior limbs oedema and cardiac echography was normal.

Patient 2

- 8 weeks ago, he travelled to Thailand (big city, any malaria prophylaxis) for 15 days. A few days after his return, he presented diarrhea without fever, that resolved spontaneously.
- ATCD :
  - High Blood Pressure
  - Surgical ombilical hernia cure
  - Perforated gastric ulcus 30 years ago
- Travel's vaccination ?
- Retiree, babysitting his young grandchildren occasionally

Clinical exam

- Pale, sweaty
- PR 120’ RR 28’ BP 130/80
- Abdomen : diffuse pain,
  tenderness at deep palpation of right flank
- Moderate oedema of bilateral inferior limbs

Complementary diagnosis tests

- Biology :
  - WBC 17000/ PN 76%
  - CRP 6.6 mg/dl
  - LDH 522 UI/L (125-250)
  - creatinemia 1.43 mg/dl
- Chest RX : normal
- Abdominal TD (-C) : fluid around liver and oedema of terminal small intestine
- Blood culture
- Urine culture
- Faeces culture + clostridium toxin
- Serologies : hep A, B, EBV, CMV, …

Diagnosis and treatment at the admission

- Infectious enterocolitis
- Treatment with broad spectrum antibiotic therapy and metronidazol…

Evolution day 2

- Increase of abdominal pain, nausea and dyspnea
- Elective pain on right abdominal flank with rebound tenderness

- Biology :
  - Increase of CRP : 6.6 to 11.8 mg/dl
  - Decrease of Hb : 15 to 11g/dl
  - d-dimeres > 9000
  - LDH 590 IU/l (125-250), gamma-gt 169UI/l (10-64)
  - Amylase, lipase, GOT, GPT, bili, CPK normal

What is/are your differencial diagnosis ? *(several answers possible)*

1. Typhoid ? Or other complicated invasive infectious enteritidis (*entamoeba histolytica*, clostridium difficile,...)

17%

2. Perforated ulcus

17%

3. Malaria

17%

4. Mesenteric ischemia

17%

5. Pelvis vein thrombosis and/or pulmonary embolism

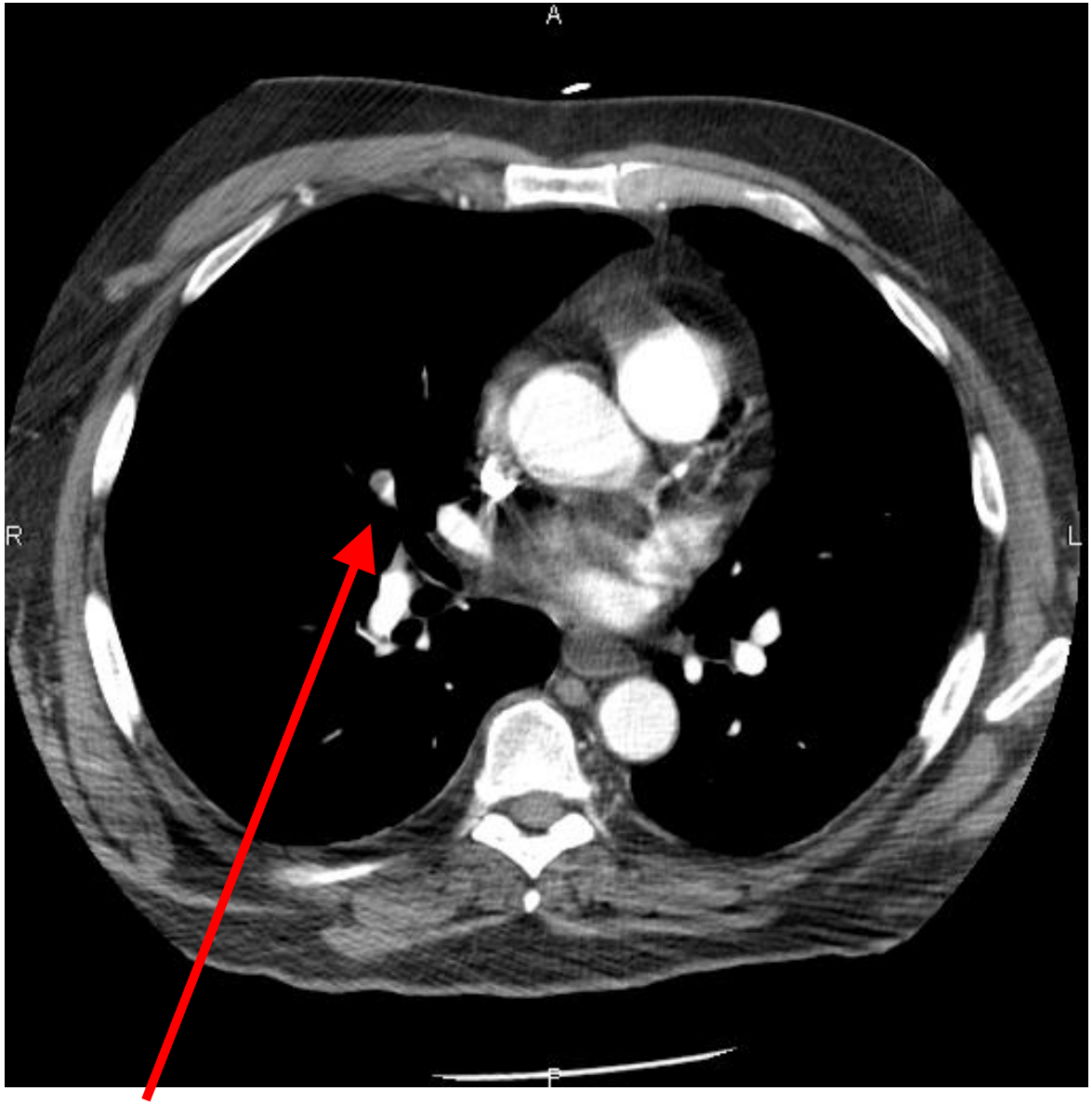
17%

6. Other

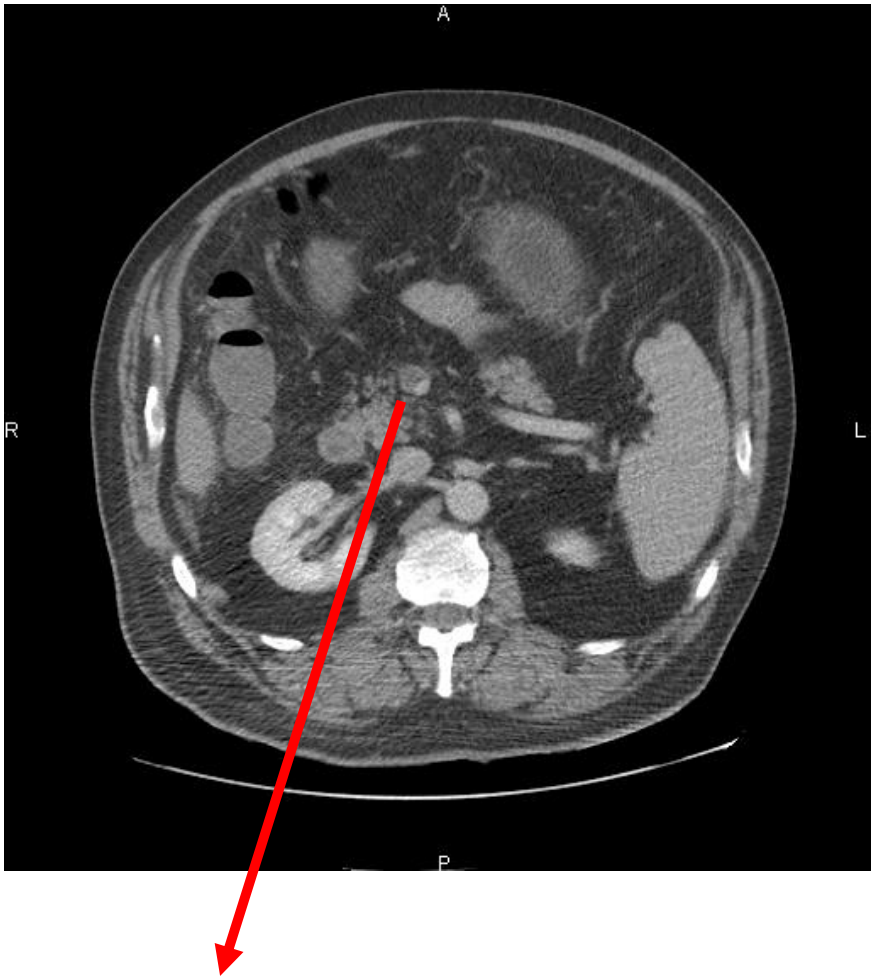
17%

Complementary diagnosis tests

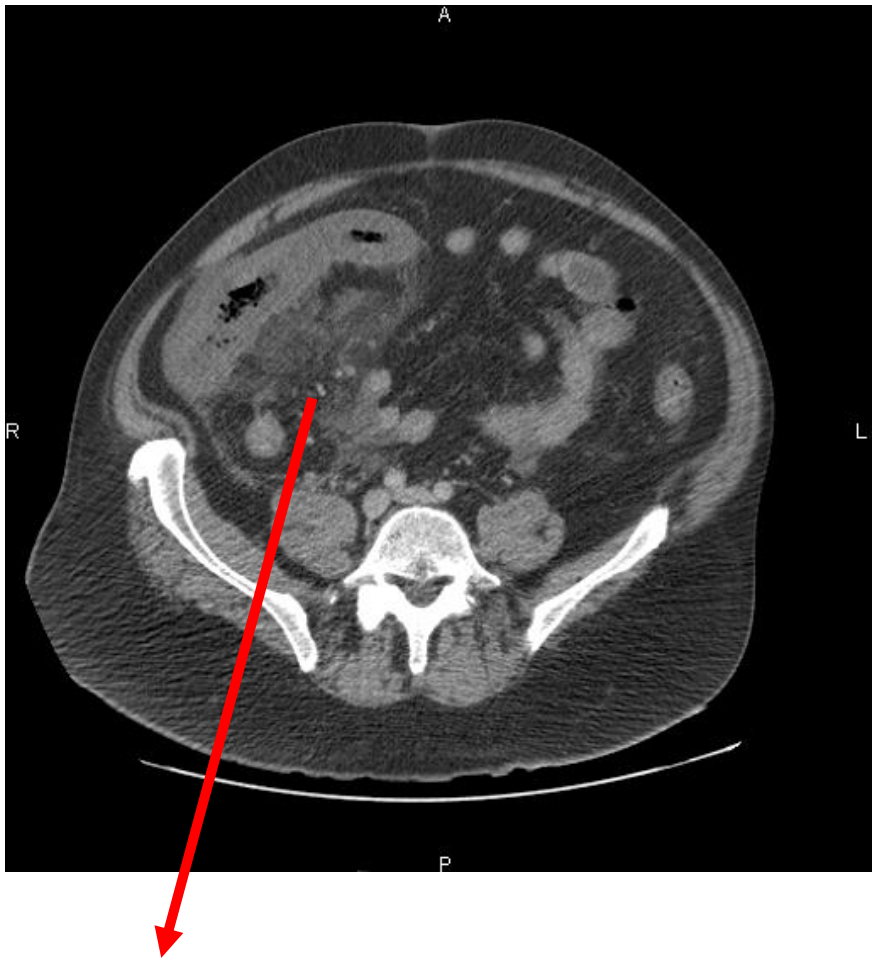
- Abdominal TB enhanced by contrast + pulmonary angiography
- Gastroscopy
- Blood smear
- Faeces : research blood / parasites / clostridium



Pulmonary embolism



Iliac vein thrombosis



Mesenteric Oedema

Evolution day 3

- Abdominal surgery : ileon 44 cm resection
  - AP : absence of neoplasy, multiple venous thrombosis and necrosis with polynuclear infiltration
- ICU, heparinotherapy, broad spectrum antibiotic therapy

You screen serologic results and …

CMV				
CMV IGG (EIA)	*	67	UA/ml	0 - 7
CMV IGM (EIA)	*	466	UA/ml	0 - 100
CMV IGM (2ème Elisa)	*	215	UA/ml	0 - 100
CMV : avidité des IGG		13	%	> 80%
		si > 80%: séroconversion > 3 mois.		
CMV : conclusion		Commentaire ci-dessous		
		Séroconversion actuelle ou récente. Suivi sérologique souhaitable.		

Do you think that CMV primoinfection can produce vascular thrombosis ?

1. **No**, I screen coagulation predisposing factors for thrombosis (before heparinotherapy)

33%

2. **Yes**, if associated with coagulation factors predisposing for thrombosis

33%

3. **Yes**, CMV alone can produce vascular thrombosis

33%

Severe CMV infection in apparently immunocompetent patients : a systematic review

Petros I Rafailidis and al. Virology Journal 2008,5:47

Severe life-threatening complications of CMV primoinfection in non-immunocompromised patients may not be as rare as previously thought*

- 89 articles/ 290 patients
- Most frequent sites of severe CMV infection :
  - **Gastrointestinal tract (colitis)**
  - **Central nervous system (meningitidis, encephalitidis, transverse myelitis)**
- Others :
  - **Haematological disorders (haemolytic anemia, thrombocytopenia)**
  - **Thrombosis of venous or arterial system**
  - **Ocular involvement (uveitis)**
  - **Lung disease (pneumonitis)**

***Severe CMV infection in apparently immunocompetent patients: a systematic review.**
Petros I Rafailidis and al. Virology Journal 2008,5:47

Do you treat CMV primoinfection in this adult immunocompetent patient ?

1. **Yes**, the patient's disease is severe

25%

2. **No**, the veinous thrombosis is a late complication

25%

3. **Yes** if isolated fever remains high

25%

4. **Yes** if CMV antigenemia remains high

25%

Need for specific antiviral treatment in immunocompetent patients with severe CMV infection*

- Data are conflicting, no definitive conclusions about potential benefit, need randomized controlled trials
- Presumed benefit should be weighed against the potential toxicity of therapy
  - Gancyclovir : myelosuppression, CNS disordes, hepatotoxicity, irreversible infertility
- Risk of emergence of resistant viral strains
- Antiviral treatment prescribed for :
  - Meningoencephalitidis (seizures and coma)
  - Ocular involvement
  - Lung involvement

***Severe CMV infection in apparently immunocompetent patients: a systematic review.**
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AIMS INTERACTIVE VOTING

PLEASE

DON'T GO AWAY

WITH YOUR KEYPAD !