

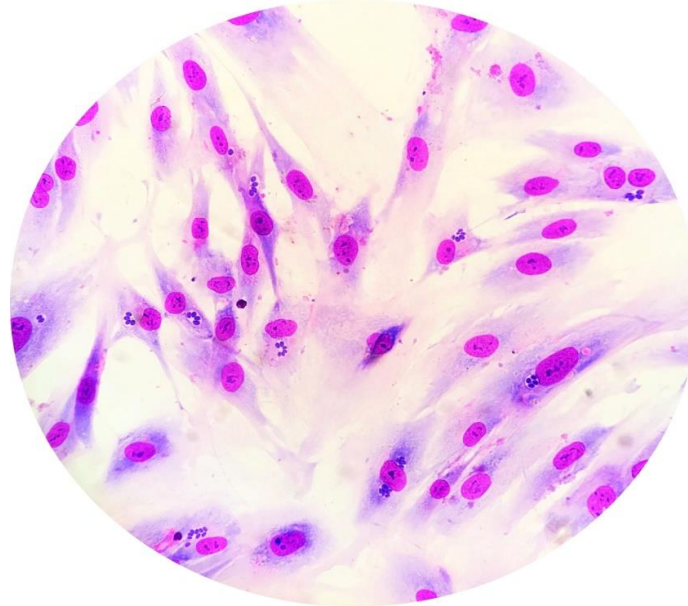
Toksoplazmoz



Dr Özlem Altuntaş Aydın
SBÜ Bakırköy Dr Sadi Konuk SUAM
Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji

Uygun proflaktik tedavi kullanmayan AIDS olgularında
en sık SSS enfeksiyonuna neden olan durum

Etken → Zorunlu intraselüler parazit *Toxoplasma gondii*



İmmünkompetanlarda

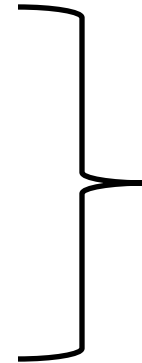
primer enfeksiyon genellikle asemptomatik seyreder
yaşam boyu latent kalır

HIV ile enfekte olgularda

özellikle $CD4 < 100/mm^3$
parazitin reaktivasyonu ile ortaya çıkar

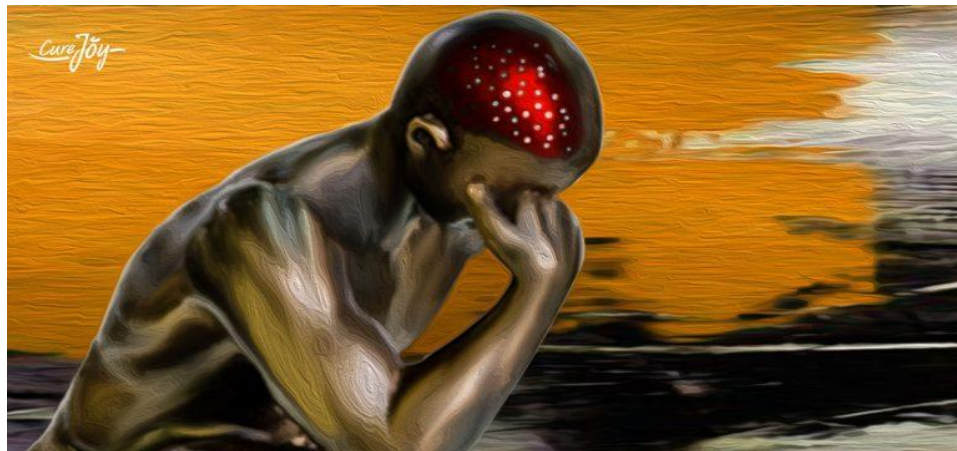


- Toksoplazma seropozitif
- $CD4 < 100/mm^3$
- Proflaksi kullanmayan
- ART kullanmayan

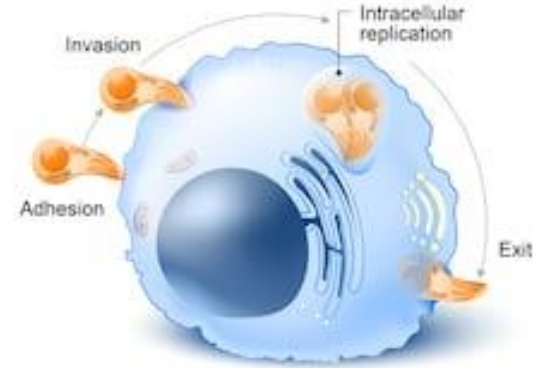


%30
reaktivasyon

- En sık reaktivasyon SSS



Toxoplasma



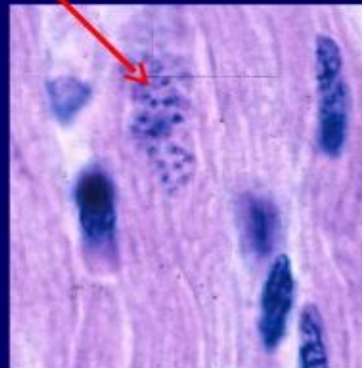
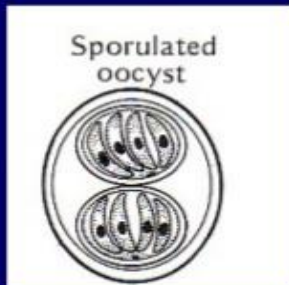
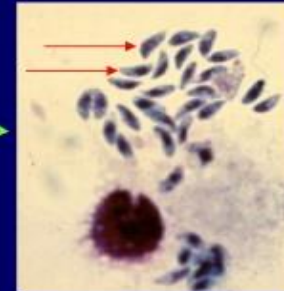
Apicomplexa Şubesi

- Sporozoa Sınıfı
- *Toxoplasma gondii*
 - insan/diğer tüm memeliler
 - kanatlılarda yerleşip hastalık etkeni olabilen tek tür

Nükleus içeren tüm memeli hücrelerini enfekte edebilir

Toxoplasma gondii FORMS

- TACHYZOITES
- BRADYZOITES (TISSUE CYSTS)
- 4. OOCYSTS



A Cat-astrophic Threat for Seals

How *Toxoplasma gondii* makes its way from mountain to ocean

A Microscopic Parasite

Toxoplasma gondii is a parasite that causes the disease toxoplasmosis.



Develops in the Guts of Cats

T. gondii can infect any warm-blooded animal (including humans, birds, and seals), but only reproduces in the digestive system of a cat.

Spreads Via Cat Feces

Millions of *T. gondii* eggs can be spread into the environment via the feces of just one cat and survive for many months. These eggs are the source of *T. gondii* infection in monk seals. It only takes one egg to cause an infection.



Contaminates Natural Resources

T. gondii eggs contaminate water and soil, along with the plants that grow in it. Wildlife and livestock can consume the eggs and become infected. Even people can get infected by accidentally ingesting cat litter/fecal particles or consuming under-cooked meat or unwashed produce.

Travels Through Waterways

Rainwater and runoff transport the eggs to the ocean through streams and gutters.

Exacerbated by Human Behavior

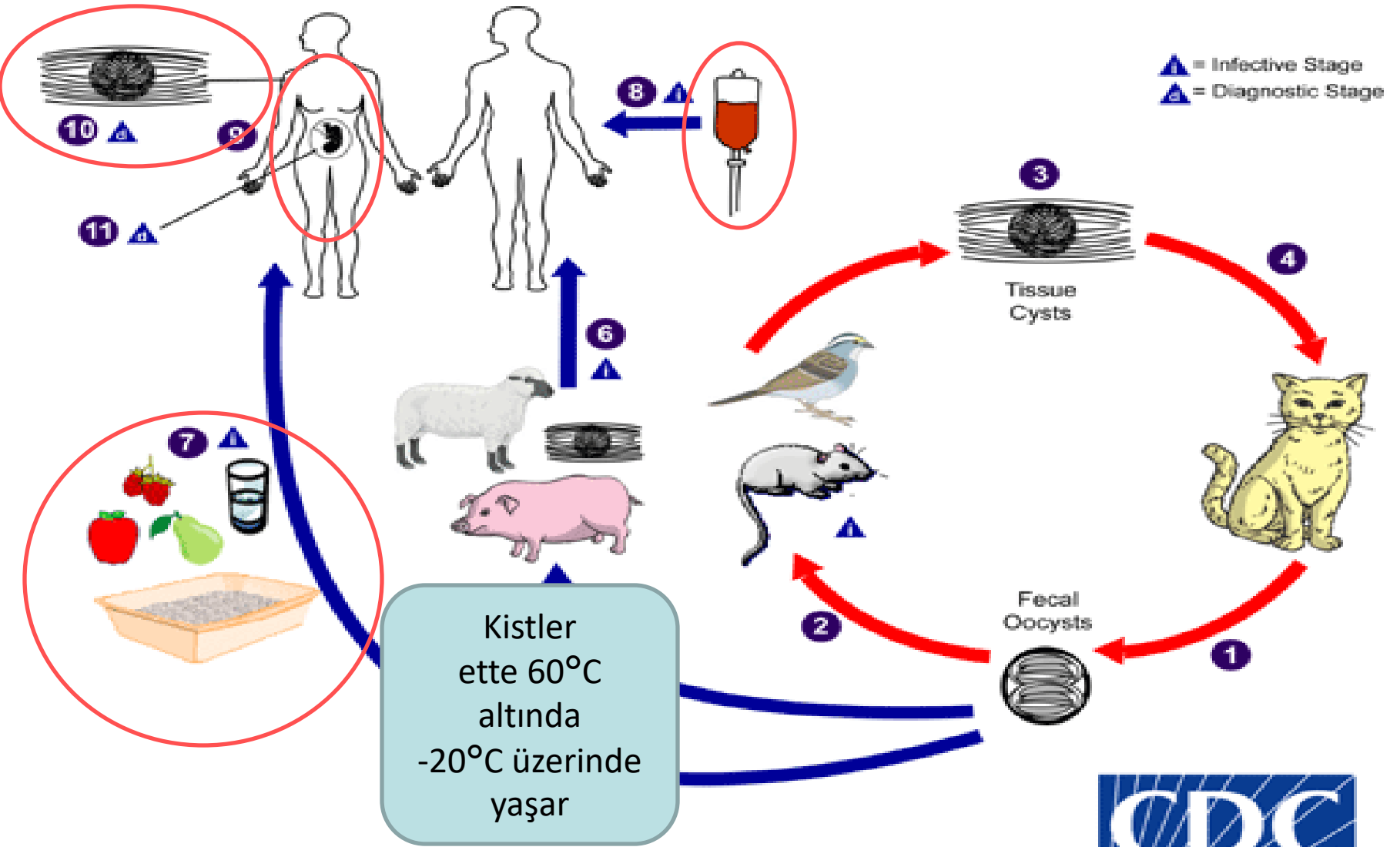
People promote the spread of *T. gondii* by allowing pet cats to roam outdoors, abandoning unwanted cats, and nourishing feral cat populations.

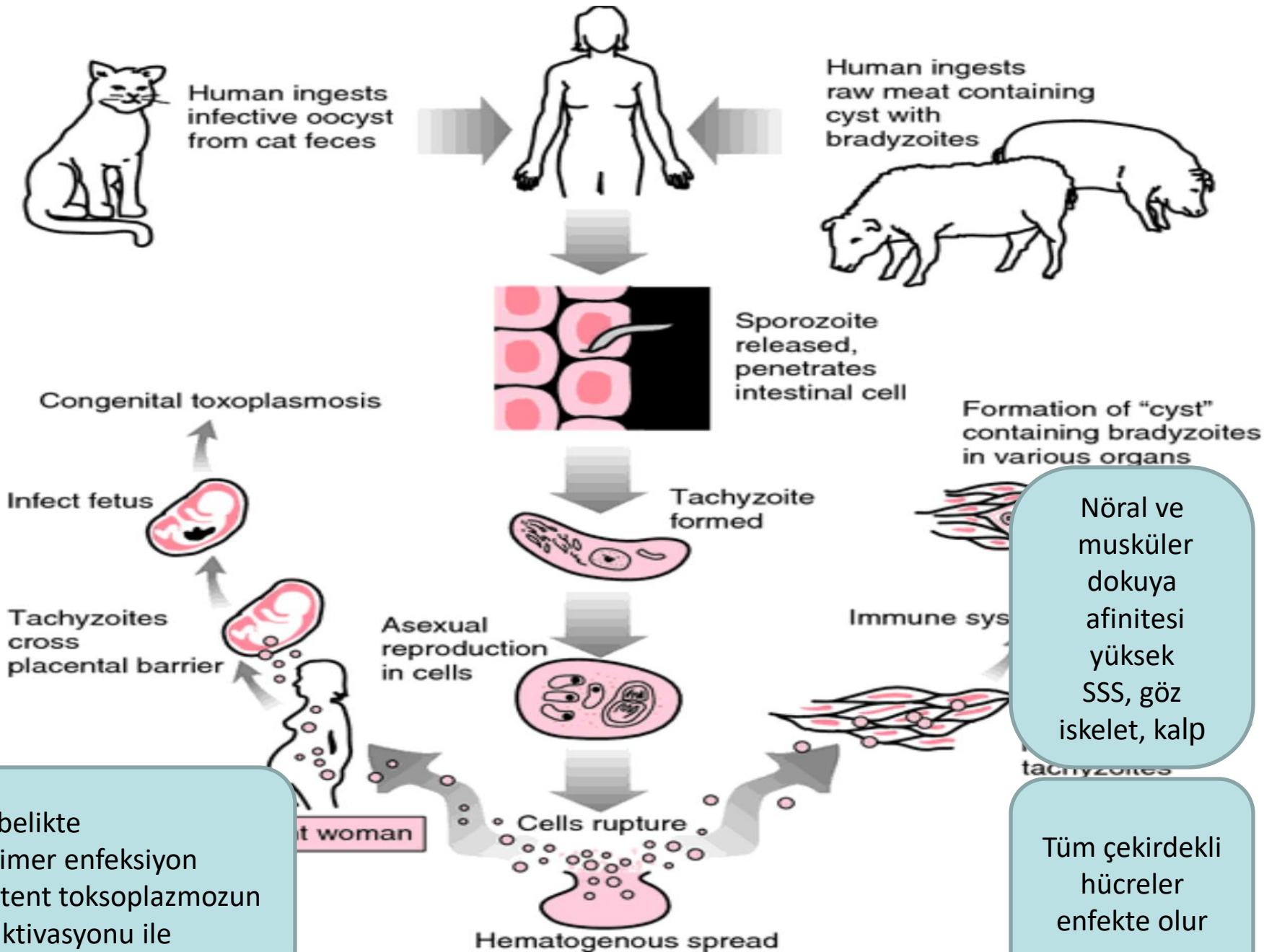
Impacts Marine Environment

Hawaiian monk seals become infected with *T. gondii* by consuming contaminated water or prey.

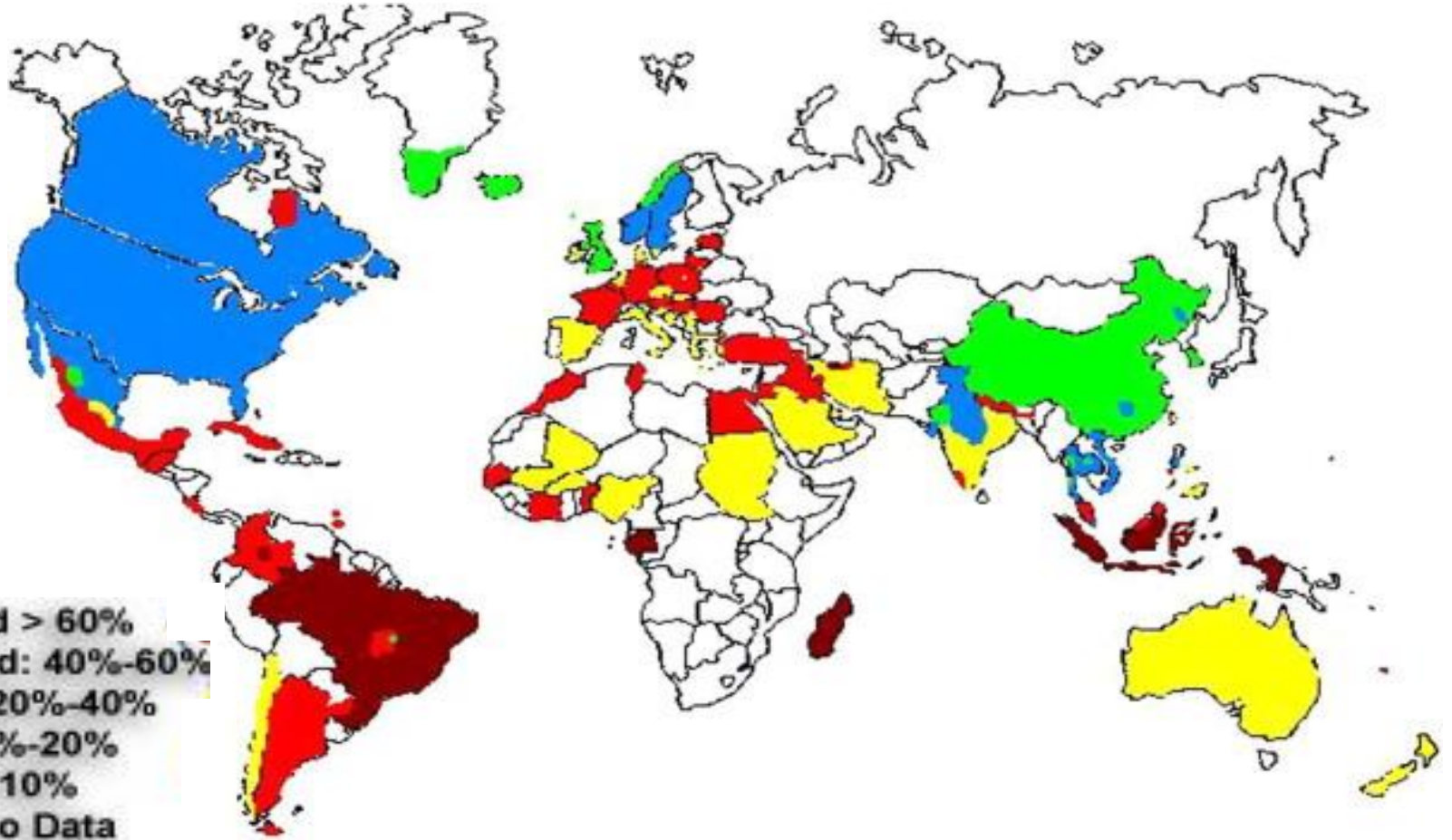


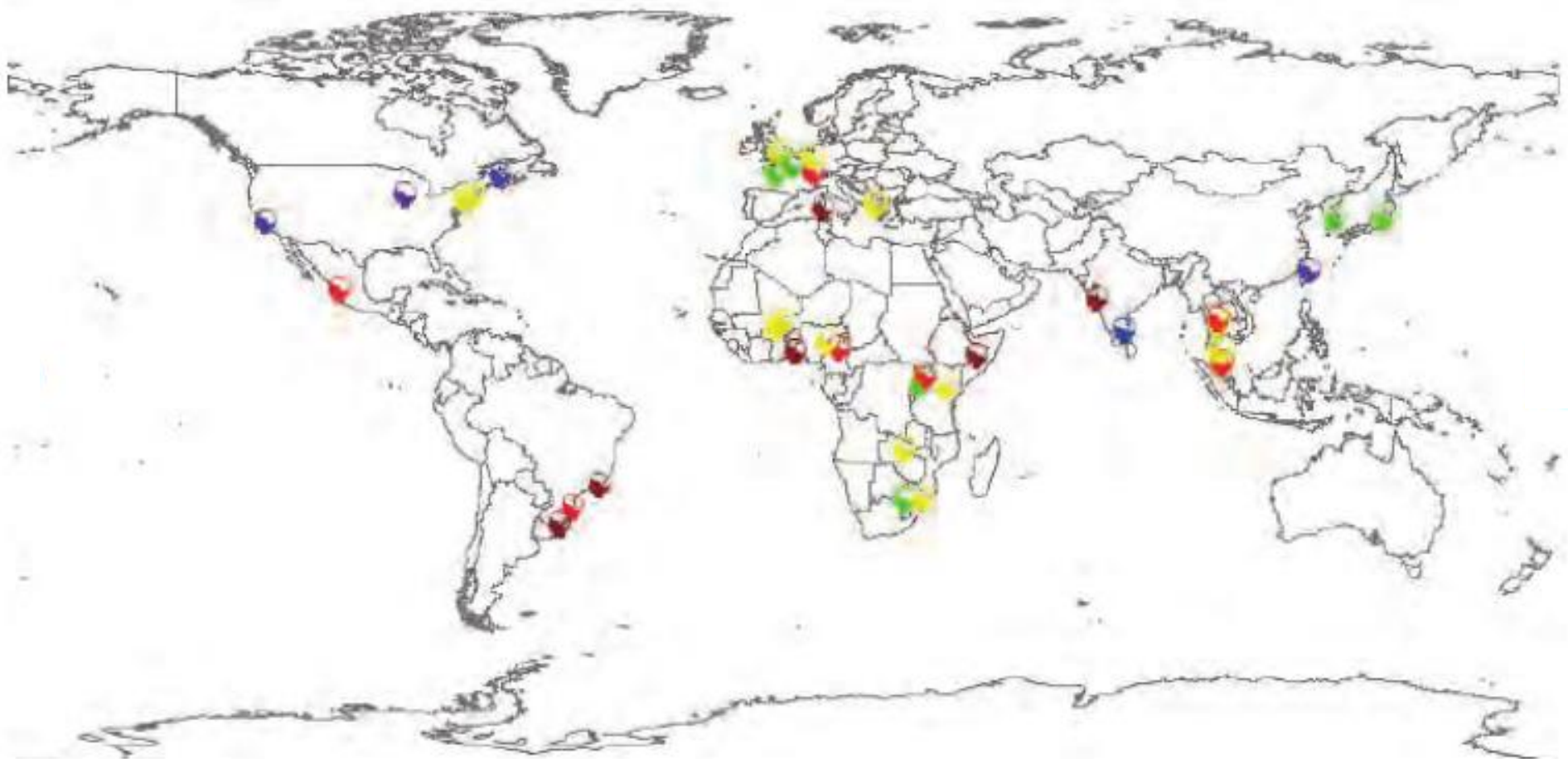
NOAA
FISHERIES





Dünya nüfusunun 1/3'ü *Toxoplasma gondii* ile enfekte





Global status of latent Toxoplasma infection in HIV-infected patients. Dark red equals prevalence above 60 %, light red equals 40-60 %, yellow 20-40 %, blue 10-20 % and green equals prevalence <10 %. White equals absence of data.

Prevalence and burden of *Toxoplasma gondii* infection in HIV-infected people: a systematic review and meta-analysis.

Wang ZD¹, Wang SC², Liu HH³, Ma HY³, Li ZY³, Wei F³, Zhu XQ⁴, Liu Q⁵.

⊕ Author information

Abstract

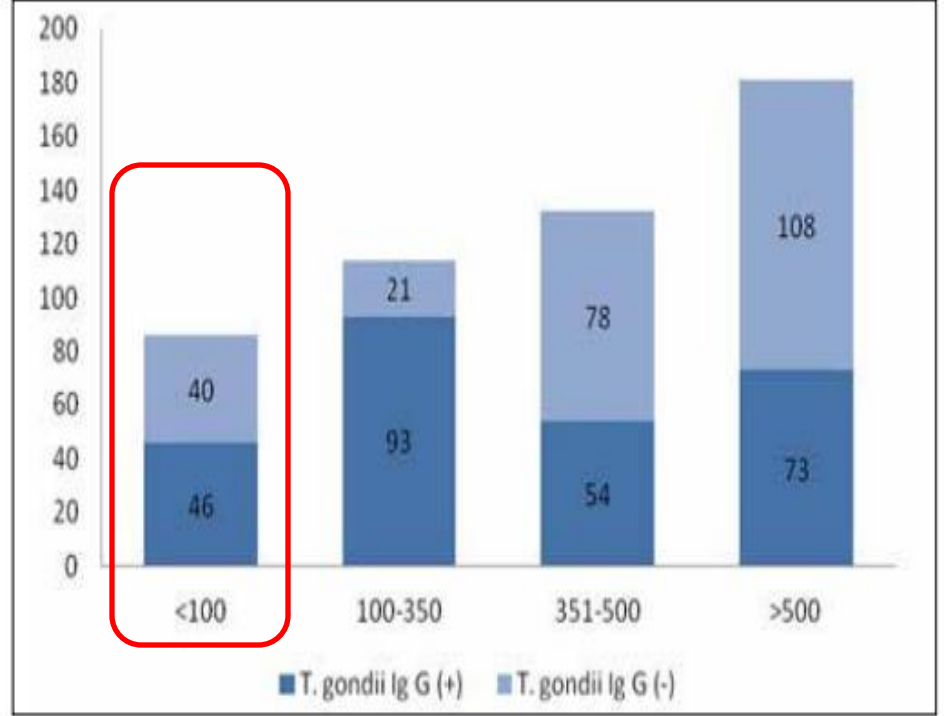
BACKGROUND: Worldwide, 30% of the world's population have antibodies to the intracellular protozoan parasite *Toxoplasma gondii* and about 36·7 million people are infected with HIV, but little is known about the prevalence of co-infection with *T gondii* and HIV. We aimed to characterise the epidemiology and burden of *T gondii* co-infection in people with HIV infection.

METHODS: In this systematic review and meta-analysis, we searched PubMed, Embase, Google Scholar, ScienceDirect, Chinese Web of Knowledge, Wanfang, and Chongqing VIP databases for studies reporting *T gondii* infection in HIV-infected people from inception to Feb 29, 2016. Studies were included if they investigated people with HIV infection and presented data that allowed us to establish the prevalence of *T gondii* infection. We excluded reviews, repeated studies, or animal studies, as well as studies that provided the final results without raw data, had a sample size less than 30 people, had unclear diagnostic methods of *T gondii* infection, or that included populations with increased risk of *T gondii* infection. We extracted the numbers of patients with HIV infection and *T gondii* co-infection from the identified studies. We estimated pooled prevalence of *T gondii* infection in HIV-infected people by a random-effects model, and evaluated its overall infection burden worldwide.

FINDINGS: Our search identified 7843 records and after removal of duplicates and initial screening, we reviewed 312 studies in full. Of these articles, 238 were excluded, leaving 74 studies that included 25 989 HIV-infected people from 34 countries. Of these people, 7326 had *T gondii* co-infection and we estimated the pooled worldwide prevalence of *T gondii* infection to be 35·8% (95% CI 30·8-40·7). 2353 of 8837 of people in Asia and the Pacific had co-infection with *T gondii* and HIV (prevalence 25·1%, 95% CI 19·0-31·2), and prevalence was low in this region compared with that in sub-Saharan Africa (44·9%, 32·3-57·5, 2129/5686; odds ratio [OR] 0·61), Latin America and the Caribbean (49·1%, 27·9-70·4, 510/980; OR 0·33), and North Africa and the Middle East (60·7%, 24·1-97·3, 245/439; OR 0·29). 1561 of 3780 people in low-income countries had co-infection (54·7%, 95% CI 35·8-73·5), which was higher than in middle-income countries (34·2%, 27·4-40·9, 3632/11 540; OR 1·53) and high-income countries (26·3%, 20·4-32·2, 2133/10 669; OR 2·82). Worldwide, we calculated that there were roughly 13 138 600 (95% CI 11 303 600-14 936 900) cases of *T gondii* co-infection in HIV-infected people, with 87·1% in sub-Saharan Africa (11 449 500 cases, 95% CI 8 236 500-14 662 500).

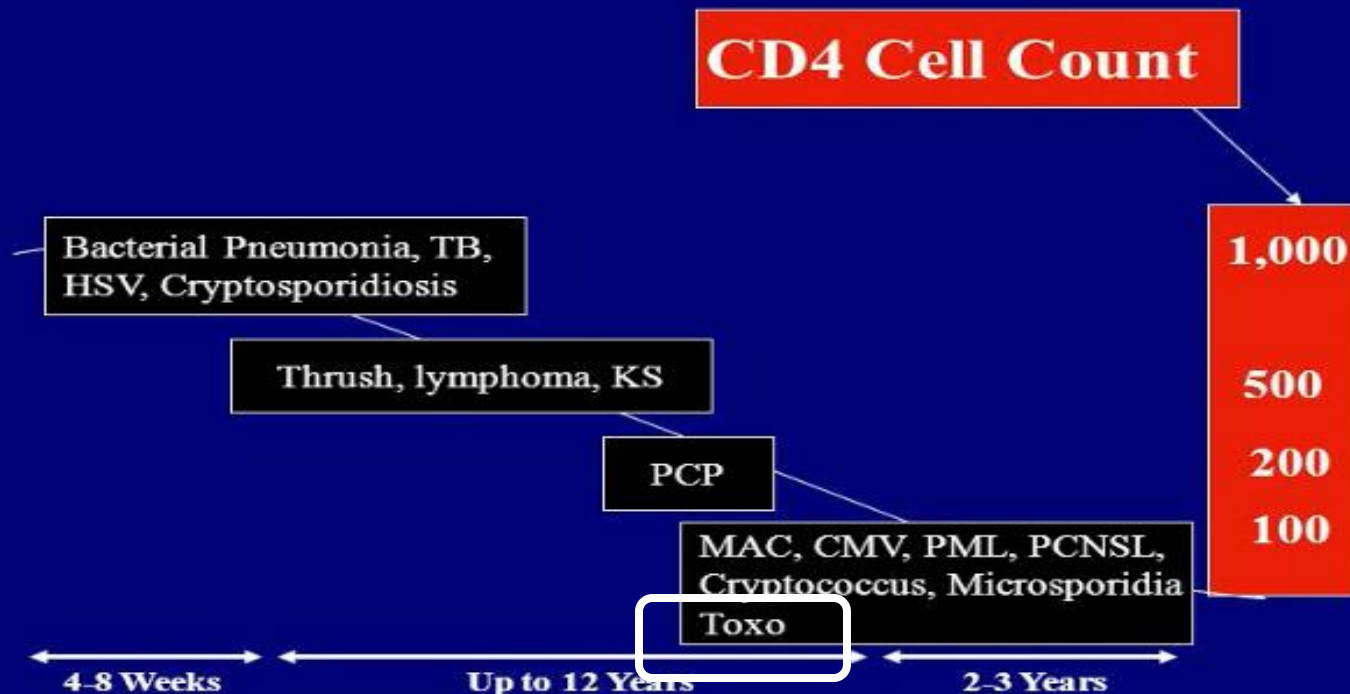
Tablo 2. HIV enfekte hastalarda *T. gondii* Ig G seropozitifliğinin risk faktörleri

	<i>T. gondii</i> IgG (+)	<i>T. gondii</i> IgG (-)	Pam
Yaş	40,2±11,8	33,4±9,6	0,001
Cinsiyet			
Erkek	232 (%43,9)	296 (%56,1)	
Kadın	35 (%40,7)	51 (%59,3)	0,57
Bulaş yolu			
Heteroseksüel temas	162 (%48,4)	173 (%51,6)	
Homoseksüel temas	105 (%37,6)	174 (%62,4)	0,01
CD4 sayısı (mm³/mL)			
<200	75 (%48,4)	80 (%51,6)	
>200	192 (%41,8)	267 (%58,2)	0,15
Tanı yılı			
2006-2011	106 (%46,9)	120 (%53,1)	
2012-2017	161 (%41,5)	227 (%58,5)	0,19
Eğitim			
Üniversite mezunu	71 (%37)	121 (%63)	0,02



Şekil 1. Hastalarda CD4 T lenfosit sayısına göre *T. gondii* IgG seropozitifliği

CD4 Count and Opportunistic Infections



Toxoplasmosis hospitalizations in the United States, 2008, and trends, 1993-2008.

Jones JL¹, Roberts JM.

⊕ Author information

Abstract

BACKGROUND: Toxoplasmosis-related hospitalizations often occur in persons with human immunodeficiency virus (HIV) infection and other causes of immunosuppression.

METHODS: Using the National Inpatient Sample (NIS), we examined trends in toxoplasmosis-related hospitalizations by race or ethnicity in 2008. The NIS is designed to represent all discharges from non-federal hospitals in the United States. In 2008, there were up to 8 million discharges per year from ~1000 hospitals. We examined hospitalization codes 130-130.9 for toxoplasmosis and 04.

RESULTS: Estimated HIV-associated toxoplasmosis hospitalizations increased from 9395 in 1993 to 10583 in 1995 ($P = .0002$), then dropped to 3643 in 2001 ($P < .0001$), with similar levels thereafter. The rate of HIV-associated toxoplasmosis hospitalizations among all HIV-related hospitalizations decreased from 3.33% in 1993 to 1.25% in 2008 ($P < .0001$). Estimated non-HIV-associated toxoplasmosis hospitalizations were less variable from 1993 to 2008 (range, 386-819; 0.0020% in 1993, 0.0015% in 2008). In 2008, the rates of both HIV- and non-HIV-associated toxoplasmosis hospitalizations were higher in Hispanic persons than in white persons.

CONCLUSIONS: HIV-associated toxoplasmosis hospitalizations decreased after the introduction of antiretroviral therapy. However, toxoplasmosis-related hospitalizations were still higher in Hispanic persons than in white persons. Antiretroviral therapy was introduced; however, toxoplasmosis-related hospitalizations were still higher in Hispanic persons than in white persons.

HAART sonrası
hospitalizasyon azalmıştır

Toksoplazma ensefaliti (TE)
insidansı da azalmıştır

Ekstraserebral toksoplazmoz (EST) daha az sıklıkta görülür

[Clin Infect Dis.](#) 1999 Mar;28(3):575-81.

Incidence and risk factors of toxoplasmosis in a cohort of human immunodeficiency virus-infected patients: 1988-1995. HEMOCO and SEROCO Study Groups.

[Belanger F¹](#), [Derouin F](#), [Grangeot-Keros L](#), [Meyer L](#).

⊕ Author information

Table 1. Characteristics of HIV-infected patients included in the SEROCO and HEMOCO cohorts (1988–1995).

Variable	Patients with toxoplasmosis	All patients
No. of patients	116	1,699
Median age (y) at inclusion	30	28
Median CD4 cell count at inclusion (no./ μ L)	286	462
No. (%) with negative <i>Toxoplasma</i> serology* at inclusion	10 (8.6)	468 (27.5)
Median <i>Toxoplasma</i> IgG antibody titer at inclusion (IU/mL) [†]	142	66
Median follow-up (mo)	46.8	60.5
No. (%) of deaths during follow-up	94 (81.0)	390 (22.9)
No. (%) who received primary prophylaxis for toxoplasmosis	18 (15.5)	501 (29.5)

* *Toxoplasma* IgG antibody titer of <10 IU/mL.

[†] In patients seropositive for *Toxoplasma*.

Table 2. Cases of toxoplasmosis, according to their localization, occurring in the SEROCO and HEMOCO cohorts (1988–1995).

Localization	No. of diagnoses of toxoplasmosis			
	Possible	Probable	Definite	Total (%)
Cerebral	48	54	1	103 (88.8)
Pulmonary	0	4	3	7 (6.0)
Ocular	0	4	0	4 (3.5)
Disseminated	1	0	1	2 (1.7)
Total (%)	49 (42.2)	62 (53.5)	5 (4.3)	116 (100.0)

EST risk faktörleri

CD4 <100/mm³

Eşzamanlı serebral toksoplazmoz varlığı

Medicine (Baltimore). 1994 Nov;73(6):306-14.

Extracerebral toxoplasmosis in patients infected with HIV. A French National Survey.

Rabaud C¹, May T, Amiel C, Katlama C, Leport C, Ambroise-Thomas P, Canton P.

⊕ Author info

Abstract

A French
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Fransa, 1990-92
EST olan 199 hasta (%1.5)
Ort CD4: 57/mm³

%50 göz
%26 akciğer
%11.5 dissemine
%3 kalp
%3 Ki
%1 mesane

Olguların %41'inde beraberinde serebral toksoplazmoz

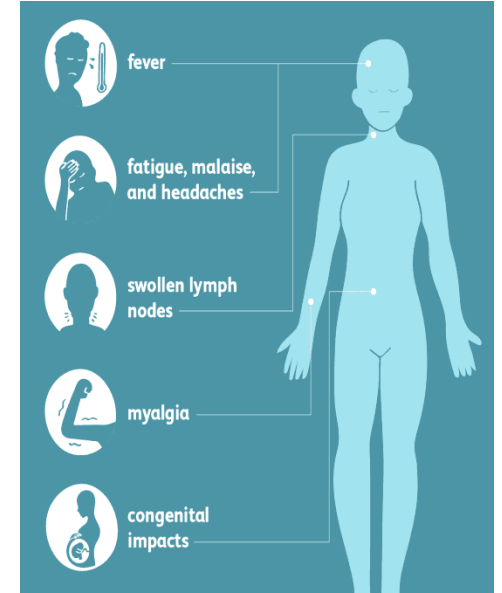
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WORDS).

Klinik

CD4<100/mm³ olan HIV ile enfekte bireylerde çoğunlukla latent toksoplazmozun reaktivasyonuna bağlı

En sık SSS tutulumuna ait bulgular (TE)

EST birden fazla bölgede ortaya çıkabilir



Toksoplazma ensefaliti

Subakut başlangıçlı

- Baş ağrısı
- Konfüzyon
- Bilinç değişiklikleri
- Ateş
- Nörolojik bulgular

hemiparezi, konuşma bozuklukları, motor güç kaybı



- Nöbet
- Serebellar disfonksiyon
- Nöropsikiyatrik bulgular (şizofreni??)

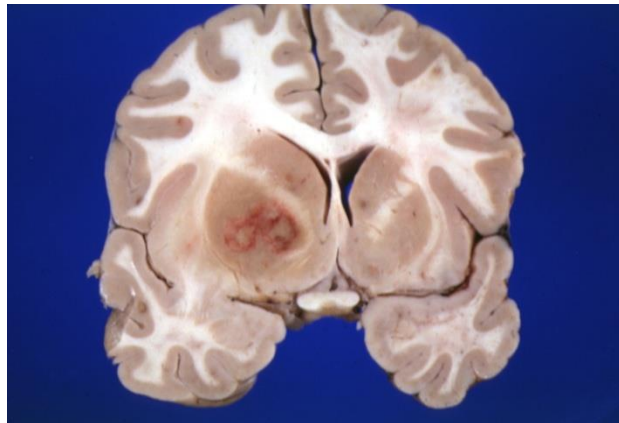
HIV ile enfekte kişilerde HLA-DQ3 antijen varlığı ile ilişkilidir

Destrüktif multifokal, intraserebral kitleler

En sık beyinde kortikal-subkortikal bileşkede

Beyin sapı, bazal ganglia, serebellum etkilenebilir

Spinal kord tutulumu – tranvers miyelit, konus sendromu



Ekstraserebral toksoplazmoz

En sık

- Koryoretinit
- Pnömoni

© 2006 British HIV Association

HIV Medicine (2006), 7, 415–420

CASE REPORT

Fulminant toxoplasmosis causing fatal pneumonitis and myocarditis

DE Eza^{1*} and SB Lucas²

¹*Department of Histopathology, Guy's and St Thomas' NHS Trust, St Thomas' Hospital, London, UK, and* ²*Department of Histopathology, King's College London School of Medicine, St Thomas' Hospital, London, UK*

Otopsi çalışmalarının *

- Çoğunda multiorgan tutulumları
- Yarısında beraberinde SSS toksoplazmozunu olmadan EST

**Rabaud et al. Medicine 1994 Nov;73(6):306-14.*

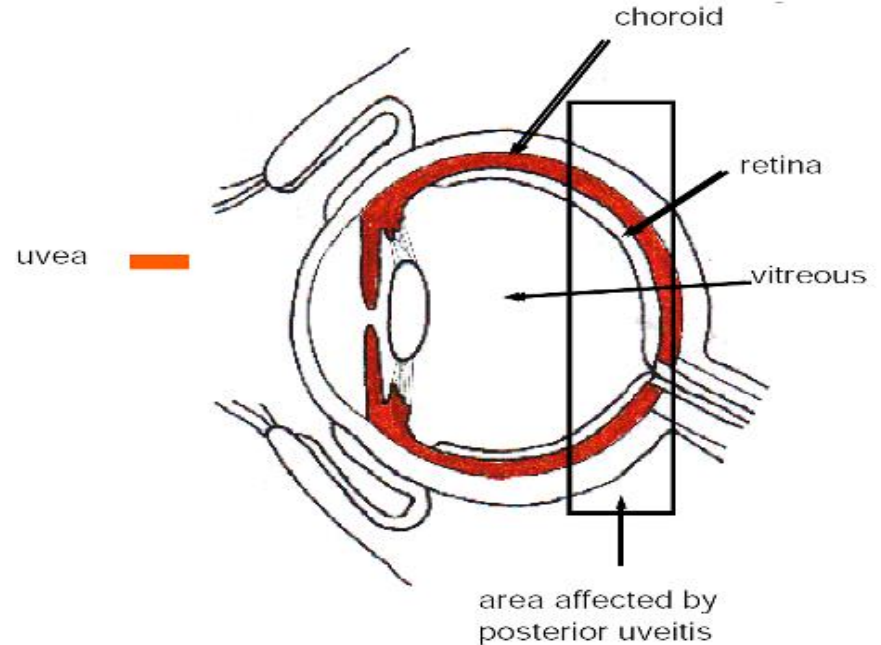
Koryoretinit

Birincil olarak retinayı enfekte eder, koroid ve vitreus ikincil olarak tutulur (posterior üveit)

%30-60'ında beraberinde TE

Görsel bulgular

- Gözde ağrı
- Görme keskinliğinde azalma
- Miyodezopsi
- Skotom
- Fotofobi

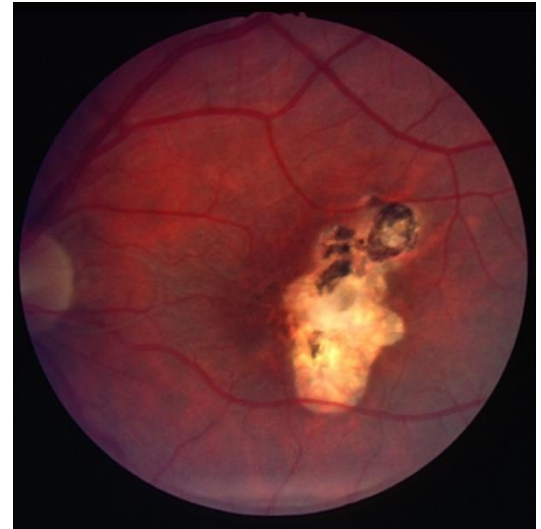


Koryoretinit

Fundoskopide

- Retinada kenarları belirgin olmayan, kabarık, sarı-beyaz pamuksu lezyonlar (nekrotizan retinit)
- Bazen hemoraji ve vaskülit

Lezyonlar çoğunlukla unilateral



Toksoplazma pn6monisi

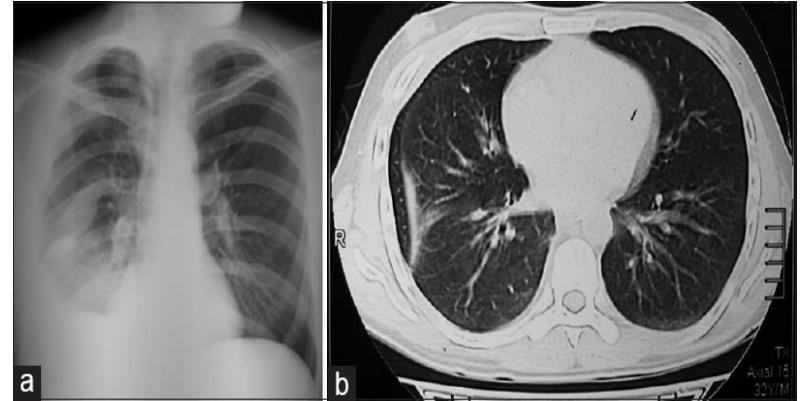
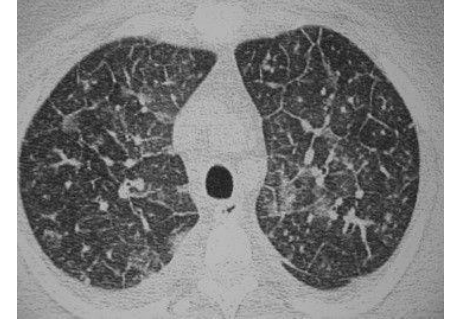
- Ateř
- Dispne
- Nonproduktif 6ks6r6k

Klinik bulgularla PCP'den ayırt etmek zor

Akcięer grafisinde

- bilateral diff6z infiltrasyon (PCP benzeri)
- retik6lonod6ler infiltratlar

LDH'da masif artıř tipik



Diğer organ tutulumları

Her organ tutulabilir

(GIS, kalp, kemik iliği, mesane, testis,....)

Yaygın toksoplazmoz

- Ateş
- Sepsis benzeri sendrom

(DİK, hipotansiyon, artmış LDH, pulmoner infiltrasyon)

Yüksek oranda mortal



Akut toksoplazmoz

Hücresel immünitinin belirgin azaldığı durumlarda

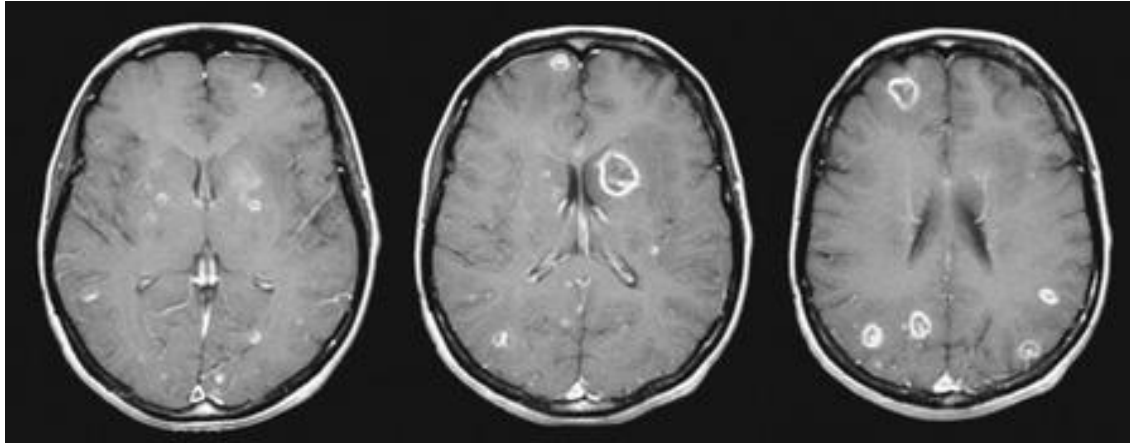
- ciddi viseral tutulumlar
- yaygın enfeksiyon (pnömoni, miyozit, miyokardit, diffüz ensefalit)
- Çok nadiren SSS etkilenebilir



Tanı

Serebral toksoplazmozdan şüphelenildiğinde acilen görüntüleme

MRI > CT



Korteksin gri cevherinde, bazal gangliada

Multipl, bilateral fokal intraserebral lezyonlar (%80) ↑

Kontrast tutan ve sıklıkla ödemin eşlik ettiği ring form

CT ile tek lezyon varsa, MRI ile konfirme edilmeli

SSS lenfoması ile benzer radyoloji

- Tedaviden önce kanama bulguları
 - Hedef işareti
- } toksoplazma
lehine

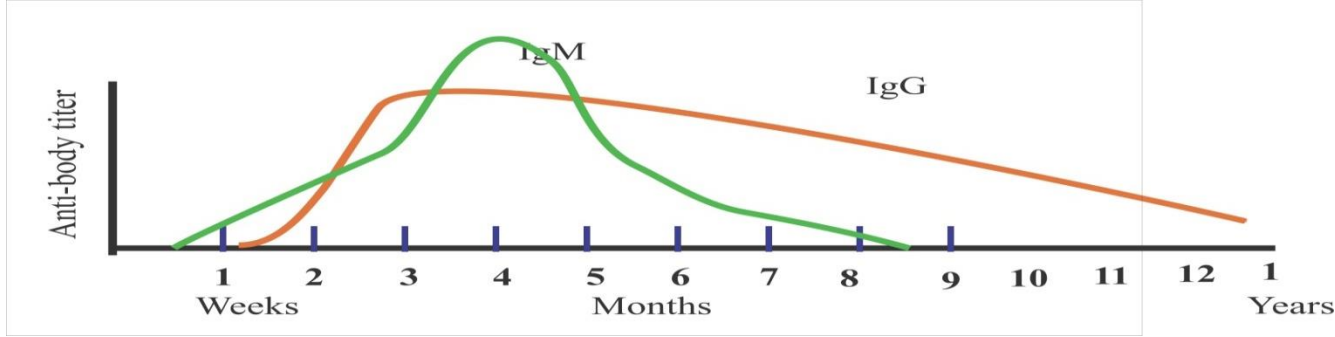
Lenfomada ileri MRI

- Difüzyon ağırlıklı görüntüleme (azalmış difüzyon)
- MRI perfüzyon (artmış serebral kan akımı)
- Single photon emission CT - SPECT (artmış kolin piki)

SPECT

Positron emission tomography (PET)

8 mm altındaki lezyonlarda sensitif değil



En sık kullanılan serolojik test *T. gondii* IgG ve IgM

Ciddi immün yetmezlikte serolojik cevap yetersiz/yanıltıcı

TE olan HIV enfekte kişilerin %97-100'üne *T. gondii* IgG (+)

Seronegatif olguda toksoplazmoz

- Primer enfeksiyon
- Kullanılan testin duyarlılığı düşük
- Hasta Ab oluşturamıyor

BOS alınabilirse *T. gondii* IgG olguların %30-70'inde (+) Ancak tek başına tanı koydurucu değil

BOS

- Mononükleer pleositoz ve orta düzeyde artmış protein
- Kültür
- Sitoloji

PCR

- *T. gondii*
- EBV (lenfoma)
- TB
- JCV
- Cryptococcal Ag



Duyarlılık %50 Özgüllük %96-100

Esas sorun:

PCR tekniklerinde *T. gondii* genetik materyalinin amplifikasyonunda standart protokol olmaması (B1 en sık)

- BAL
- Vitreus ve aköz humor
- Plevral, peritoneal sıvı
- Kİ aspiratı
- Etkilenen dokular (beyin, vb) - latent enf olabilir
- Kan – (+) olması TE açıklanamaz, multipl enf olabilir
- Amniyon mayii – İntrauterin enfeksiyon tanısında önemli

TE için kesin tanı

- Klinik bulgular
- Görüntülemede lezyonlar
- Biyopsi ile organizmanın tespiti



Ancak

SSS bulguları ile gelen olguların çoğunda beyin biyopsisinden kaçınılarak **olası TE** tanısı konur

TE'de pratikte

Tedavi (10-14 gün) ile klinik veya radyolojik iyileşme yoksa



beyin biyopsisi

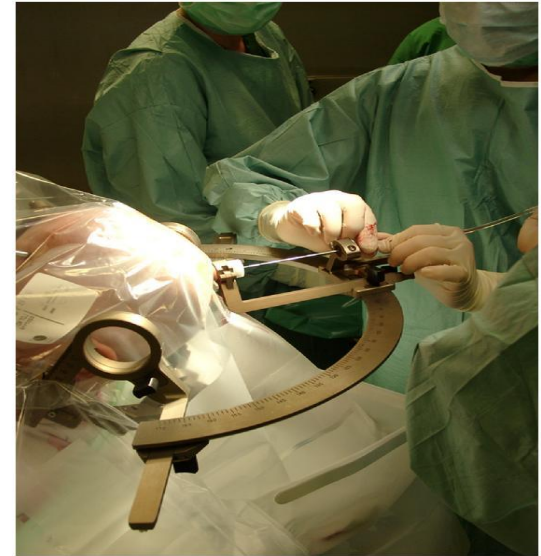
Nörolojik yanıt

- %51'inde 3.gün
- %91'inde 14.gün

Radyolojik yanıt

- 3.hafta

Görüntüleme tekrarı 2-4 hafta sonra



Beyin biyopsisi

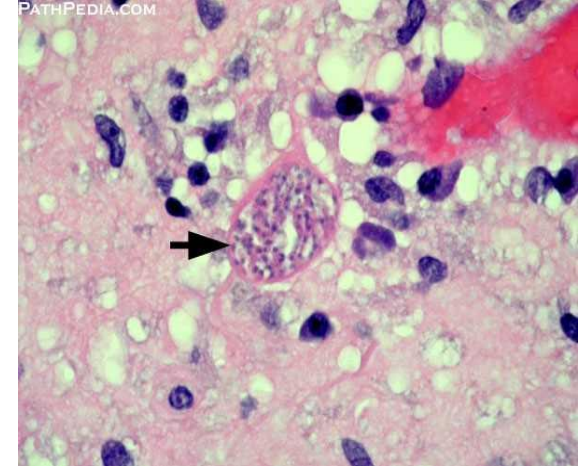
Uygun tedaviye rağmen

- İlk haftada klinik veya radyolojik kötüleşme varsa
- 10-14 günde klinik iyileşme yoksa

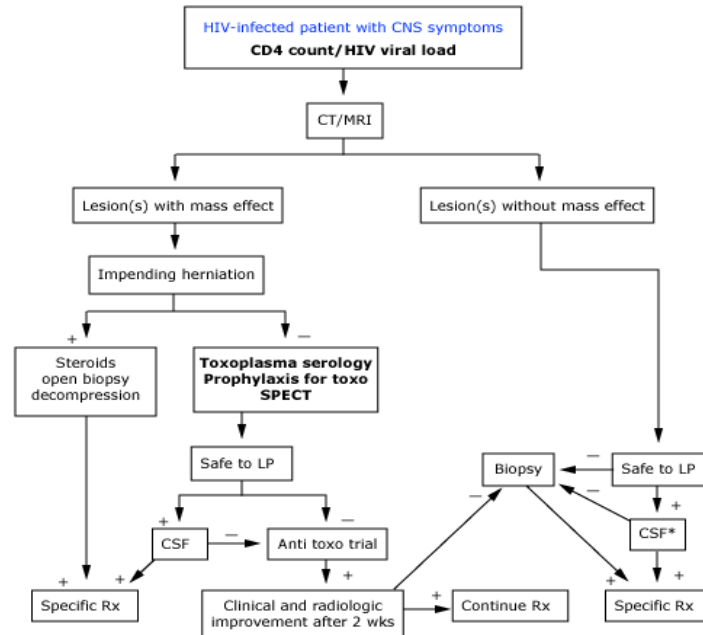
Hematoksilen-eozin < immünperoksidaz boyama

Serebral kitle toksoplazmoz olsa bile

- Biyopsi nekrotik bölgeden yapılmışsa
- Alınan örnek yetersizse
- Patolog deneyimsizse tanı değeri düşük



Algorithm for the management of HIV-infected patients with central nervous system mass lesions



Elements in **bold** represent data which contribute to the decision-making process (see text for details).

CD4<100/mm³ ve efektif toksoplazmoz profilaksisi almayanlarda

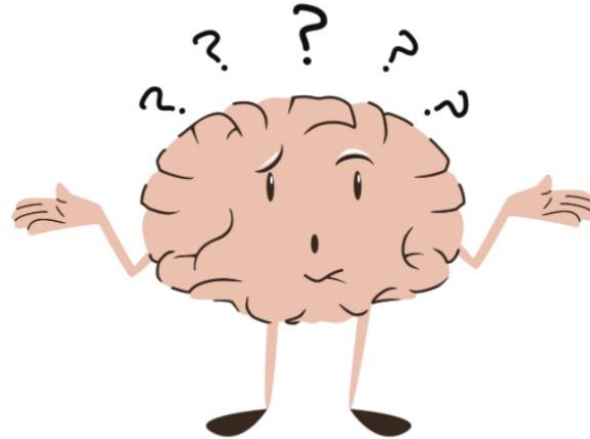
- TE klinik bulguları
- *T. gondii* IgG
- Kraniyal MR

%90 TE

Ayırıcı tanı

Serebral toksoplazmoz

- SSS lenfoması
- Tuberkülom
- PML
- Kriptokokoma
- Nokardiyoz
- CMV
- Kaposi sarkoma



Koryoretinit; CMV, VZV, Sy, fungal etkenler

Pnömoni; PCP

Tedavi

- Klinik olarak aktif enfeksiyonun tedavisi
- İdame tedavisi
 - CD4 < 200/mm³ olanlarda relapsı engellemek

Klinik ve radyolojik
düzelmeye varsa
en az 6 hafta

Recommendations for

Treating *Toxoplasma gondii*

Preferred Regimen (AI):

- Pyrimethamine 200 mg PO once, followed by dose based on body weight:

Body weight ≤60 kg:

- pyrimethamine 50 mg PO (once or BID)

Body weight >60 kg:

- pyrimethamine 75 mg PO (once or BID)

%65-90'ına başlanır
Yan etkiler nedeniyle %40'ı
tedaviye devam edemez

Raş- hafif olgularda antihistaminiklerle devam
Sulfadiyazin- kristalüri, nefrotoksisite, RY
(sıvı alımına dikkat)

page 2 of 2)

se to 50 mg daily

se to 50 mg daily

Note: if pyrimethamine is unavailable or there is a delay in obtaining it, TMP-SMX should be used in place of pyrimethamine-sulfadiazine **(BI)**. For patients with a history of sulfa allergy, sulfa desensitization should be attempted using one of several published strategies **(BI)** Atovaquone should be administered until therapeutic doses of TMP-SMX are achieved **(CIII)**.

Alternative Regimens:

- Pyrimethamine (leucovorin)^c plus clindamycin 600 mg IV or PO q6h **(AI)**; or who do not respond to pyrimethamine-sulfadiazine; must add additional agent
- TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) (IV or PO) BID (BI), or
- Atovaquone^b 1500 mg PO BID + pyrimethamine (leucovorin)^c (BII), or
- Atovaquone^b 1500 mg PO BID + sulfadiazine^d (BII), or
- Atovaquone^b 1500 mg PO BID **(BII)**, or

Etkinliği aynı
PCP profilaksisi için ajan eklenmeli
Raş ve diyare sık

Antimicrob Agents Chemother. 1998 Jun;42(6):1346-9.

Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. Italian Collaborative Study Group.

Torre D¹, Casari S, Speranza F, Donisi A, Gregis G, Poggio A, Ranieri S, Orani A, Angarano G, Chiodo F, Fiori G, Carosi G.

⊕ Author information

Abstract

The aim of the study was to compare the standard treatment of toxoplasmic encephalitis (TE) with a multicenter, randomized trial. The study included 100 patients (50 mg/kg/day of pyrimethamine and 250 mg/kg/day of sulfadiazine) of the original study. The patients were treated with the standard treatment or randomized to the study treatment. The study treatment was significantly more effective. In conclusion, the study treatment is the treatment of choice for opportunistic bacterial infections.

Clin Infect Dis. 2002 May 1;34(9):1243-50.

Randomized phase II trial of atovaquone with pyrimethamine or sulfadiazine for treatment of toxoplasmic encephalitis in patients with acquired immunodeficiency syndrome: ACTG 237/ANRS 039 Study. AIDS Clinical Trials Group 237/Agence Nationale de Recherche sur le SIDA, Essai 039

Chirgwin K¹, Luft BJ.

77 TE
Randomize 40'ı TMP-SMX, 37'si P-S ile tedavi
Klinik etkinlikte fark yok
Aksine TMP-SMX kolunda tam radyolojik yanıt daha
P-S kolunda yan etki daha fazla



Etkin alternatif , klinik ve radyolojik yanıt %77
Yan etki yüksek, aktif enf ted sırasında %5 relaps

with those of
was a pilot,
) and SMX
months at half
MX and 37
ts
s were
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with

e JL, Luft BJ.

Pyrimethamine-clarithromycin combination for therapy of acute Toxoplasma encephalitis in patients with AIDS.

Fernandez-Martin J¹

⊕ Author information

Abstract

Clarithromycin, a new macrolide antibiotic, was evaluated in combination with pyrimethamine for the treatment of acute Toxoplasma encephalitis (TE) in patients with AIDS. The combination was compared with the conventional regimen of pyrimethamine and sulfadiazine. The combination was well tolerated and stopped in five patients (because of adverse events) in two patients, and the response rates were 80 and 50%, respectively. Two patients died, one of toxoplasmic encephalitis and the other of cerebral bleeding due to pyrimethamine-induced thrombocytopenia. Adverse events related to therapy were nausea and/or vomiting (38%), skin rash (38%), significant increase of liver tests (24%), hearing loss (15%), and severe hematological abnormalities (31%). In this pilot study, a pyrimethamine-clarithromycin combination was shown to be comparable to the conventional regimen for the treatment of acute Toxoplasma encephalitis in AIDS patients.

AIDS. 2001 Mar 30;15(5):583-9.

Dose-escalation, phase I/II study of azithromycin and pyrimethamine for the treatment of toxoplasmic encephalitis in AIDS.

Jacobson JM¹, Hafner R, Remington J, Farthing C, Holden-Wiltse J, Bosler EM, Harris C, Jayaweera DT, Roque C, Luft BJ; ACTG 156 Study Team.

⊕ Author information

Abstract

OBJECTIVE: To assess the safety, tolerance and activity of increasing doses of azithromycin in combination with pyrimethamine for the treatment of toxoplasmic encephalitis (TE) in patients with AIDS.

DESIGN: A phase I/II dose-escalation study of oral azithromycin in combination with pyrimethamine.

SETTING: Eight clinical sites in the United States.

PATIENTS: Forty-two adult HIV-infected patients with confirmed or presumed acute TE.

METHODS: Patients were enrolled into three successive cohorts receiving azithromycin 900, 1200 and 1500 mg a day with pyrimethamine as induction therapy.

MAIN OUTCOME

RESULTS: Of the 42 patients, 15 patients died as a result of TE disease progression. Of the 15 patients, 7 patients died during the induction period and 8 patients died during the maintenance period receiving the 1500 mg dose.

CONCLUSION: The combination of azithromycin and pyrimethamine is not superior to conventional therapy for TE. The combination is associated with a high relapse rate. The

13 TE

Klinik yanıt %80, radyolojik yanıt %50
Yan etkiler yüksek
(döküntü, raş, kc enz artışı, ciddi hematolojik anomaliler)
Günlük doz 2X500 mg'ı aşmamalı

42 TE

Tedavinin akut fazında %67 yanıt
Ancak relaps %47

Other Considerations:

- Adjunctive corticosteroids (e.g., dexamethasone) should only be administered when clinically indicated to treat a mass effect associated with focal lesions or associated edema (**BIII**); discontinue as soon as clinically feasible.
- Anticonvulsants should be administered to patients with a history of seizures (**AIII**) and continued through at least through the period of acute treatment; anticonvulsants should not be used as seizure prophylaxis (**BIII**).

TE'de serebral ödem ve intrakraniyal hipertansiyon varsa
deksametazon eklenebilir

Mümkün olduğunca kısa süre (2 haftadan az)

SSS lenfoması da steroide yanıt verir, dikkat!

CMV retinitisi, TB gibi diğer fırsatçı enfeksiyon gelişimine dikkat

Antikonvülzanlar nöbet geçiren/öyküsü olanlara

Fenobarbital ve fenitoin ART etkileşimi nedeniyle önerilmez

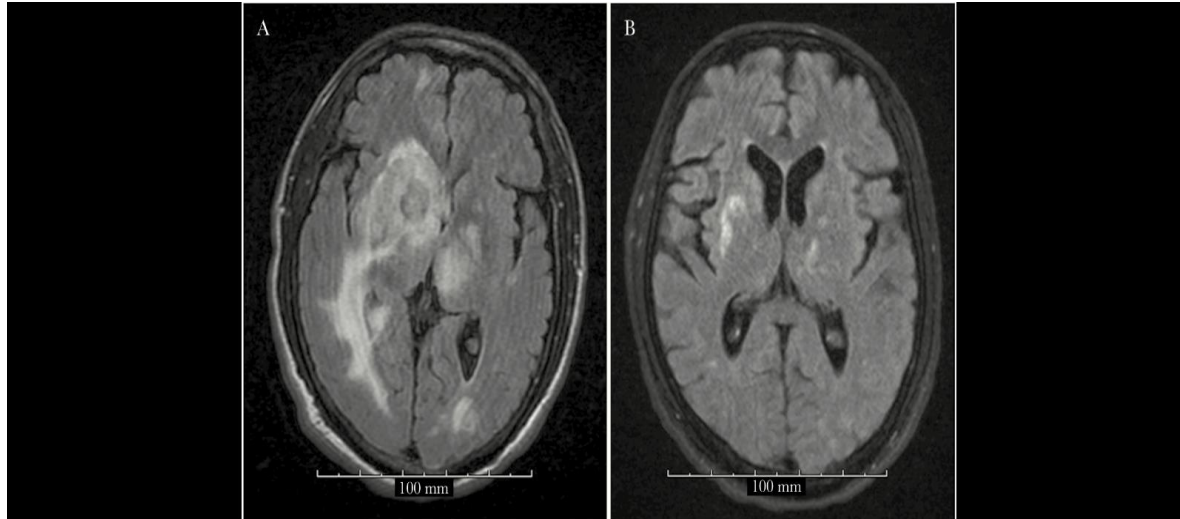
Başlanırsa aktif enf tedavisi süresince kullanılır

Radyolojik hedef:

Lezyonların

- Boyutlarında
 - Kontrast tutumunda
 - Ödemde
- } rezolusyon

Rezidüel kontrast tutan lezyonlar uzun süre kalabilir



Pre-pyrimethamine, leucovorin, and clindamycin (PLC) regimen: Magnetic resonance imaging (MRI) showing multiple bilateral T2 isodense round lesions with surrounding extensive edema and midline shift to the left (A). Post-PLC regimen: MRI showing interval decrease in lesion sizes and interval near complete resolution of the previously seen vasogenic edema (B).

Kullanılan ajanlar ile doku kistleri eradike edilemiyor
Etkin ART olmadığında ve idame tedavisi kullanılmadığında
12 ay içerisinde relaps %50-80

Chronic Maintenance Therapy

Preferred Regimen:

- Pyrimethamine 25–50 mg daily (A1)

Alternative Regimen:

- Clindamycin 600 mg PO q6h to prevent PCP (AII), or
- TMP-SMX DS 1 tablet BID (BII), or
- TMP-SMX DS 1 tablet daily (BII), or
- Atovaquone^b 750 mg PO bid
- Atovaquone^b 750 mg PO bid
- Atovaquone^b 750 mg PO bid

Discontinuing Chronic Therapy

- Successfully completed 6 months in response to ART

Criteria for Restarting Therapy

- CD4 count <200 cells/mm³

ART ile immün yapılanma oluşana kadar
Aynı ajanlar daha düşük dozlarda
TMP-SMX'de kademeli doz azaltma önerilir

- Aktif enf tedavisini tamamlayan
- TE semptom ve bulguları kaybolan
- ART ile 6 aydan uzun CD4 >200 /mm³
olanlarda idame tedavisi sonlandırılabilir

CD4< 200 /mm³ olursa yeniden başlanmalıdır

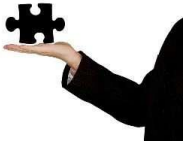
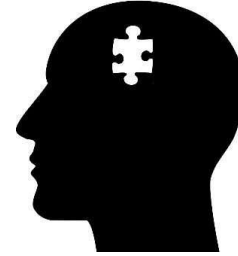
ucovorin 10–25 mg PO

add additional agent to

>200 cells/mm³ for >6

Tedaviye klinik, radyolojik yanıt

- tedavi başlandığı zamanki nöronal hasara
- immün cevaba bağlı



Koryoretinitte 6 hafta içerisinde görme keskinliği artar

Tedavide kullanılan ajanlara direnç bildirilmemiştir

Mortalite %5-20

Pnömonide ve yaygın enfeksiyonda prognoz daha kötüdür

Gebelik ve toksoplazmoz

HIV enfekte, ağır immün yetmezliği olan gebelerde kronik enfeksiyonun reaktivasyonu ile perinatal bulaş olabilir

ART kullanan
Serolojik olarak yeni edinilmiş toksoplazmoz
Fetal toksoplazmoz düşündüren detaylı USG



Amniyosentez
T. gondii PCR

Amniyosentez ART almakta olan gebelerde perinatal bulaş riskini arttırmamaktadır

18 hf'dan önce amniyosentez yapılmamalı (yanlış negatiflik)

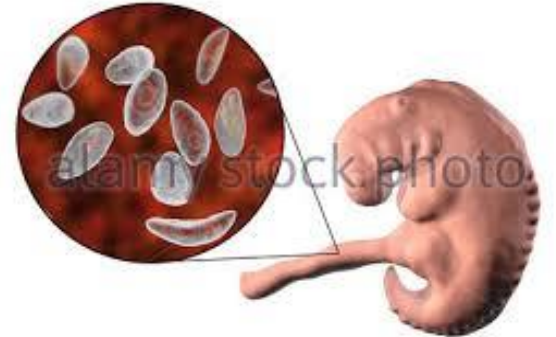
Kronik enfeksiyonda bulaş riski düşük olduğu için
rutin amniyosentez önerilmez

Akut toksoplazmozda

Fetusu konjenital bulaştan korumak amacıyla spiramisin (3X1 gr)
doğuma veya negatif PCR ve USG tespit edilene kadar

Fetal enfeksiyon şüphesi varsa

Primetamin+sulfadiazin+lökovorin



ART başlama zamanı

ART'nin **iki - üç hafta içerisinde** başlanması prognoza olumlu etki

TE'de IRIS çok nadirdir (~%5)

Yine de ART başlandıktan sonra ilk haftalarda yakın izlem

SSS penetrasyonu daha iyi olan ART tercih edilmesinin prognoza olumlu etkisi olduğu gösterilmemiştir



Korunma

HIV enfekte kişiler latent enfeksiyon açısından taranmalıdır

Preventing 1st Episode of *Toxoplasma gondii* Encephalitis (Primary Prophylaxis)

Indications for Initiating Primary Prophylaxis:

- *Toxoplasma* IgG positive patients with CD4 count <100 cells/mm³ (AII)

Note: All the recommended regimens for preventing 1st episode of toxoplasmosis are also effective in preventing PCP.

Preferred Regimen:

- TMP-SMX 1 DS PO daily (AII)

Alternative Regimens:

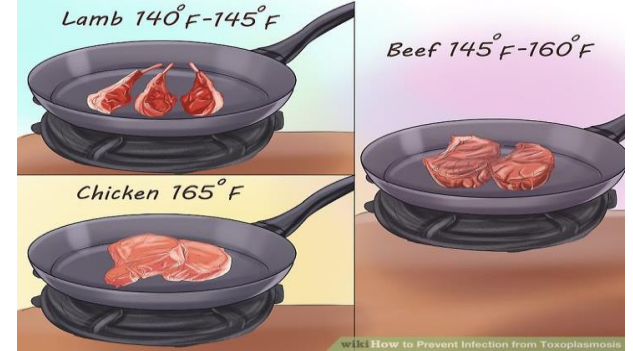
- TMP-SMX 1 DS PO three times weekly (BIII), *or*
- TMP-SMX SS PO daily (BIII), *or*
- Dapsone^a 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly (BI), *or*
- (Dapsone^a 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly (BI), *or*
- Atovaquone^b 1500 mg PO daily (CIII), *or*
- (Atovaquone^b 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily (CIII)

Indication for Discontinuing Primary Prophylaxis:

- CD4 count >200 cells/mm³ for >3 months in response to ART (AI); *or*
- Can consider if CD4 count is 100-200 cells/mm³ and HIV RNA levels remain below limits of detection for at least 3-6 months (BII).

Indication for Restarting Primary Prophylaxis:

- CD4 count <100 to 200 cells/mm³ (AIII)



Toxoplasma IgG negatif olanlara

- Çiğ veya az pişmiş et (kuzu, dana, domuz, geyik) ve
- Çiğ kabuklu deniz hayvanı (midye, ıstrıdye) yememesi
- Etlerin iç kısmı pembe kalmayacak şekilde pişirilmesi
- Çiğ et veya toprakla temas sonrası ellerin yıkanması
- Yıkanmadan çiğ sebze, meyve yememesi



HIV/AIDS patients
who care for cats and
come in contact with cat
litter or cat feces
face an increased
risk of toxoplasmosis.



Kedi besleniyorsa

- Kedinin evde tutulması
- Çiğ et veya az pişmiş etle beslenmemesi, kuru veya kuru mama verilmesi
- Kedi kumunu mümkünse başkasının günlük olarak temizlemesi
- Değilse eldivenle temizlenip ellerin yıkanması önerilir



Sonuç olarak

- Ciddi immünoompromize HIV enfekte kişilerde TE halen yüksek mortalite ve morbidite nedeni
- Tüm HIV enfekte bireyler *T. gondii* ile latent enfeksiyon varlığı açısından taranmalıdır
- CD4 <100/mm³ olup proflaksi kullanmayan olgular risk altındadır
- İleri evre olgularda, sadece SSS tutulumu olduğunda değil, pnömoni, koryoretinit, sepsis vb tablolarında da ayırıcı tanıda toksoplazmoz düşünölmelidir

RESULT TIME!

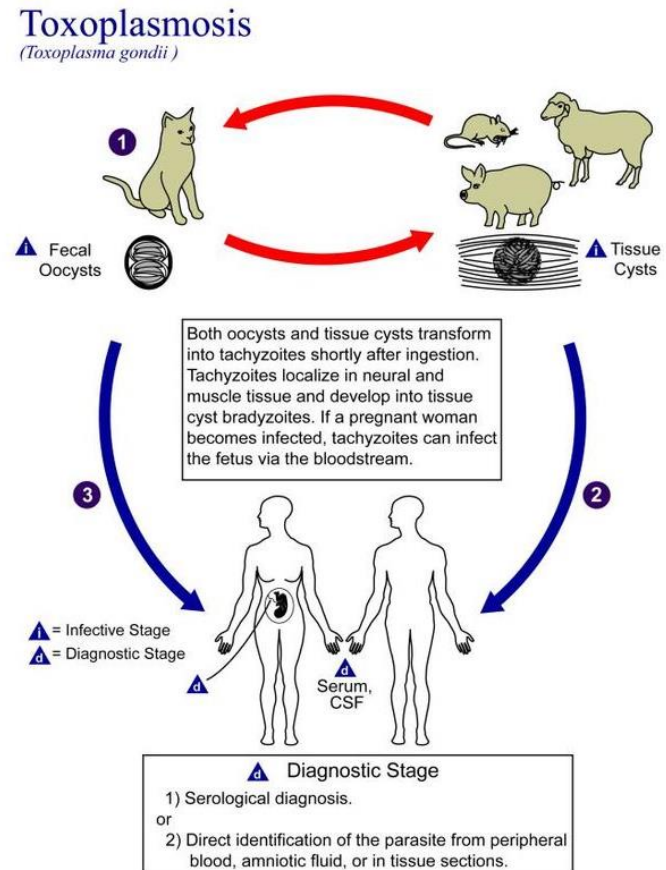




- SSS lenfoması tanısında faydalı
- Enfeksiyonlar soğuk, hipometabolik lezyonlar

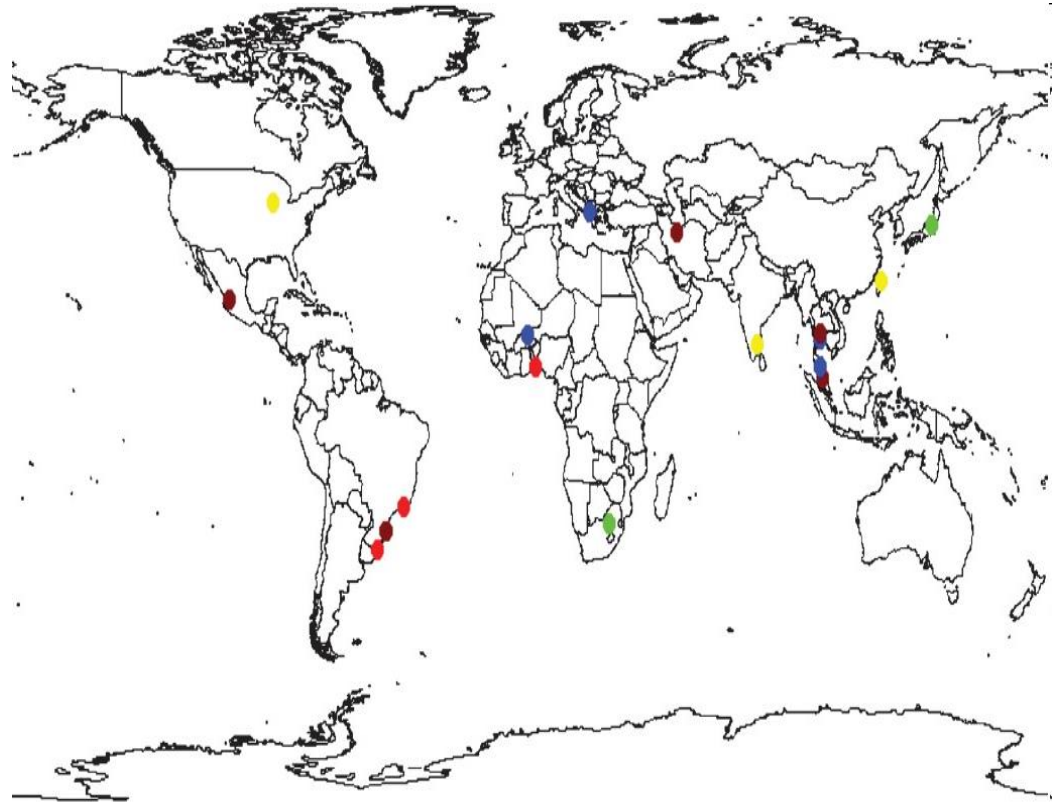
Background

- Toxoplasmosis is a parasitic disease caused by the protozoan *Toxoplasma gondii*.
- The parasite infects most animals, including humans, but the **primary host is the felid (cat) family**
- Toxoplasma may be transmitted via mouth-to-hand contact from improper handling or ingestion of raw meat or undercooked meat containing cyst from cat feces.



HIV population

- Findings on the association of HIV and toxoplasmosis seroprevalence are varied in different parts of the world.
 - some authors found **higher prevalence of *T. gondii*** specific IgG in HIV-infected patients (>70%) compared to non-infected individuals
 - others **did not find any differences** between the two groups



Seroprevalence of toxoplasmosis in HIV-infected patients.

Light red equals prevalence above 60%, brown equals 40-60%, blue 20-40%, yellow 10-20% green equals prevalence <10%, White equals absence of data.

Acute toxoplasmosis

- **Immunocompetent** persons with primary infection are usually asymptomatic (90%), but latent infection can persist for the rest of the hosts life.
- The most common signs in acute infection are:
 - **influenza-like** symptoms
 - **enlarged lymph nodes**, especially around the neck in adults, but in children multiple sites may be more common

Latent toxoplasmosis

- Recent research has also linked toxoplasmosis with attention deficit hyperactivity disorder, obsessive compulsive disorder, and schizophrenia.
- Numerous studies found a positive correlation between latent toxoplasmosis and suicidal behavior in humans.
- “Crazy cat lady syndrome” is a term coined by news organizations to describe scientific findings that link the parasite *Toxoplasma gondii* to several mental disorders and behavioral problems.
- Jaroslav Flegr (biologist) is a proponent of the theory that toxoplasmosis affects human behavior

Weiss LM, Dubey JP (2009). "Toxoplasmosis: A history of clinical observations". International Journal for Parasitology 39 (8): 895–901. doi:10.1016/j.ijpara.2009.02.004. PMC 2704023. PMID 1921790

- Toxoplasma gondii can sometimes cause or contribute to **Chronic Fatigue Syndrome**
 - is a neurological condition characterized by cognitive dysfunction, mood disorders, fatigue

Immunosuppressed persons

- More serious disease can develop due to *Toxoplasma* reactivation in AIDS, especially when the lymphocyte CD4 cell count drops below 100 cells / mm³
 - cerebral toxoplasmosis (Fig.1)
 - chorioretinitis (Fig.2)
- Toxoplasmosis is the most common parasitic CNS opportunistic infection in AIDS patients
- The HLA-DQ3 antigen is associated with susceptibility to toxoplasmic encephalitis in HIV-infected patients

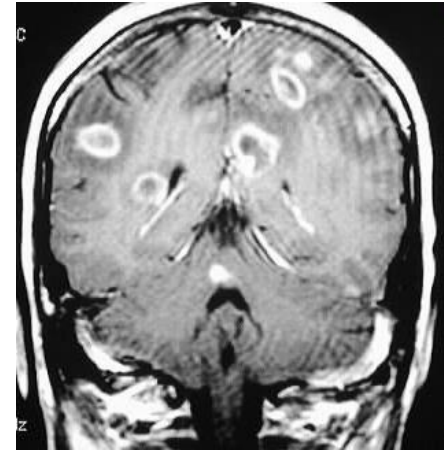


Fig. 1. Cerebral toxoplasmosis

Multiple ring enhancing lesions are present throughout both cerebral hemispheres, with associated marked edema.



Fig. 2. Toxo chorioretinitis

Cutaneous toxoplasmosis

- Skin lesions may occur in the acquired form of the disease, including
 - roseola
 - erythema multiforme-like eruptions,
 - prurigo-like nodules,
 - urticaria, and
 - maculopapular lesions.



Fig. After bone Marrow transplant

- Chemotherapy patients can develop eye, heart (myocarditis), lung or brain involvement when parasites become reactivated.
- In transplant patients, Toxoplasmosis
 - may result from reactivation of latent infection or from primary infection and
 - involve febrile myocarditis, encephalitis or pneumonitis.

Aim

- The aim of the study was to evaluate:
 - prevalence of toxoplasmosis
 - clinical manifestations in immunocompetent and immunocompromised persons.
 - risk factors for toxoplasma infection

Material and methods

- Were analyzed a total of 386 adult patients diagnosed with toxoplasmosis in the Clinical Infectious Diseases Hospital Constanta in the last 5 years.
- The reported acute toxoplasmosis cases were considered when serologic assays indicated an acute infection in according with clinical manifestation
 - IgM Toxo – positive
 - Low IgG Toxo avidity

Results

- Of these 386 adult patients
 - 173 were diagnosed with acute infection based on laboratory protocol (44.8%).
 - most of them were female, majority aged between 30-49 years, 85% from urban area
 - 3% were diagnosed with HIV infection (12 patients),
 - in 3 patients, toxoplasmosis was the primary clinical manifestation.

Gender F/B (pts)	297 / 89
Age (median) (years)	32
Urban/rural area (pts)	328 / 58
Immunocompetent pts (No)	374
HIV infected pts (No)	12
Pregnant female (No)	56
Toxocara positive (pts)	43

- The most common clinical manifestation in nonHIV infected patients was **painless cervical adenopathy**
- **Cerebral toxoplasmosis** (mass lesions) only in a female with chronic hepatitis B and nonHodgkin lymphoma, after chemotherapy
-
- **Pulmonary involment** – after chemotherapy or renal transplantation (1 patient) - PCR assay for T. gondii

Cervical adenopathy	102 pts	27.3%
Flulike symptoms and generalized lymphadenopathy	36 pts	9.6%
Retroperitoneal and mesenteric lymphadenopathy	30 pts	8.1%
Seizures, persistent headache	62 pts	16.6%
Retinochoroiditis	42 pts	11.2%
Pulmonary involvement	4 pts	1.1%
Cerebral toxoplasmosis	1 pt	0.3%
Skin itching and rash (<i>Toxocara canis</i> positive)	43pts	11.5%
Pregnant women (acute/chronic)	56 pts (5/51)	14.9%

Total =374 nonHIV infected patients

Acute toxoplasmosis

- 173 were diagnosed with acute infection (44.8%)
 - **Cervical adenopathy – 102 pts**
 - Flulike symptoms and generalized lymphadenopathy – 36 pts
 - Retroperitoneal and mesenteric lymphadenopathy – 30 pts
 - **Pregnant women with** Flulike symptoms – 5 pts

*Note - other possible etiologies were excluded by pathological examination of the lymph nodes (67 pts)



Fig.3 Cervical adenopathy

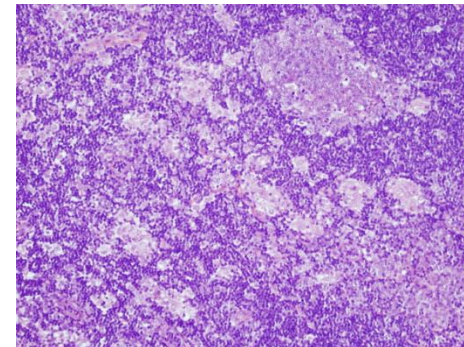


Fig.4 Toxoplasmic adenopathy

A microscopic examination of the specimens of cervical and axillary lymph node shows marked follicular hyperplasia with proeminent small granulomas composed almost entirely of epithelioid cells.

- In **HIV infected** patients prevailed **cerebral toxoplasmosis**
 - toxoplasmic encephalitis, +/- focal CNS lesions



Cerebral toxoplasmosis	11 pts
Generalized lymphadenopathy and pulmonary involvement	1pt

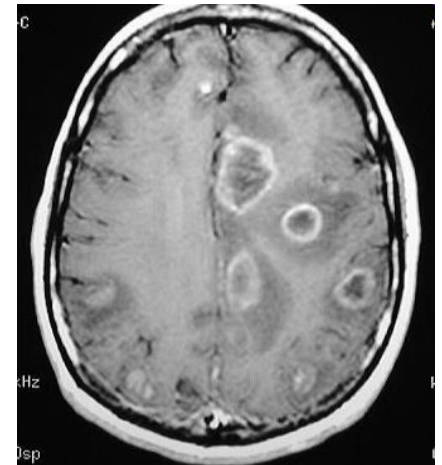
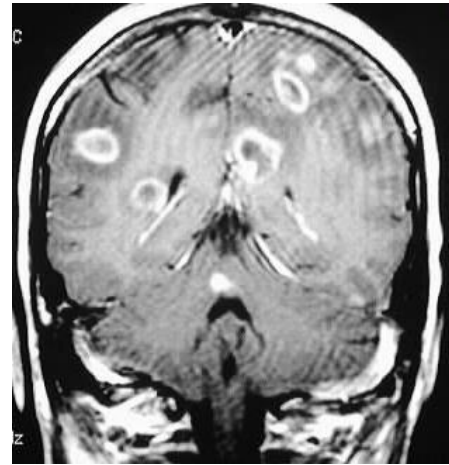


Fig. 5.6 Cerebral toxoplasmosis

Multiple ring enhancing lesions are present throughout both cerebral hemispheres, with associated marked edema.

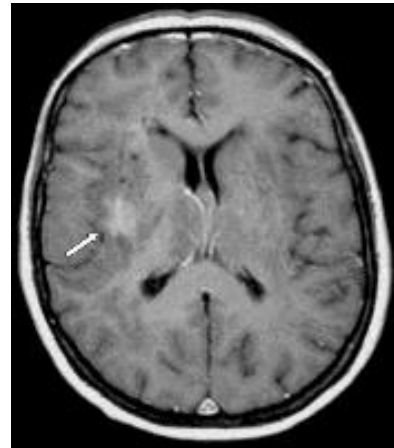


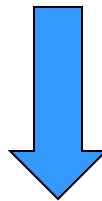
Fig.7. Toxoplasmic encephalitis



Fig.8. Toxo pneumonia

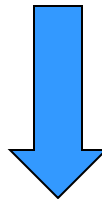
TOXO Seroprevalence in HIV infected patients

- 1024 patients under the supervision of the HIV/AIDS Regional Center Constanta,



We tested for Toxo all patients

- 798 (78%) have positive ToxoIgG (latent toxoplasmosis)



12 patients with AIDS ($CD4 = 2 - 62 \text{ cel/mm}^3$) were developed symptomatic toxoplasmosis in the last 5 years

Risk factors

- in all 386 patients we applied a standardized [questionnaire on risk factors](#) for infection with toxoplasma and compared the responses of these patients with another 200 noninfected patients.

Risk factor (Yes/No}	Toxoplasma positive pts	Toxoplasma negative pts	95 % CI	P
Contact with cat	95/291	49/151	0.6765 - 1.4961	0.9763
Living on farm, working with animals	58/308	33/167	0.5974 to 1.5202	0.8398
Contact with soil	64/312	41/184	0.5974 to 1.4185	0.7075
Raw/undercooked meet (pork, lamb, sheep)	102/284	22/178	1.7671 to 4.7785	0.0001
Taste meat cooking	153/233	48/152	1.4174 to 3.0507	0.0002
Unpasteurised milk	24/362	12/188	1.0390 to 2.9101	0.5382
Untreated water	14/372	9/191	0.6412 to 2.0875	0.5944
Travel outside Europe	22/364	10/190	0.5329 to 2.4748	0.7240

Risk factors for infection with Toxoplasma in our county were: **Raw / undercooked meat, taste meat cooking**

Conclusion

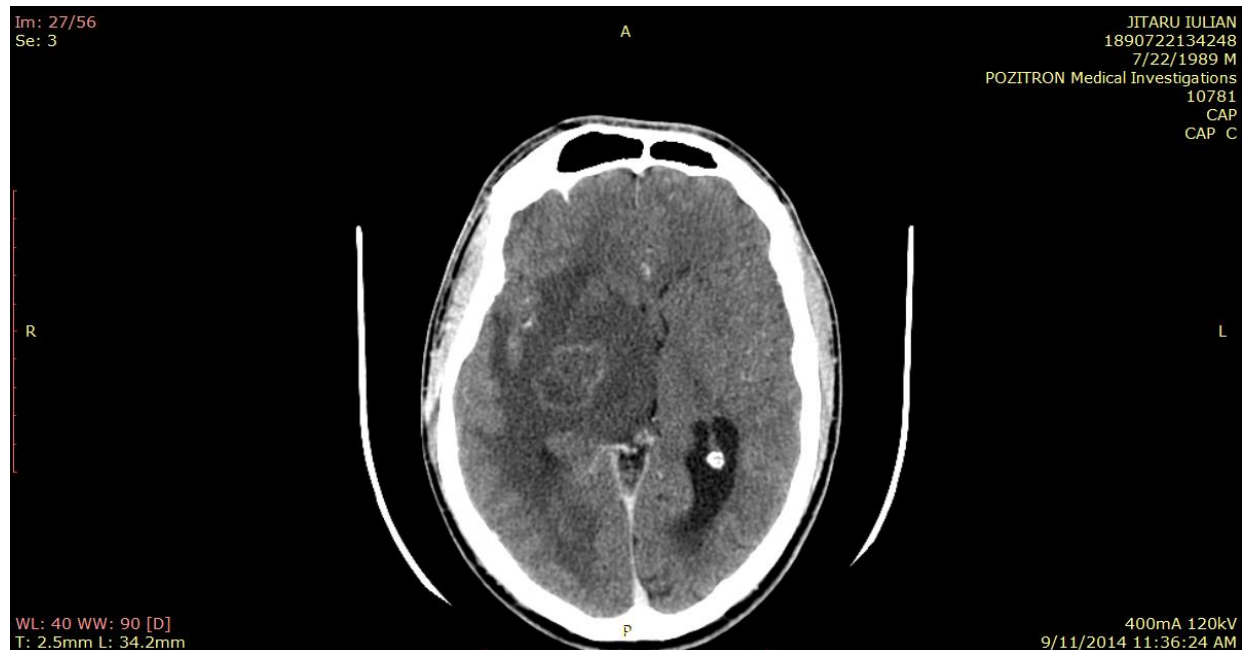
- Reporting the number of cases of toxoplasma infection in Constanta population (254.693 inhabitants), we obtained a prevalence of **151.5 cases/100.000 inhabitants = patients with symptomatic toxoplasmosis**
- Most patients were female and their supervision is required for possible implications in pregnancy.
- Risk factors for infection with Toxoplasma in our county were:
 - raw/ undercooked meat,
 - taste meat cooking

Conclusions

- Because in the general population 90% of people infected with Toxoplasma are asymptomatic and TOXO Seroprevalence in HIV infected patients is 78%
 - we believe that Toxoplasma infection is underdiagnosed in our county.
- It requires a screening study
 - to establish real seroprevalence
 - to prevent developing complications

Last case (11.09.2014)

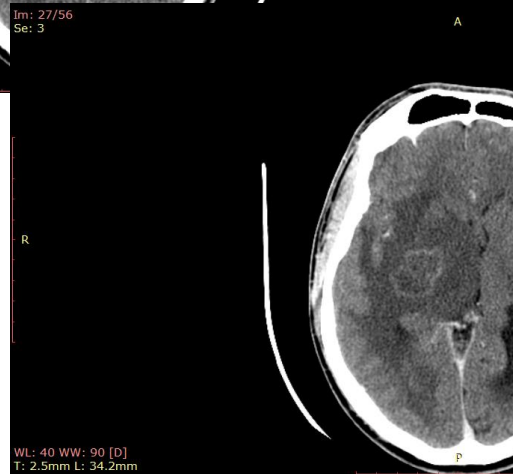
- male, 25 years old
- admitted to hospital with
 - seizures, persistent headache
 - severe labial herpes simplex
 - oftalmic herpez zoster
 - wasting syndrome
- **HIV positive**
- **Cerebral Toxoplasmosis**



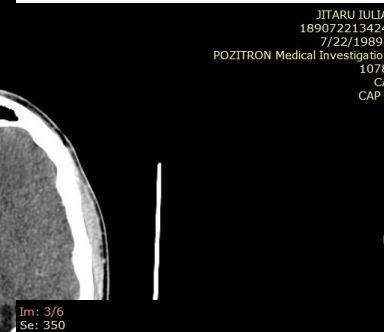
Cerebral Toxoplasmosis



← Associated marked edema



Ring enhancing lesion



THE TOXOPLASMA LIFE CYCLE

Sexual stage:
The parasite can only reproduce and produce oocysts in a feline host. The oocytes are shed in faeces.

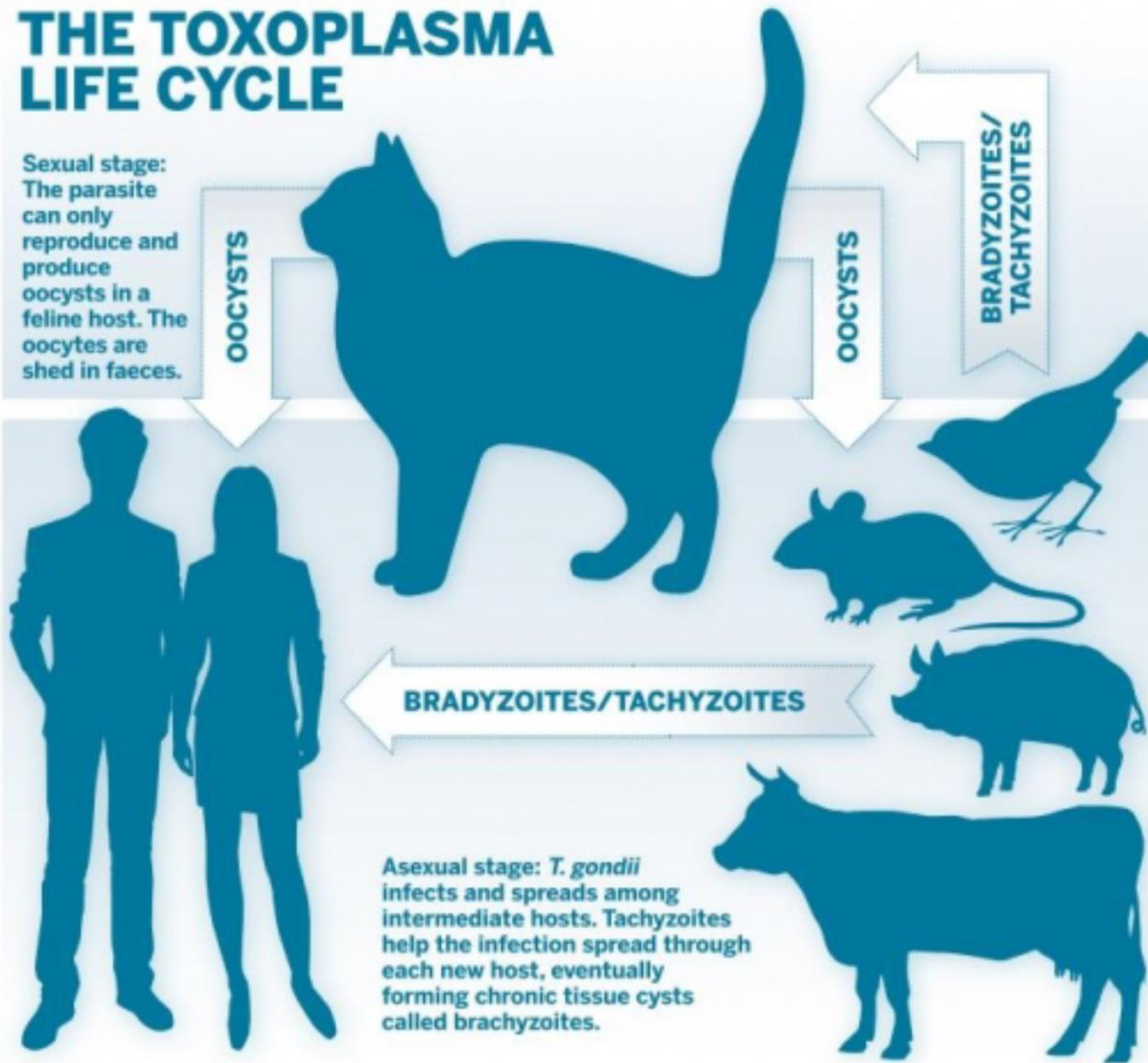
OOCYSTS

OOCYSTS

BRADYZOITES/
TACHYZOITES

BRADYZOITES/TACHYZOITES

Asexual stage: *T. gondii* infects and spreads among intermediate hosts. Tachyzoites help the infection spread through each new host, eventually forming chronic tissue cysts called brachyzoites.





Dr Özlem Altuntaş Aydın
SBÜ Bakırköy Dr Sadi Konuk SUAM
Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji