

# **Bruselloz**

## **Klinik Formlar ve Tedavi**



**Hakan Erdem**

**V. Türkiye Zoonotik Hastalıklar Sempozyumu**

**24-25 Ekim 2014, Erzurum**

# Enfeksiyon Kliniklerinde Bruselloz



*Haziran-Temmuz 2013*  
*Fransa 'da (-), Türkiye' de % 2.8*

*Erdem H, Stahl JP, Inan A, et al. The features of infectious diseases departments and anti-infective practices in France and Turkey: a cross sectional study. European Journal of Clinical Microbiology & Infectious Diseases (in press) DOI: 10.1007/s10096-014-2116-9*

# Bölgemizde YBÜ' ler



*Haziran-Temmuz 2012*  
*Bruselloz (-)*

*Erdem H, Inan A, Elaldi N, et al. Surveillance, control and management of infections in intensive care units in southern Europe, Turkey and Iran. Journal of Infection 2014; 68: 101-110.*

# Klinik Sunum

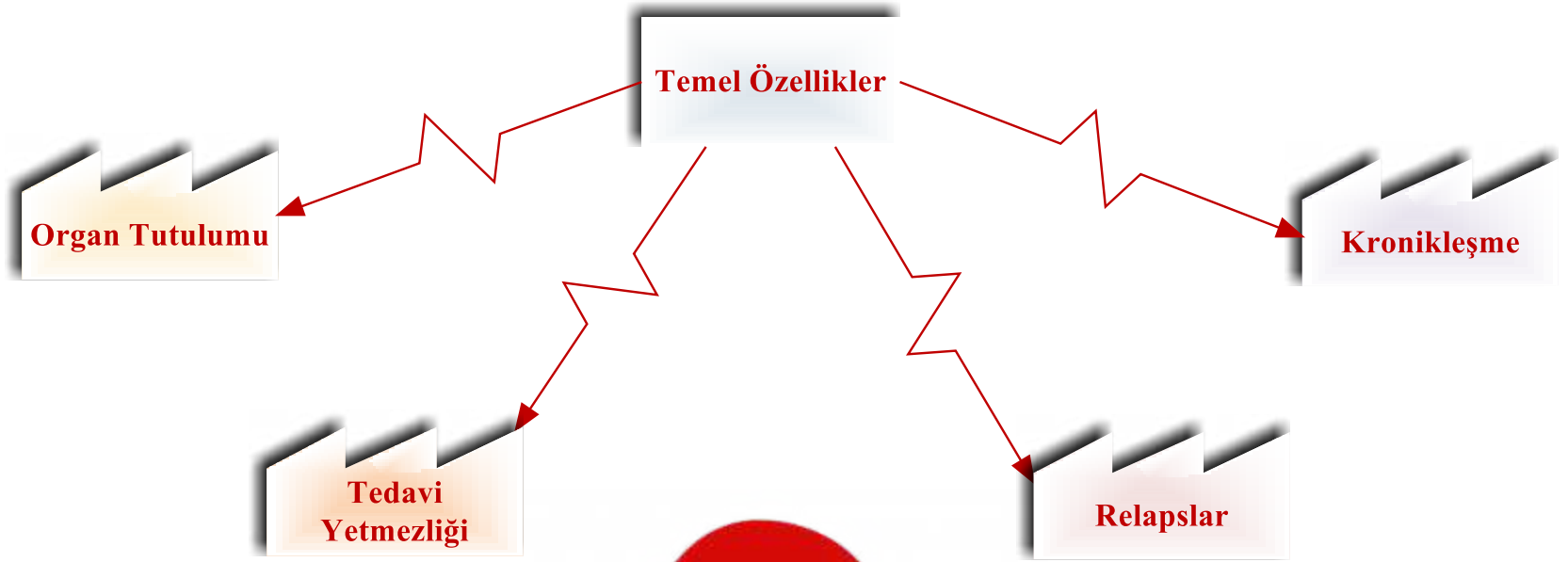


*Bruselloz herşeyi taklit edebilir*

# Hastalığın Başlangıcı

- ♣ İnkübasyon 1-4 hafta
- ♣ Bazen akut, sıklıkla kronik
- ♣ Bariz ya da maskeli yakınmalar







*Vakaların yarısında fokal tutulum  
mevcut*





*B. melitensis* , *B. abortus* , *B. suis* enfeksiyonları  
çok benzer





## *Bruselloz N'BA' nın önde gelen nedenlerinden*

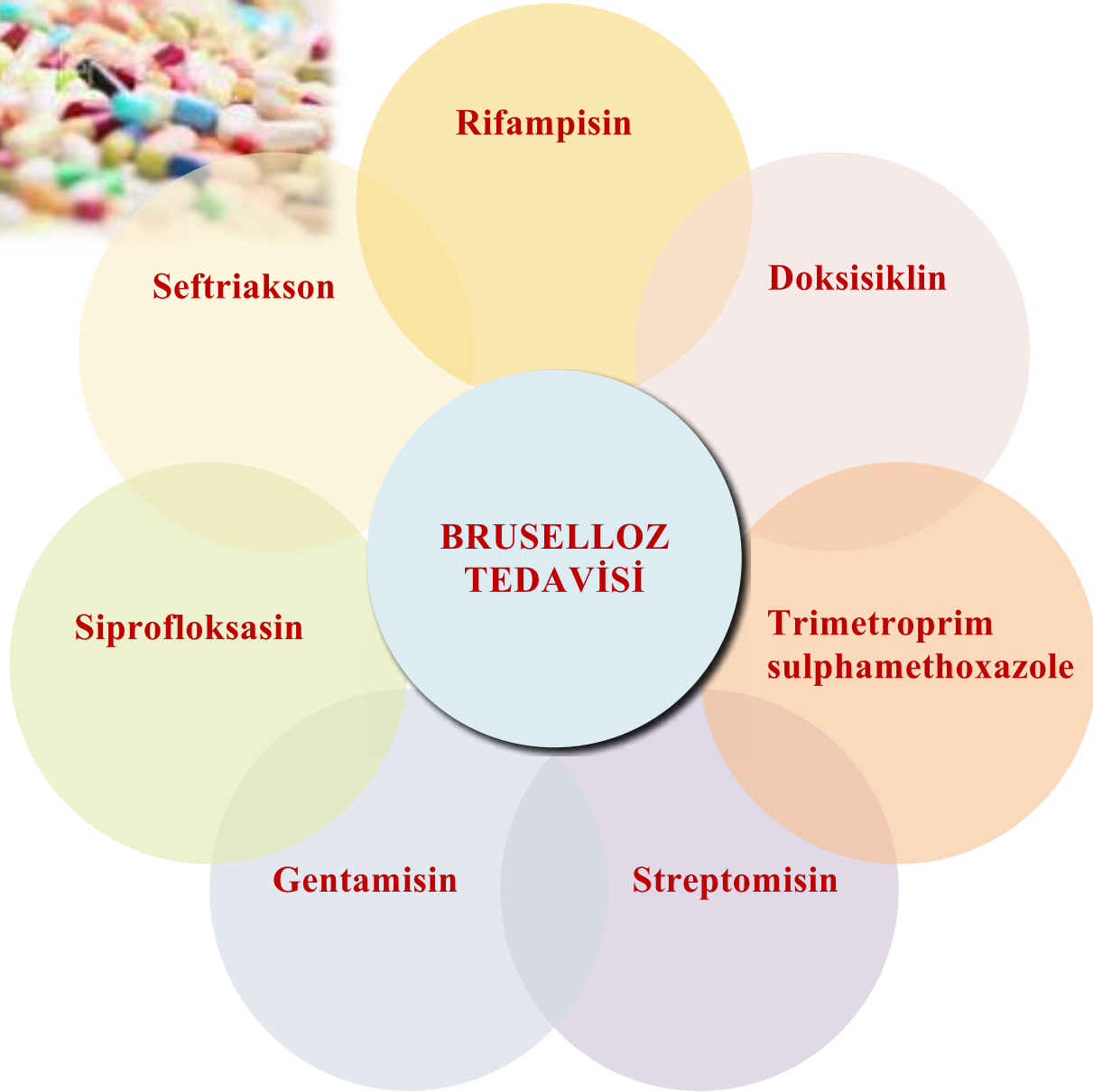
*Erdem H, Akova M. Leading Infectious Diseases Problems in Turkey. Clinical Microbiology and Infection 2012;18(11):1056-67.*

*Sipahi OR, et al. Pooled analysis of 857 published adult fever of unknown origin cases in Turkey between 1990-2006. Med Sci Monit 2007; 13(7): CR318-22.*

# Temel Tedavi Yaklaşımı

- ♣ Fagositlerde biriken antibiyotikler
- ♣ Tekli tedavi önerilmez





# Aminoglikozidli Kombinasyon

- ♣ Doksisisiklin 2x100, 6 hafta
- ♣ Aminoglikozit
  - ♣ IM streptomisin 1 gr, 2-3 hafta
  - ♣ Gentamisin, 5 mg/kg, 7 gün



# Oral Rejim

- ♣ Doksi 2x100 mg/gün, 6 hafta
- ♣ Oral rifampin, 6 hafta
  - ♣ 600-900 mg
  - ♣ Ya da 15 mg/kg



# İlaç Seçimi

- ♣ Aminoglikozidli rejimler, biraz daha iyi
- ♣ Doksi+Rif, daha ucuz
  - ♣ Fakir ülkelerde erişim kolay



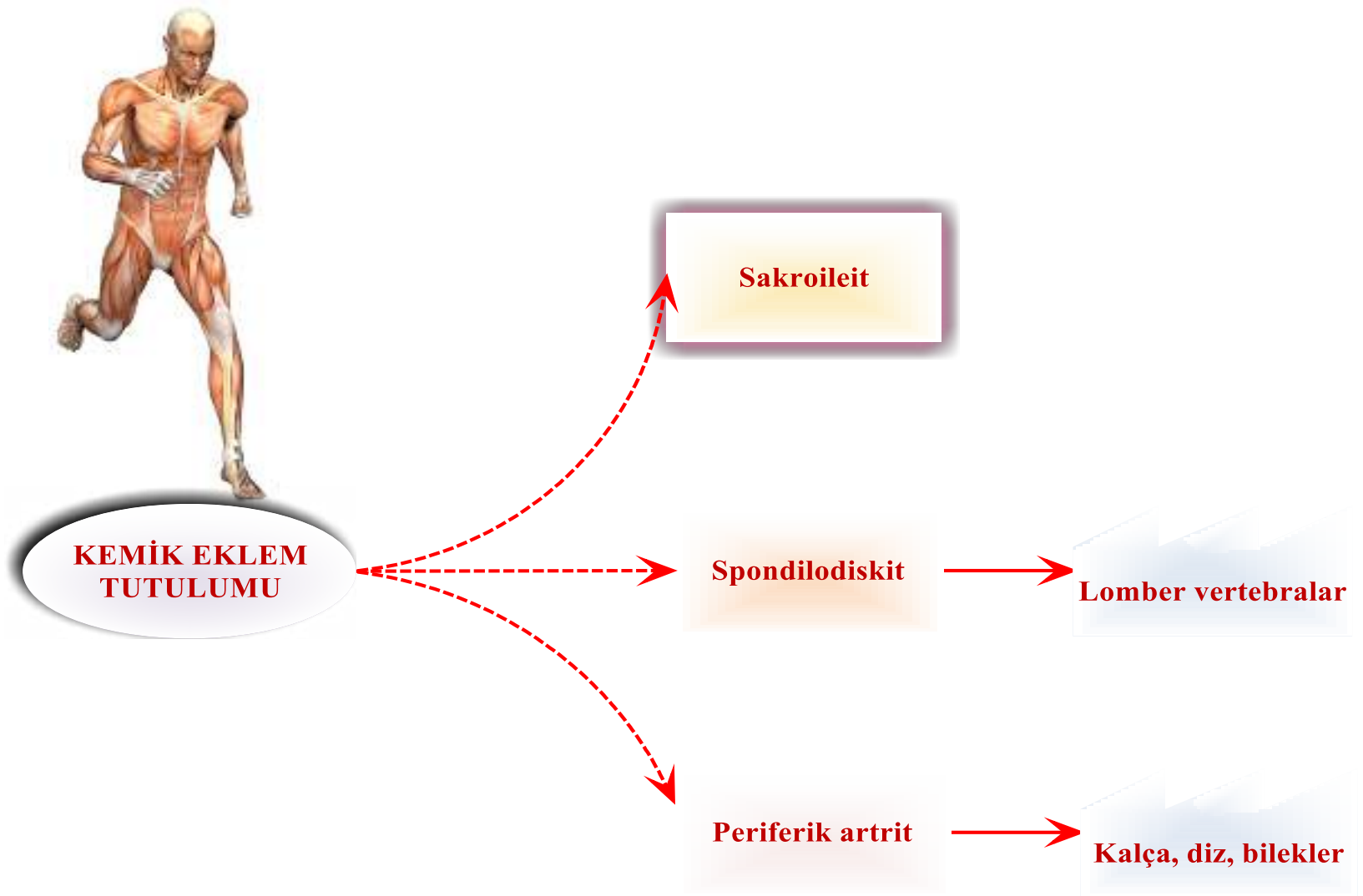


- ♣ Relaps, 10-15%
- ♣ Antibiyotik direnci sorun değil
- ♣ Aynı kombinasyon kullanılabilir



# Bruselloz' da Kemik Eklem Tutulumu





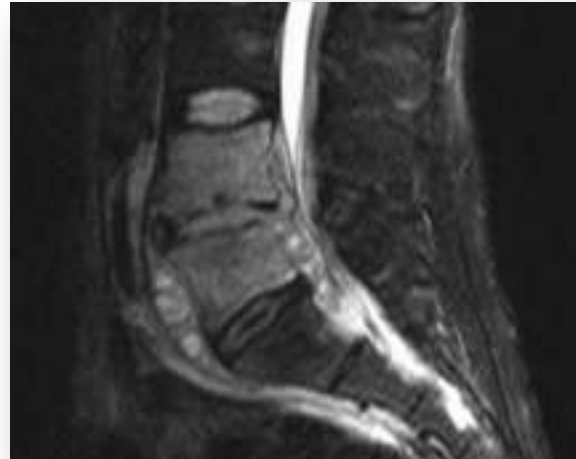
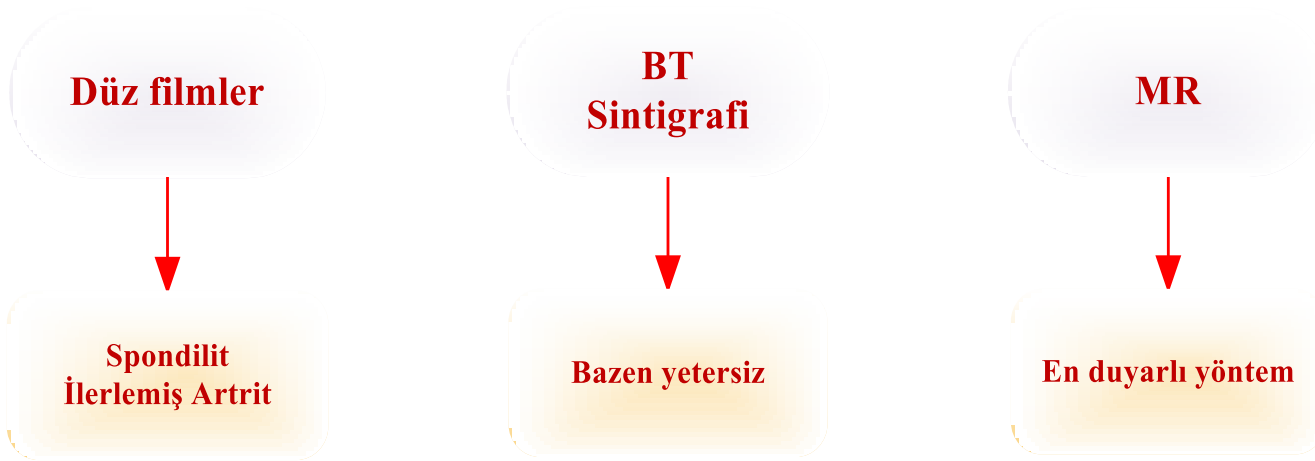
*Buzgan T, Karahocagil MK, Irmak H, et al. Clinical manifestations and complications in 1028 cases of brucellosis: a retrospective evaluation and review of the literature. Int J Infect Dis 2010; 14(6): e469-78*

*Ulu-Kilic A, Karakas A, Erdem H, et al. Update on Treatment Options for Spinal Brucellosis. Clinical Microbiology and Infection 2014;20(2):O75-82*



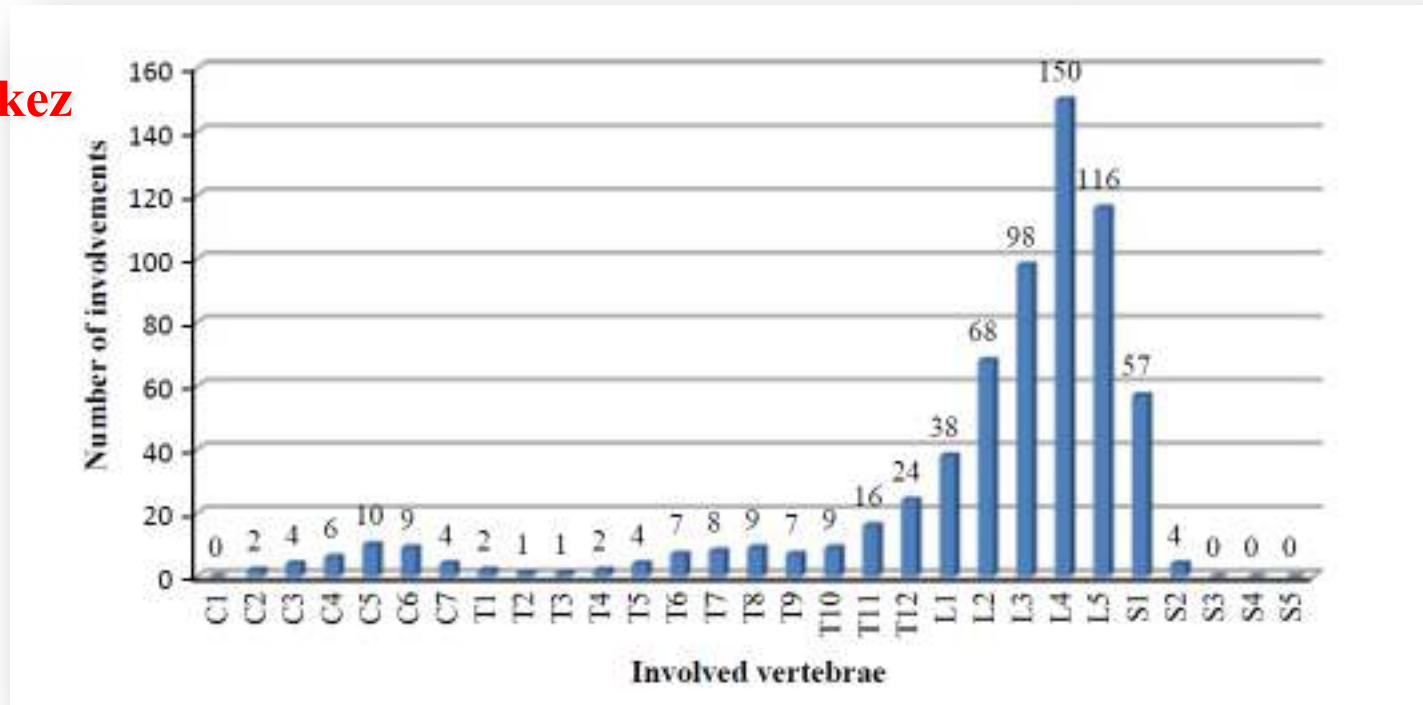
*Spondilite özgün karakteristik  
Pedro-Pons arazı*

# Kemik Eklem Brusellozu Radyoloji



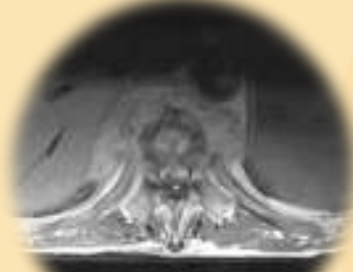
# Vertebra Tutulumu

n=293  
19 merkez

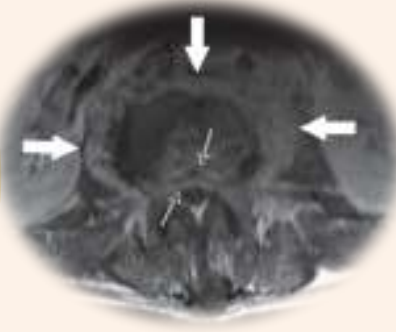


*Ulu-Kilic A, Karakas A, Erdem H, et al. Update on Treatment Options for Spinal Brucellosis. Clinical Microbiology and Infection 2014;20(2):O75-82*

**Paravertebral yayılma**



**Epidural yayılma**



**% 27**

**SPONDİLİT  
KOMPLİKASYONLARI**

**Psoas invazyonu**



**Radikülit**



# Tedavi Etkinliđi-1

Patient groups	Regimens	Successful, n (%)	Failure, n (%)	p-value
Uncomplicated (n = 215)	DS	5 (100)	0 (0.0)	0.470
	DRS	94 (92.2)	8 (8.8)	
	DRG	14 (100)	0 (0.0)	
	DRC	6 (85.7)	1 (14.3)	
	DR	70 (90.9)	7 (9.1)	
	Others	9 (90)	1 (10)	
Complicated (n = 78)	DS	2 (66.6)	1 (33.3)	0.816
	DRS	36 (92.3)	3 (7.7)	
	DRG	8 (100)	0 (0.0)	
	DRC	4 (100)	0 (0.0)	
	DR	17(94.4)	1 (5.6)	
	Others <sup>a</sup>	5 (83.3)	1 (6.7)	

D, doxycycline; S, streptomycin; R, rifampicin; G, gentamicin; C, ciprofloxacin.  
<sup>a</sup>Other: DR plus trimethoprim/sulphamethoxazole or ceftriaxone.

*Ulu-Kılıc A, Karakas A, Erdem H, et al. Update on Treatment Options for Spinal Brucellosis. Clinical Microbiology and Infection 2014;20(2):O75-82*



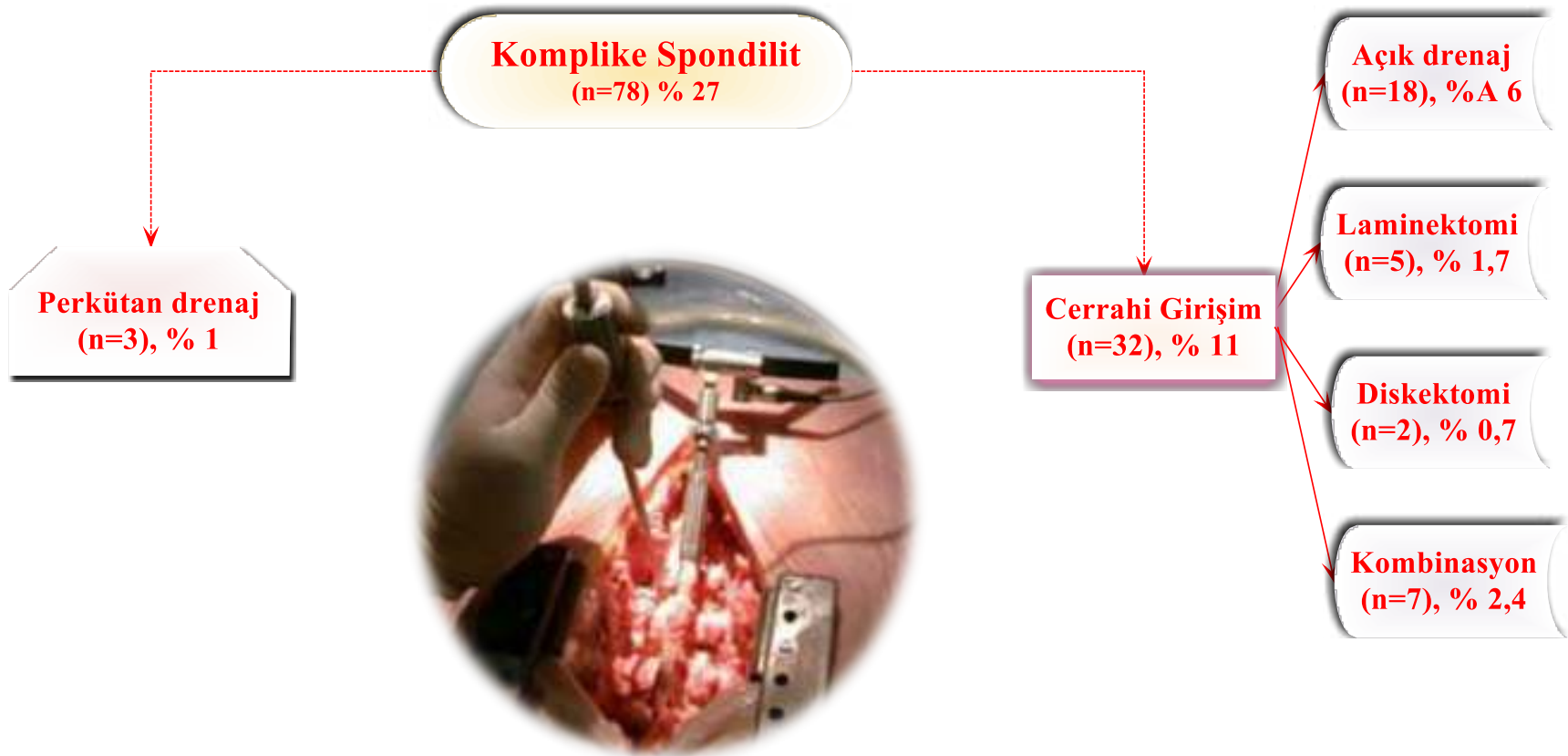
# Tedavi Etkinliđi-2

**TABLE 3.** Comparison of durations of successful antibiotic regimens between groups ( $n = 239$ )

Patient groups	DR, median week (1st–3rd quartiles)	DR plus aminoglycoside, median week (1st–3rd quartiles)	p-value
Complicated ( $n = 61$ )	16 (12–23)	20 (12–35)	0.130
Uncomplicated ( $n = 178$ )	12 (12–13.25)	12 (12–16)	0.876
p-value	0.241	0.001	

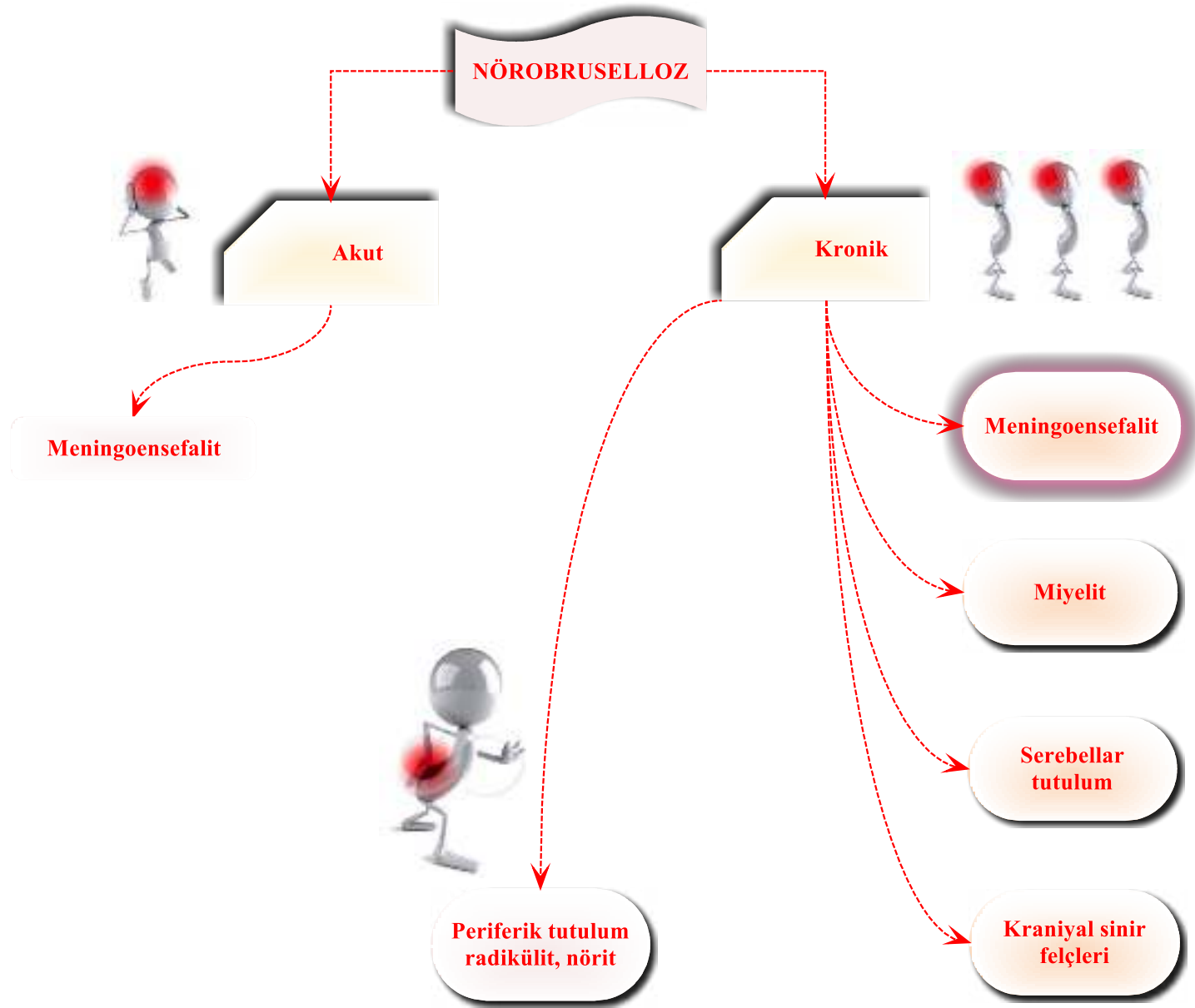
D, doxycycline; R, rifampicin; aminoglycoside, gentamicin or streptomycin.

*Ulu-Kılıc A, Karakas A, Erdem H, et al. Update on Treatment Options for Spinal Brucellosis. Clinical Microbiology and Infection 2014;20(2):O75-82*



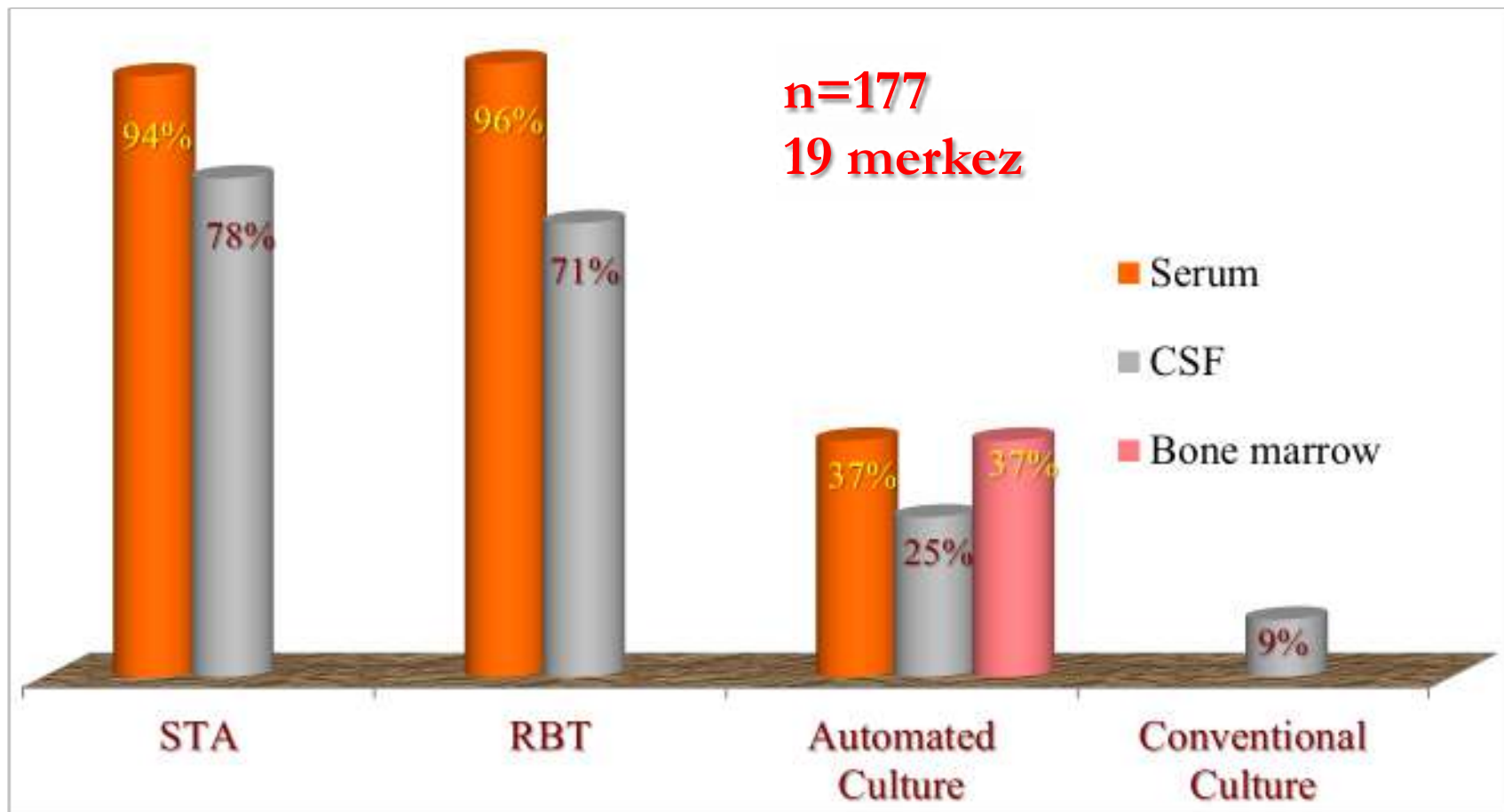
# Nörobruselloz



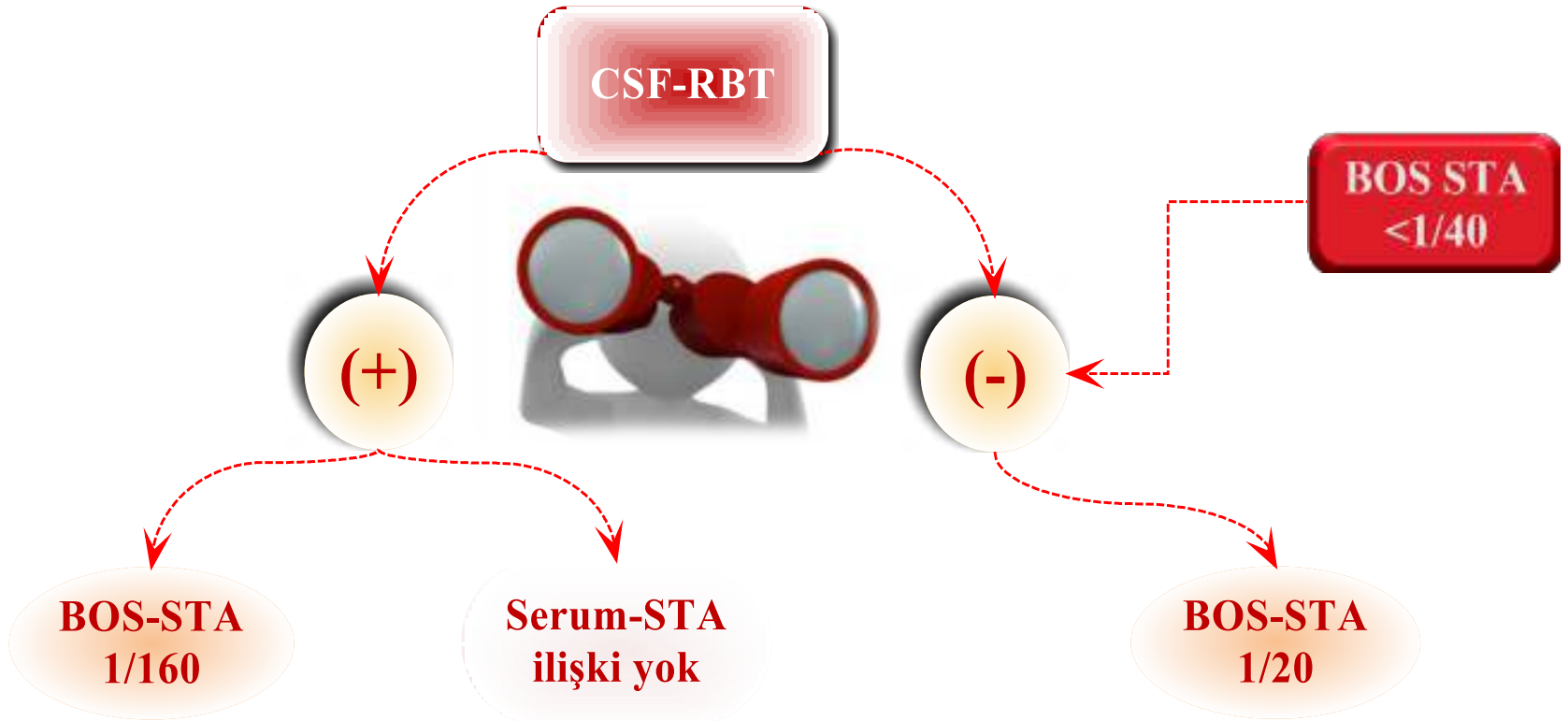


1) Franco MP, Mulder M, Gilman RH, Smits HL. Human brucellosis. *Lancet Infect Dis.* 2007;7(12):775-86.

2) Demiroğlu YZ, Turunç T, Karaca S, et al. Neurological involvement in brucellosis; clinical classification, treatment and results. *Mikrobiyol Bul.* 2011;45(3):401-10.



*Erdem H, Kilic S, Sener B, et al. Diagnosis of chronic brucellar meningitis and meningoencephalitis: the results of the Istanbul-2 study. Clin Microbiol Infect 2013; 19: E80-E86.*



*Duyarlılıklar farklı deęil:*

*1. BOS-BT ve BOS-STA ( $p = 0.163$ )*

*2. Serum RBT ve serum-STA ( $p = 0.500$ )*

# Meningoensefalit

## En sık yakınmalar

- ♣ Baş ağrısı, % 57
- ♣ Ateş, % 57
- ♣ Terleme, % 30
- ♣ Sırt ağrısı, % 28



## En sık bulgular

- ♣ Ense sertliği, % 37
- ♣ Konfüzyon, % 18
- ♣ Karaciğer büyüklüğü, % 15
- ♣ Hipoestezi, % 12

*Gul HC, Erdem H, Bek S. Overview of neurobrucellosis: a pooled analysis of 187 cases. Int J Infect Dis. 2009 ;13(6):e339-43.*





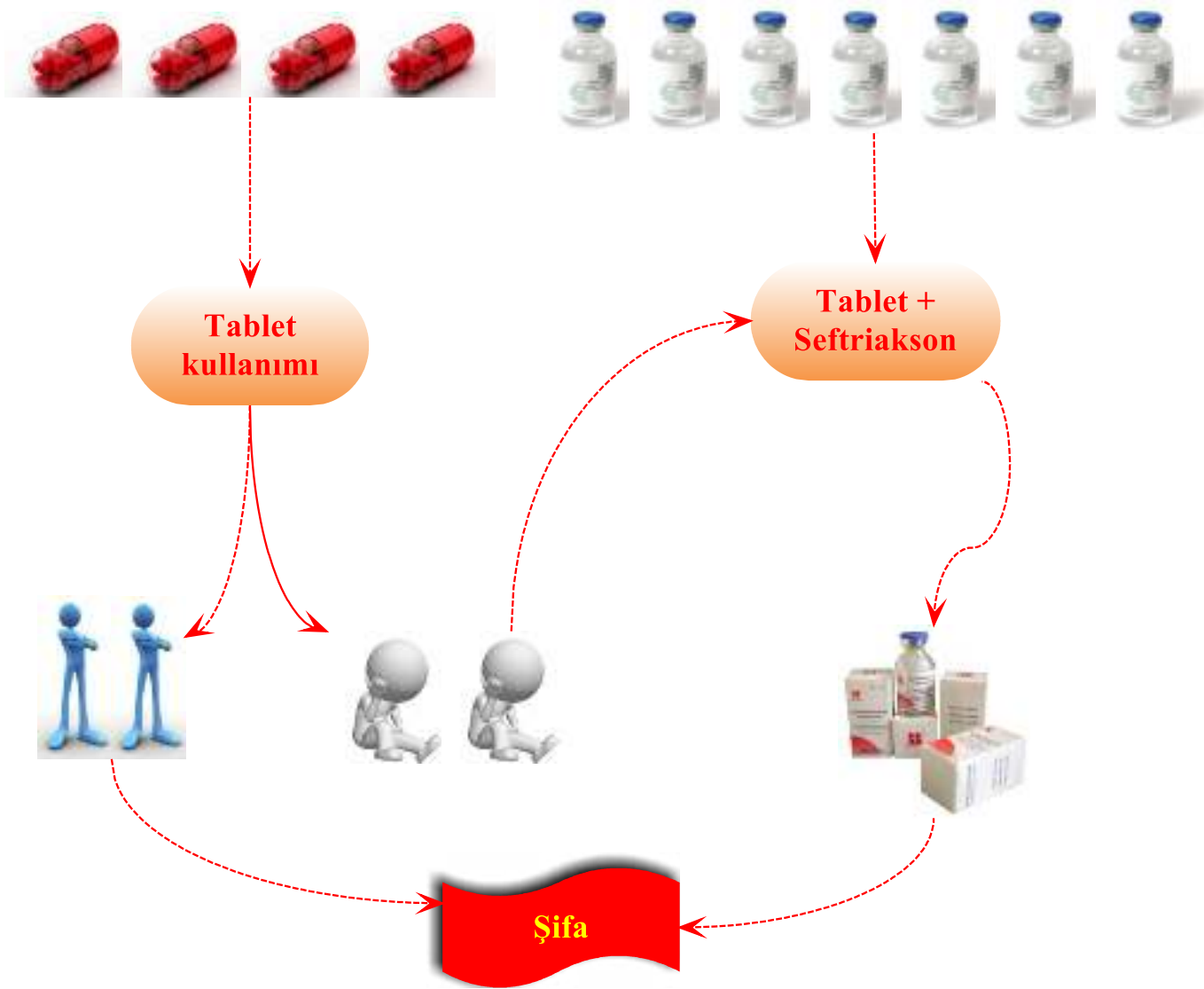
*Tanı öncesi yakınmaların süresi:  
90 ±138 gün*

*Colmenero JD, Queipo-Ortuño MI, Reguera JM, et al. Real time polymerase chain reaction: a new powerful tool for the diagnosis of neurobrucellosis. J Neurol Neurosurg Psychiatry. 2005;76(7):1025-7.*

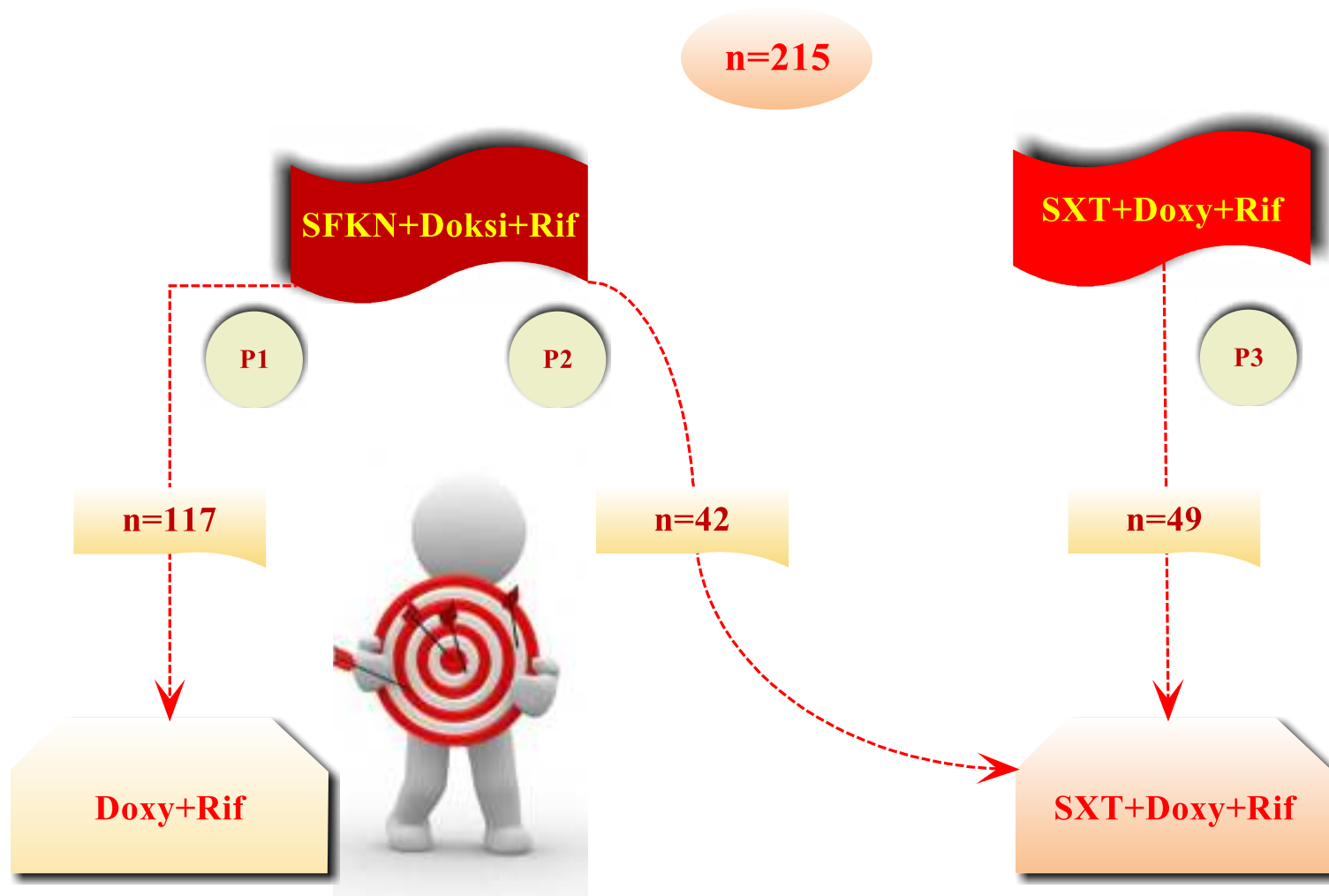
# Meningoensefalit Sekelleri



*Erdem H, Ulu-Kılıç A, Kılıç S, et al. Efficacy and tolerability of antibiotic combinations in neurobrucellosis: results of the Istanbul study. Antimicrob Agents Chemother. 2012;56(3):1523-8.*

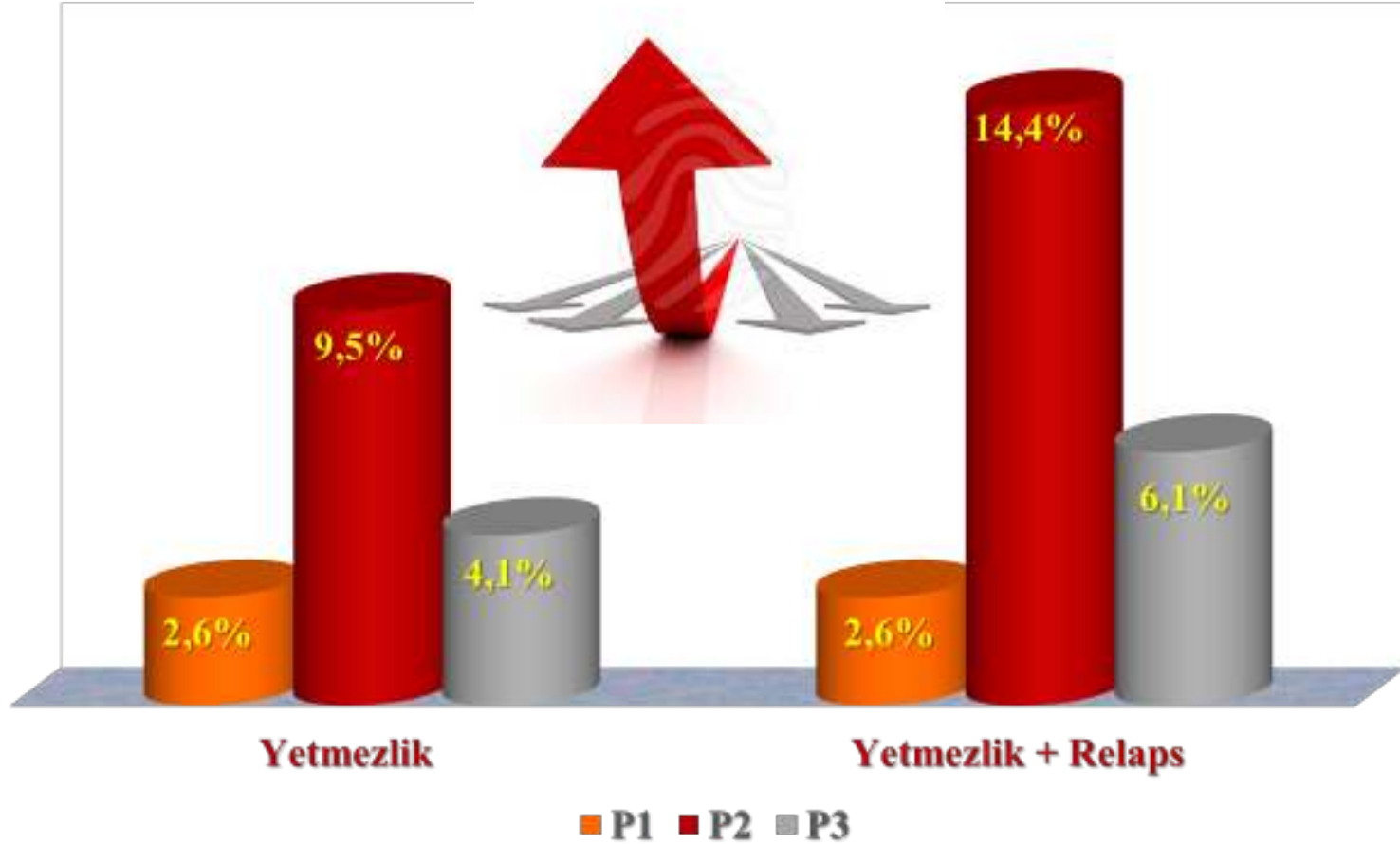


*Gul HC, Erdem H, Gorenek L et al. Management of neurobrucellosis: an assessment of 11 cases. Intern Med. 2008;47(11):995-1001.*



*Erdem H, Ulu-Kılıç A, Kılıç S, et al. The efficacy and tolerability of antibiotic combinations in neurobrucellosis: Results of the Istanbul study. Antimicrobial Agents and Chemotherapy. 2012; 56:1523-1528*

# Antibiyotik Etkinliđi



# İstanbul-1, Seftriakson

- ♣ Tedavi başarısı ↗
- ♣ Tedavi süresi ↘
  - ♣ 4-5 ay x 6 ay
- ♣ Tedavi altında komplikasyon gelişmesi ↘



# İstanbul-1

- ♣ Seftriakson kesildikten sonra
  - ♣ Doksi+Rif
  - ♣ SXT eklemek, faydasız...

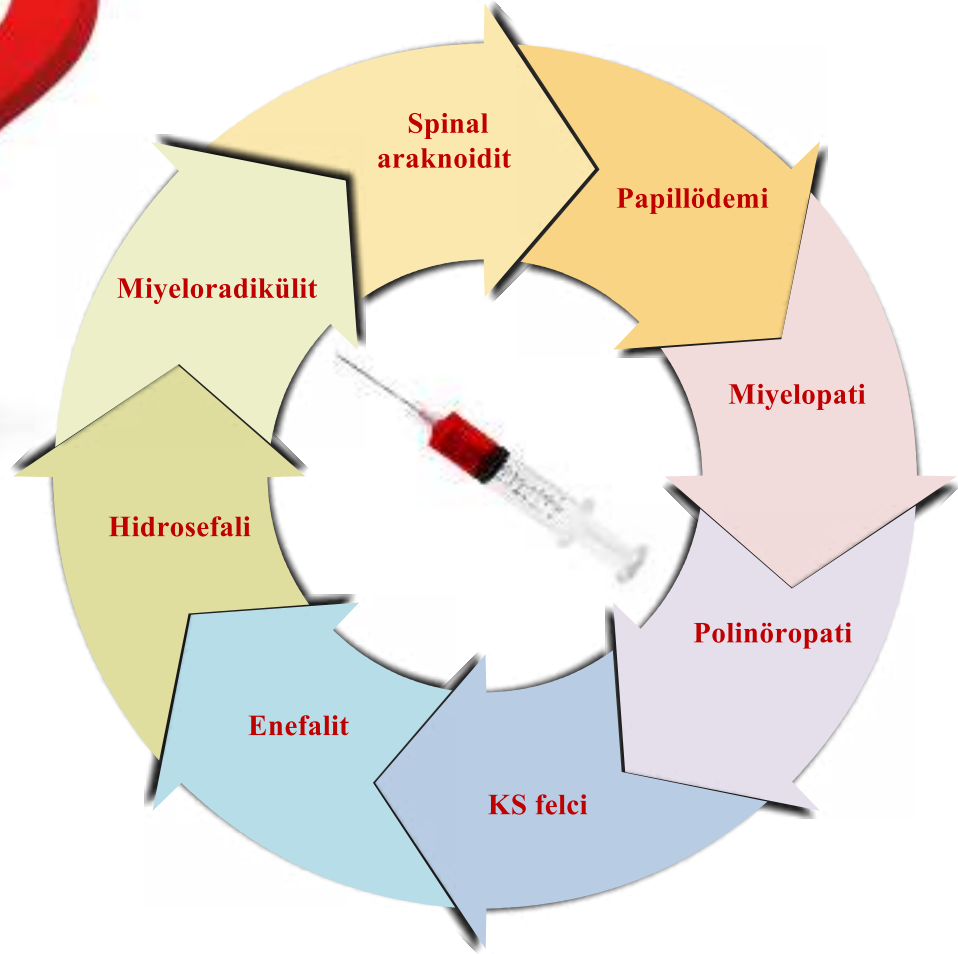




# Steroid Kullanımı

AG geçişini azaltır

Immün zayıflık



# Genitoüriner Bruselloz



# Genitoüriner Tutulum

- ♣ Vakaların % 5-10 kadarında
- ♣ Sıklıkla erkekler
  - ♣ Epididimo-orşit, erkekler
  - ♣ Piyelonefrit, kadınlar
- ♣ Tümör ya da tbc ile karışabilir
- ♣ Nefrit, endokarditte sık



# GU Bruselloz da Tedavi

n=390  
34 merkez

**TABLE 5.** Comparison of genitourinary system brucellosis patients without other coexistent focal disease (group 1) and those with another involved site (group 2)

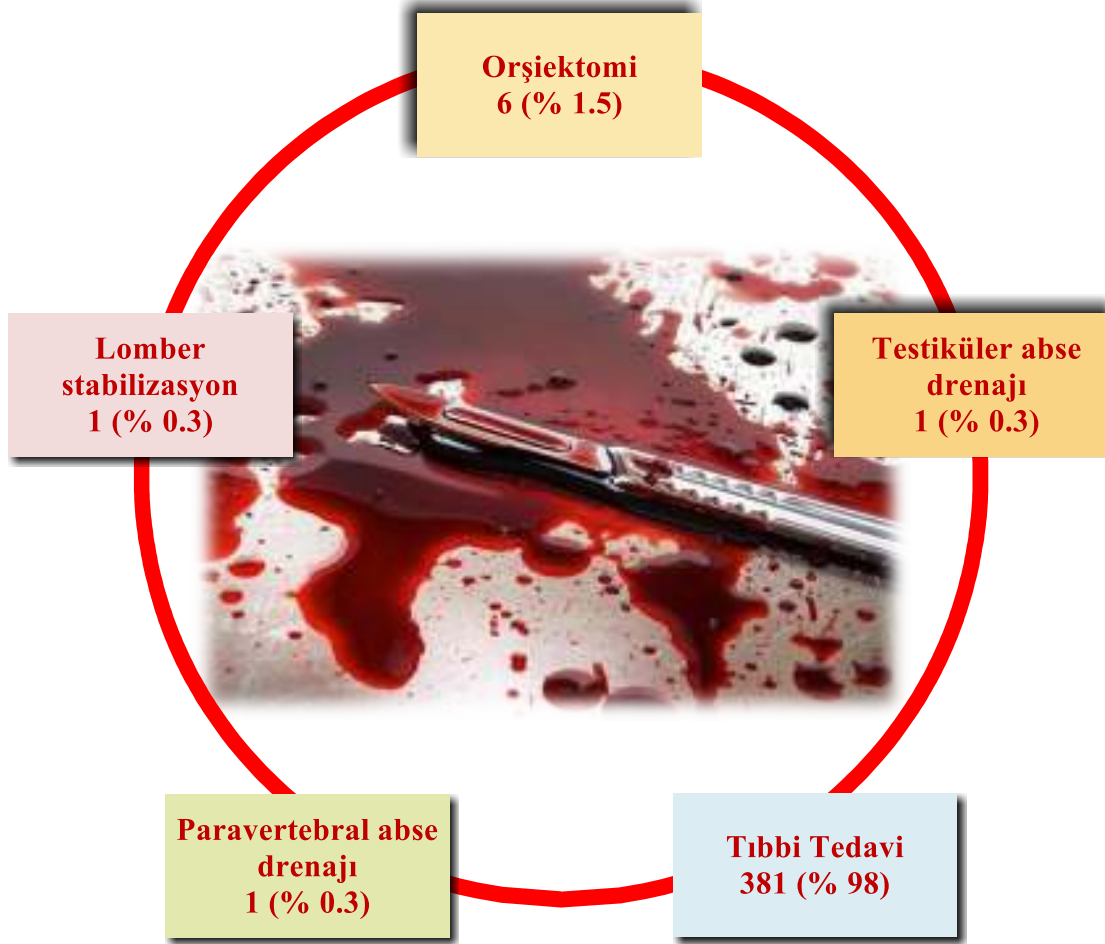
	Group 1 (n = 279)	Group 2 (n = 111)	p-Value
Mean treatment duration $\pm$ SD, days (range)	47.2 $\pm$ 11.7 (42–90)	63.0 $\pm$ 38.9 (42–240)	<0.0001
Mean LOS $\pm$ SD, days (range)	10.0 $\pm$ 5.7 (1–30)	13.2 $\pm$ 8.5 (1–60)	0.001
Failure, n (%)	4 (1.4)	2 (1.8)	1.0
Relapse, n (%)	3 (1.1)	2 (1.8)	0.626
Surgical intervention (needed), n (%)	6 (2.2) <sup>a</sup>	2 (1.8) <sup>b</sup>	1.0

LOS, length of hospital stay.

<sup>a</sup>All genital surgery.

<sup>b</sup>Spinal surgery, 1; orchiectomy, 1.

*Erdem H, Elaldi N, Ak O, Genitourinary brucellosis: results of a multicentric study. Clin Microbiol Infect. 2014 May 16. doi: 10.1111/1469-0691.12680.*





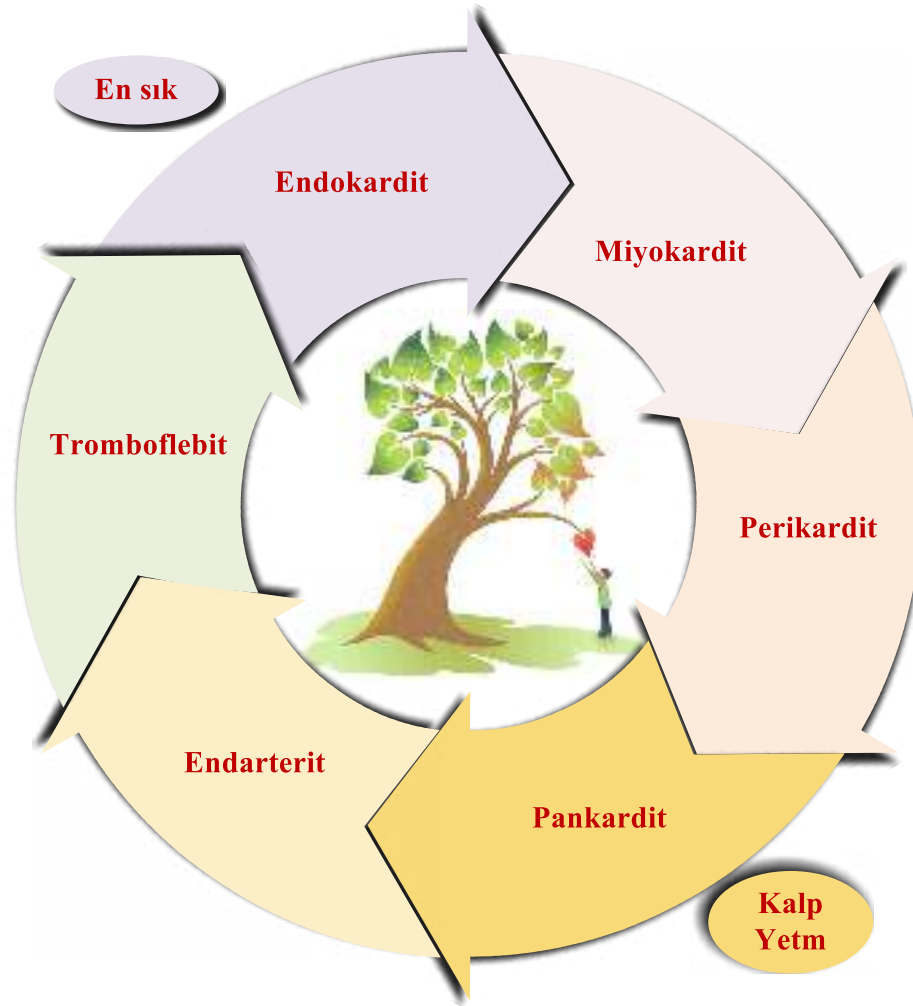
*Artrit veya artraljiye eşlik eden skrotal ağrı ve şişlik brusellozu akla getirmeli*

# Kardiyovasküler Bruselloz



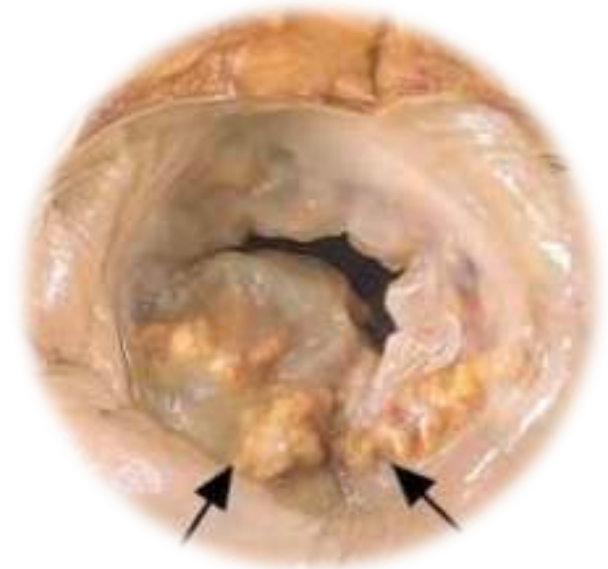


# Kalp-Damar Sistemi



# Endokardit

- ♣ Tüm bruselloz vakalarının % 1' i
- ♣ Aort, Mitral kapaklar
- ♣ Altta yatan kalp hastalıkları, % 60



*Koruk ST, Erdem H, Koruk I, et al. Management of Brucella endocarditis: results of the Gulhane study. Int J Antimicrob Agents 2012; 40(2): 145-50.*

# Endokardit, Mortalite

- ♣ Tedaviye rağmen % 13
  - ♣ Perikardiyal efüzyon ↗
  - ♣ KKY ↗



*Koruk ST, Erdem H, Koruk I, et al. Management of Brucella endocarditis: results of the Gulhane study. Int J Antimicrob Agents 2012; 40(2): 145-50.*

# Endokarditte Tedavi

n=53  
19 merkez

**Table 4**  
Antibiotic combinations used in 53 *Brucella* endocarditis patients.

Group	Antibiotic combinations	n	%
Group 1	RIF + DOX + CFX	19	35.8
	RIF + DOX + SXT + CFX	1	1.9
Group 2	RIF + DOX + STR	9	17.0
	RIF + DOX + GEN	9	17.0
	RIF + DOX + STR + CIP	1	1.9
Group 3	RIF + DOX + SXT	9	17.0
	RIF + DOX	2	3.8
	DOX + SXT + CIP	1	1.9
Group 4	CFX + STR + RIF	2	3.8
Total		53	100.0

RIF, rifampicin; DOX, doxycycline; CFX, ceftriaxone; SXT, trimethoprim/sulfamethoxazole; STR, streptomycin; GEN, gentamicin; CIP, ciprofloxacin.

*Koruk ST, Erdem H, Koruk I, et al. Management of Brucella endocarditis: results of the Gulhane study. Int J Antimicrob Agents 2012; 40(2): 145-50.*

# Endokarditte Tedavi-2

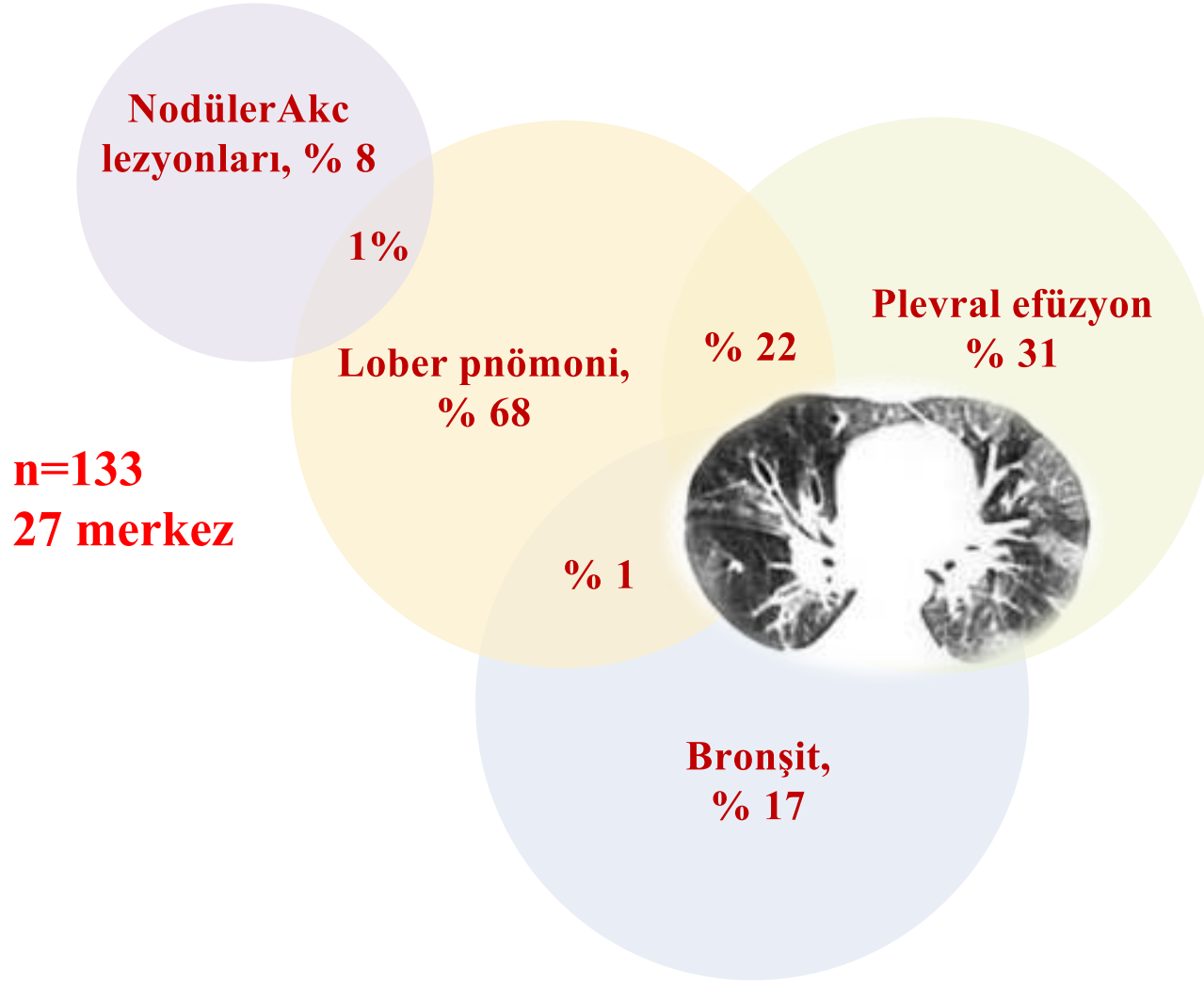
- ♣ Ortalama antibiyotik kullanım süresi
  - ♣  $151.5 \pm 61.7$  gün
- ♣ % 40, cerrahi girişim
  - ♣ Ab süresini etkilemiyor
- ♣ Cerrahi sonrası tedavi
  - ♣  $30.5 \pm 19.9$  gün
- ♣ Öncül veri, AG kollarda mortalite düşük



# Akciğer Brusellozu



# Akciğer Brusellozu



*Erdem H, Inan A, Elaldi N, and the study group. Respiratory system involvement in brucellosis: The results of the Kardelen study. Chest 2014;145(1):87-94.*



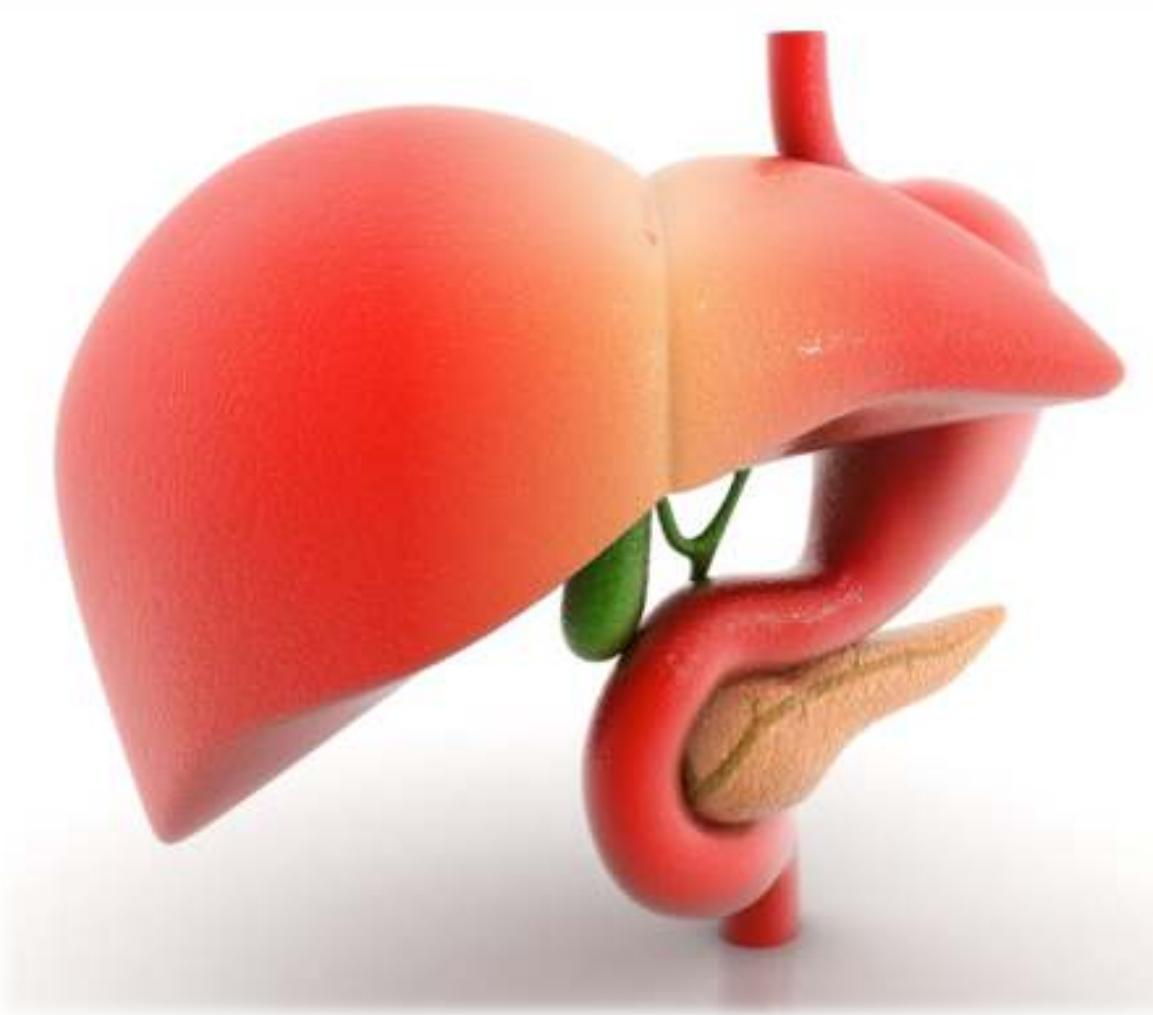
# Akciğer Brusellozu-2

- ♣ Diğer TGP' lere benzer
- ♣ % 10, YBU gereksinimi
  - ♣ Ort. 4 gün
  - ♣ Standart tedaviye yanıt tam...
- ♣ Selim bir tablo



*Erdem H, Inan A, Elaldi N, and the study group. Respiratory system involvement in brucellosis: The results of the Kardelen study. Chest 2014;145(1):87-94.*

# Karacięer Tutulumu



# Bruselloz ve Karaciğer

- ♣ Hafif-orta-siddetli KC enzim artışı
  - ♣ Histopatoloji, reaktif hepatit
- ♣ Kolestaz
- ♣ Granülomatoz görünüm, % 5
  - ♣ Tuberküloz?
- ♣ Tedavi edilmezse
  - ♣ Siroz, dekompanseasyon

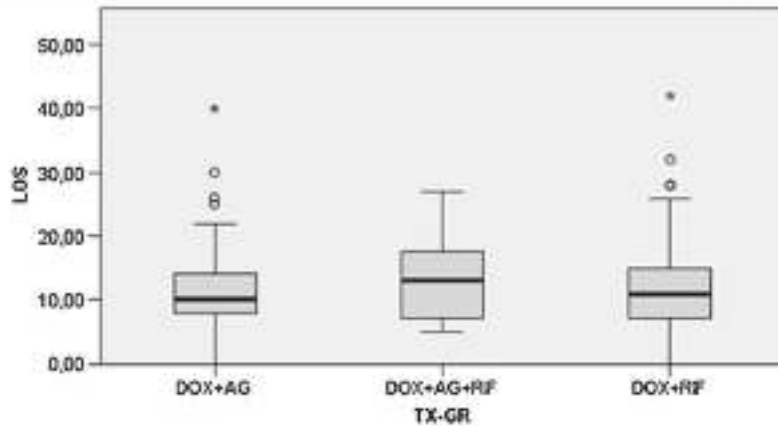


*Ozturk-Engin D, Erdem H, Gencer S, et al. Liver involvement in patients with brucellosis: The results of Marmara study. European Journal of Clinical Microbiology & Infectious Diseases. 2014;33(7):1253-62.*

# Hepatit ve Tedavi

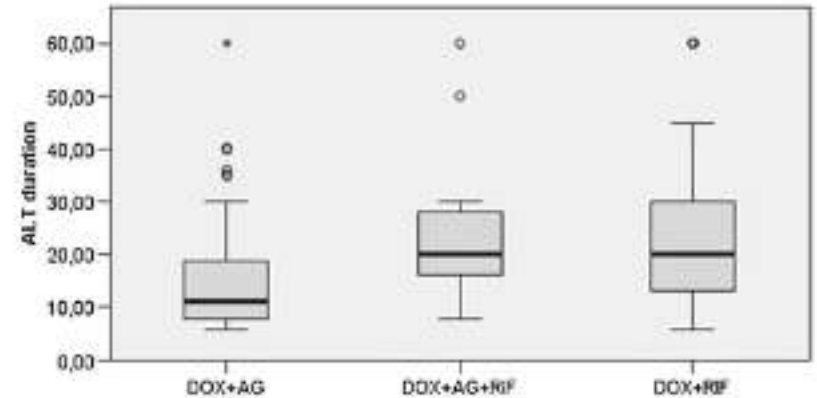
n=325

30 merkez



DOX+AG: Doxycycline plus an aminoglycoside, DOX+RIF: Doxycycline plus rifampicin, DOX+AG+RIF: Doxycycline plus an aminoglycoside plus rifampicin

Fig. 1 The comparison of three treatment arms according to length of hospital stays ( $p=0.522$ )



DOX+AG: Doxycycline plus an aminoglycoside, DOX+RIF: Doxycycline plus rifampicin, DOX+RIF+AG: Doxycycline plus rifampicin and an aminoglycoside

Fig. 2 The comparison of three treatment arms according to the duration of ALT normalization ( $p<0.001$ )

Ozturk-Engin D, Erdem H, Gencer S, et al. Liver involvement in patients with brucellosis: The results of Marmara study. *European Journal of Clinical Microbiology & Infectious Diseases*. 2014;33(7):1253-62.



*Mortalite: Endokardit*

*Morbidite: Nörobruselloz*

*Teşekkürler...*



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