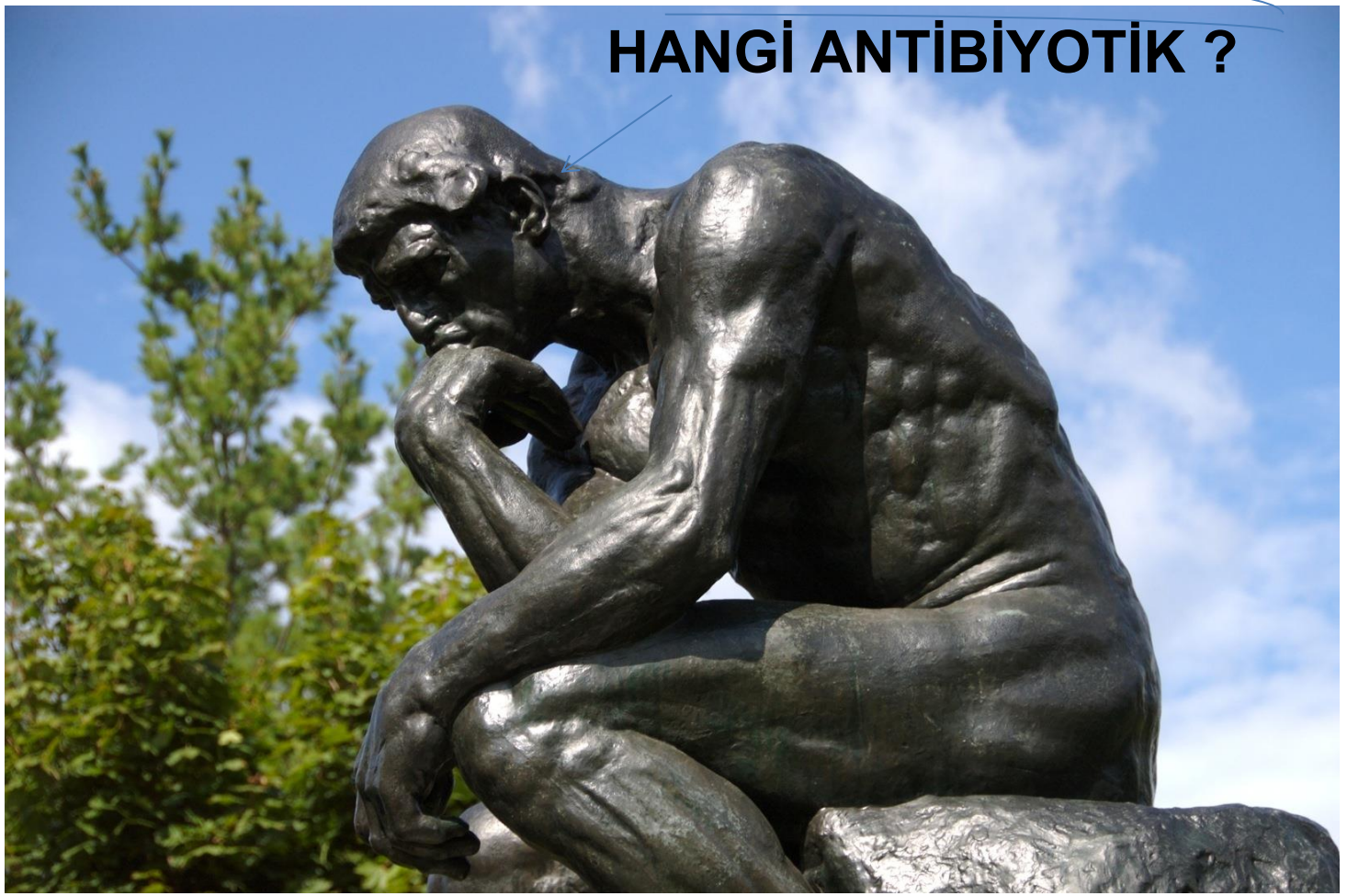
Laboratuvardan Kliniğe Dirençli Olgularla Mücadele
-Olgu-

Dr Gökhan AYGÜN
CTF Tıbbi Mikrobiyoloji AD

Dirençli Olgularla Mücadele



Olgu

80 yaş, erkek

05.05.2016

Acil servise ateş, hipotansiyon, taşikardi, bilinç değişikliği bulgularıyla gelip hızla YBÜ'ne transfer edildi. Ürosepsis ?

Tienam + Vankomisin

SVK, entübasyon, NA infüzyonu ..septik şok!

HK, idrar kültürü

Olgu

- Yaklaşık 5 yıldır kronik renal yetersizlik
- Haftada ki kez hemodiyalize giriyor
- Son bir haftadır sırt ağrısı nedeniyle birkaç kez hastane başvurusu olduğu öğrenildi.
- Yapılan incelemelerde üriner infeksiyon tanısıyla ciprofloksasin verildiği öğreniliyor
- TİT: HS'da 10-15 lökosit, 20 eritrosit
- İdrar kültürü: yapılmamış

Olgu

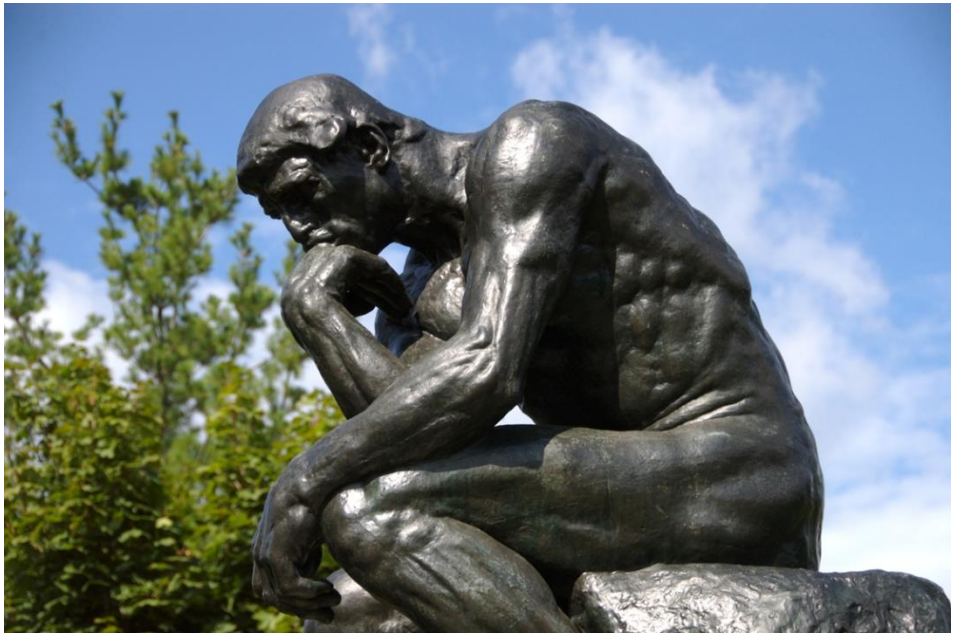
- Fizik muayenede
- YBÜ'nde görüldü: Entübe, SVK, ÜK takılmış
- Muayenede AC dinleme bulgularında solunum seslerinde kabalaşma, AC grafisinde bilateral efüzyon (+), atellektazi? Pnömoni?
- KVS: Kateter yerinda özellik yok, sistolik üfürüm (+) ,TTE: özellik yok (TÖE için stabilleşmesi planlanmış).
- Ateş: 39.2 C

Olgu

- Lökosit: 22.000/mm3 (% 80 nötrofil)
- Hct: 30, Trombosit: 120.000
- CRP: 430 (0-5) , prokalsitonin: 15
- Üre:120, kreatinin: 5 (HD uygulanıyor)
- İdrar: HS'da 10 nötrofil, 25-30 eritrosit (sondalı hasta)

Olgu

- HK: Gram (+) küme koklar!
- ETA: HS da25 lökosit, az sayıda Gram-pozitif kok, Gram-negatif çomak
- İdrar kültürü üreme yok !



Olgu

- Ampirik başlanan imipenem+ vankomisin tedavisine devam edildi
- **Kültür sonuçları:**

HK: MRSA, vankomisin MİK: 1.5 mg/L

ETA: MRSA (10 000 cfu/mL),

K.pneumonie (ESBL+) (10.000cfu/mL)

İdrar Kültürü: Üreme yok

MRSA : TEC, LZD, Daptomisin duyarlı

EUCAST

Cefaclor[2]	Note[1]	Note[1]		Note[A]	Note[A]
Cefadroxil	Note[1]	Note[1]		Note[A]	Note[A]
Cefalexin	Note[1]	Note[1]		Note[A]	Note[A]
Cefazolin	Note[1]	Note[1]		Note[A]	Note[A]
Cefepime	Note[1]	Note[1]		Note[A]	Note[A]
Cefixime	-	-		-	-
Cefotaxime	Note[1]	Note[1]		Note[A]	Note[A]
Cefoxitin (screen), *S. aureus*, *S. lugdunensis* and *S. saprophyticus*	Note[3]	Note[3]	30	22[A]	22[A]
Cefoxitin (screen), Coagulase-negative staphylococci other than *S. lugdunensis* and *S. saprophyticus*	Note[4]	Note[4]	30	25[A]	25[A]
Cefoxitin (screen), *S. pseudintermedius*	Note[4]	Note[4]	30	35[A]	35[A]
Cefpodoxime	Note[1]	Note[1]		Note[A]	Note[A]
Ceftaroline, *S. aureus*	1[5]	1[5]	5	20[B]	20[B]
Ceftazidime	-	-		-	-
Ceftibuten	-	-		-	-
Ceftobiprole, *S. aureus*	2[6]	2[6]	5	17[C]	17[C]

1/A. Susceptibility of staphylococci to cephalosporins is inferred
ceftibuten and ceftolozane-tazobactam, which do not have brea
Some methicillin-resistant *S. aureus* are susceptible to ceftarol
2. Breakpoints are based on high dose therapy (500 mg x 2).
3. *S. aureus* and *S. lugdunensis* with cefoxitin MIC values >4
methicillin resistant, mostly due to the presence of the *mecA* o
4. For staphylococci other than *S. aureus*, *S. lugdunensis* and
methicillin resistance than the disk diffusion test.
5/B. Methicillin-susceptible isolates can be reported susceptible
6/C. Methicillin-susceptible isolates can be reported susceptible

Glycopeptides and lipoglycopeptides[1]	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Dalbavancin[2]	0.125[3,4]	0.125[3]		Note[A]	Note[A]
Oritavancin, *S. aureus*[2]	0.125[3,4]	0.125[3]		Note[A]	Note[A]
Teicoplanin, *S. aureus*[2]	2	2		Note[A]	Note[A]
Teicoplanin, Coagulase-negative staphylococci[2]	4	4		Note[A]	Note[A]
Telavancin, MRSA[2]	0.125[3,5]	0.125[3]		Note[A]	Note[A]
Vancomycin, *S. aureus*[2]	2	2		Note[A]	Note[A]
Vancomycin, Coagulase-negative staphylococci[2]	4	4		Note[A]	Note[A]

VANKOMİSİN MİK: 2

Alternative Therapy to Vancomycin for MRSA

- Daptomycin
  - Concentration-dependent killing
  - Bactericidal
  - Once-daily administration
- Ceftaroline/Ceftobiprole
  - Bactericidal
  - 2-3-daily administrations
- Linezolid
  - Bacteriostatic
  - Twice-daily administration
- Telavancin
  - Concentration-dependent killing
  - Bactericidal
  - Once-daily administration
- Teicoplanin
  - Bactericidal
  - Once-daily administration
- Dalbavancin
  - Concentration-dependent killing
  - Bactericidal
  - 1st and 8th day (ABSSSI)
- Tedizolid
  - Bacteriostatic
  - Once-daily (ABSSSI)
- Oritavancin
  - Concentration-dependent killing
  - Bactericidal
  - Single-dose (ABSSSI)

Brauers J. et al. *Intern J Antimicrob Agents* 2007;29:322-25.
Rybak, J.M. et al. *Expert Opin*. 2013;14 (14): 1-14.

Ülkemizdeki seçenekler

Antibiyotik	Etki Mekanizması	Yan etkileri
Vankomisin	**Hücre duvarı sentezi inhibitörü, Yavaş bakterisidal**	**Nefrotoksik "Red man" Nötropeni Trombositopeni İlaç düzeylerinin takibi önerilir**
Daptomisin	**Membran depolarizasyonu, Hızlı bakterisidal**	**CPK artışı ve miyopati Periferik nöropati Nadiren: Rabdomiyoliz, eozinofilik pnömoni Haftalık CPK takibi**
Linezolid	**Protein sentezi, inhibitörü, Bakteriostatik**	**Trombositopeni Anemi Periferik ve optik nöropati Laktik asidoz Serotonin sendromu (MAOI)**

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus Aureus* Infections in Adults and Children

Catherine Liu,[1] Arnold Bayer,[3,5] Sara E. Cosgrove,[6] Robert S. Daum,[7] Scott K. Fridkin,[8] Rachel J. Gorwitz,[9] Sheldon L. Kaplan,[10] Adolf W. Karchmer,[11] Donald P. Levine,[12] Barbara E. Murray,[14] Michael J. Rybak,[12,13] David A. Talan,[4,5] and Henry F. Chambers[1,2]

Bacteremia and infective endocarditis		
Bacteremia	Vancomycin	15–20 mg/kg/dose IV every 8–12 h
	Daptomycin	6 mg/kg/dose IV QD
Infective endocarditis, native valve	Same as for bacteremia	
Infective endocarditis, prosthetic valve	Vancomycin and gentamicin and rifampin	15–20 mg/kg/dose IV every 8–12 h
		1 mg/kg/dose IV every 8 h
		300 mg PO/IV every 8 h

Komplike olmayan MRSA bakteriyemisi

- Protez olmaması
- 2-4 gün içinde hemokültür üremesinin olmadığının gösterilmesi
- 72 saatte klinik düzelme
- Metastatik infeksiyon olmaması

Tüm olgularda EKO (TÖE>TTE)

Tüm olgularda 2-4 gün içinde kontrol HK

Endokarditli tüm olgularda cerrahi değerlendirme!

MRSA bakteriyemi

ÖNERİLMEYENLER:

- Rifampisin eklenmesi

(bakteriyemide uzama?, ilaç etkileşimi, hepatotoksisite!)

- Gentamisin eklenmesi

(Nefrotoksisite artışı!)

- Sürekli vankomisin infüzyonu !
- Primer seçenek olarak: linezolid

MRSA bakteriyemi

ÖNERİLENLER:

- Vankomisin konsantrasyonunu izlemek
  * Ciddi olgularda
  * Obezlerde
  * Renal fonksiyon bozukluğu olanlarda
  * Sıvı dağılım dengesizliğinde
- Yükleme dozu 25 mg/kg (riskli, yavaş, +antihistaminik)
- Daptomisin 8-10 mg/kg dozlarında

Komplike olgu

- CLSI sonuçlarıyla duyarlı ise (MIK=2 ve altı) tedaviye devam edilebilir !
- ODAK KONTROLÜ !!!
- hVISA

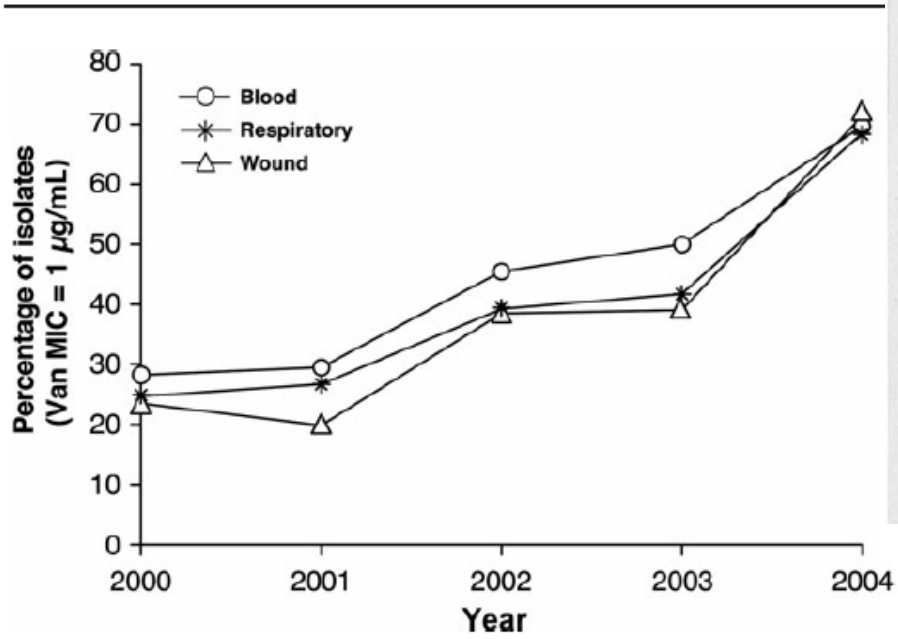
(E-test, teikoplanin 5 mg/L tarama agar)

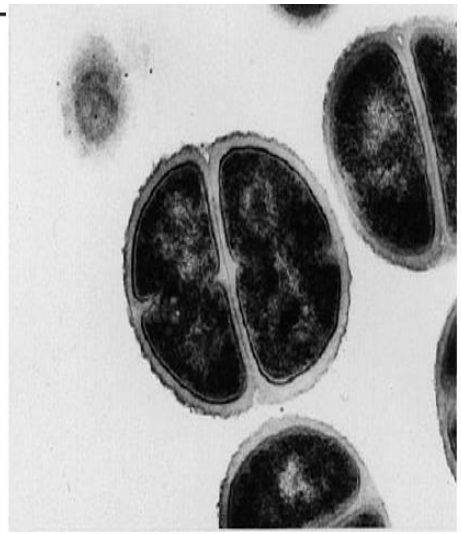
Yanıtsız, hVISA....Daptomisin (yüksek doz)

MRSA van «MIC creep»

Methicillin-Resistant *Staphylococcus aureus*: An Evolving Pathogen

Martin E. Stryjewski[1] and G. Ralph Corey[2,3]





B

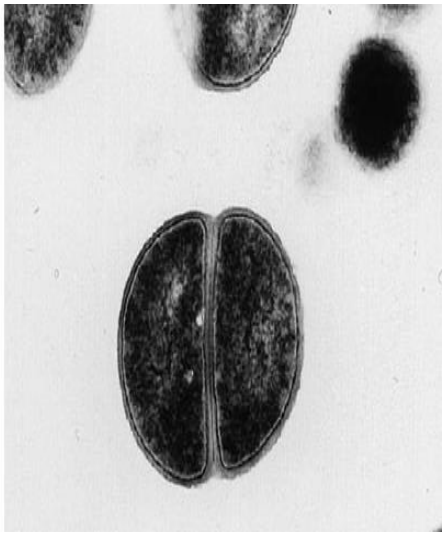


Figure 1. Percentage of *Staphylococcus aureus* isolates with vancomycin (Van) minimal inhibitory concentrations (MICs) of 1 μg/mL from blood, wound, and respiratory specimens from 2000 to 2004. Reproduced from:

MRSA «MIC creep»

- MRSA VAN MIK> 1mg/L rutin dozda uygulandığında etkin farmakodinamik parametre olan AUC/MİK seviyesinin (>400) oldukça altında kalmakta
- Doz artışı (20 mg/kg) ise MİK 2 mg/L olduğunda beklenen etkiden uzak kalmakta ve artan oranlarda nefrotoksisite riski oluşturmakta
- Artan MİK değerleri bakteri hücre duvar yapısı, transkripsiyonel değişikliklerle ilgili olarak virulans üzerine etkili ?!
- Mortalite artıyor!?

- **Falcone M, Russo A, Venditti M. J İnfect Chemo. 2015;21:330-339.**
- **Lodise TP, Graves J, Evans A, et al. AAC. 2008;52:3315-3320.**
- **van Hal SJ, Lodise TP, Paterson DL. Clin Infect Dis 2012; 54:755-771.**

Original Investigation

Association Between Vancomycin Minimum Inhibitory Concentration and Mortality Among Patients With *Staphylococcus aureus* Bloodstream Infections

A Systematic Review and Meta-analysis

Andre C. Kalil, MD, MPH; Trevor C. Van Schooneveld, MD; Paul D. Fey, PhD; Mark E. Rupp, MD

CONCLUSIONS AND RELEVANCE In this meta-analysis of SAB episodes, there were no statistically significant differences in the risk of death when comparing patients with *S aureus* exhibiting high-vancomycin MIC (≥1.5 mg/L) to those with low-vancomycin MIC (<1.5 mg/L), although the findings cannot definitely exclude an increased mortality risk. These findings should be considered when interpreting vancomycin susceptibility and in determining whether alternative antistaphylococcal agents are necessary for patients with SAB with elevated but susceptible vancomycin MIC values.

JAMA. 2014;312(15):1552-1564. doi:10.1001/jama.2014.6364
Published online October 9, 2014.

Olgu

- Yatışında 72.saat
- GD kötü, ateşleri azalarak sürüyor.
- Lökosit 17.400, CRP: 270, Prokalsitonin:8
- HK tekrarı
- SVK çıkarılıp kültüre gönderiliyor

Olgu

- HK: MRSA: Van MİK : 1.5 mg/L
  Daptomisin MİK : 0.25

  SVK ucu :üreme yok

  Daptomisin 6 mg/kg başlandı , İMP devam ediyor

  Kardiyoloji ile TÖE yeniden tartışıldı ve TÖE uygulandı

Olgu

- TÖE : Mitral kapakta 1x0.5 cm çapında vejetasyon.
- KDC ile konsültasyon: Bu klinik tabloda operasyon uygun değil
- HK tekrarı (5. gün) üreme yok
- Tedaviye devam !(daptomisin+ İmipenem)

MRSA Bacteremia: IDSA Guidelines

Antibiotic Options for Adults with MRSA Bacteremia or Native-Valve Infective Endocarditis

Treatment	Adult Dose	Comments
Vancomycin	15–20 mg/kg/dose IV every 8-12 hours	The addition of gentamicin or rifampin to vancomycin is not recommended
Daptomycin	6 mg/kg/dose IV daily	**Some experts recommend higher dosages of 8-10 mg/kg/d IV daily**

Management of Persistent MRSA Bacteremia and Vancomycin Failure

Treatment	Adult Dose
If daptomycin-susceptible	
High-dose daptomycin + another agent • Gentamicin • Rifampin • Linezolid • Trimethoprim-sulfamethoxazole • Beta-lactam antibiotic	10 mg/kg/d • 1 mg/kg IV every 8 hours (5 mg/kg daily alternative) • 600 mg PO/IV once daily or 300-450 mg PO/IV twice daily • 600 mg PO/IV twice daily • 5 mg/kg IV twice daily • dose not given

Liu C, et al. *Clin Infect Dis.* 2011;52(3):e18-e55.

J Infect Chemother 21 (2015) 330–339

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Review article

Optimizing antibiotic therapy of bacteremia and endocarditis due to staphylococci and enterococci: New insights and evidence from the literature

Marco Falcone*, Alessandro Russo, Mario Venditti

First choices of antibiotic therapy for MRSA bacteremia.

	MRSA with MIC < 1 μg/ml to glycopeptides	MRSA with MIC > 1 but <2 μg/ml to glycopeptides
Primary bacteremia	Vancomycin	Daptomycin
Secondary bacteremia		
1. SSTI	1. Daptomycin	1. Daptomycin
2. Pneumonia	2. Vancomycin or linezolid	2. Linezolid or ceftaroline
3. Bone	3. Daptomycin or teicoplanin or vancomycin	3. Daptomycin
4. Abdominal	4. Tigecycline	4. Tigecycline
Catheter-related	Daptomycin + rifampin	Daptomycin + rifampin

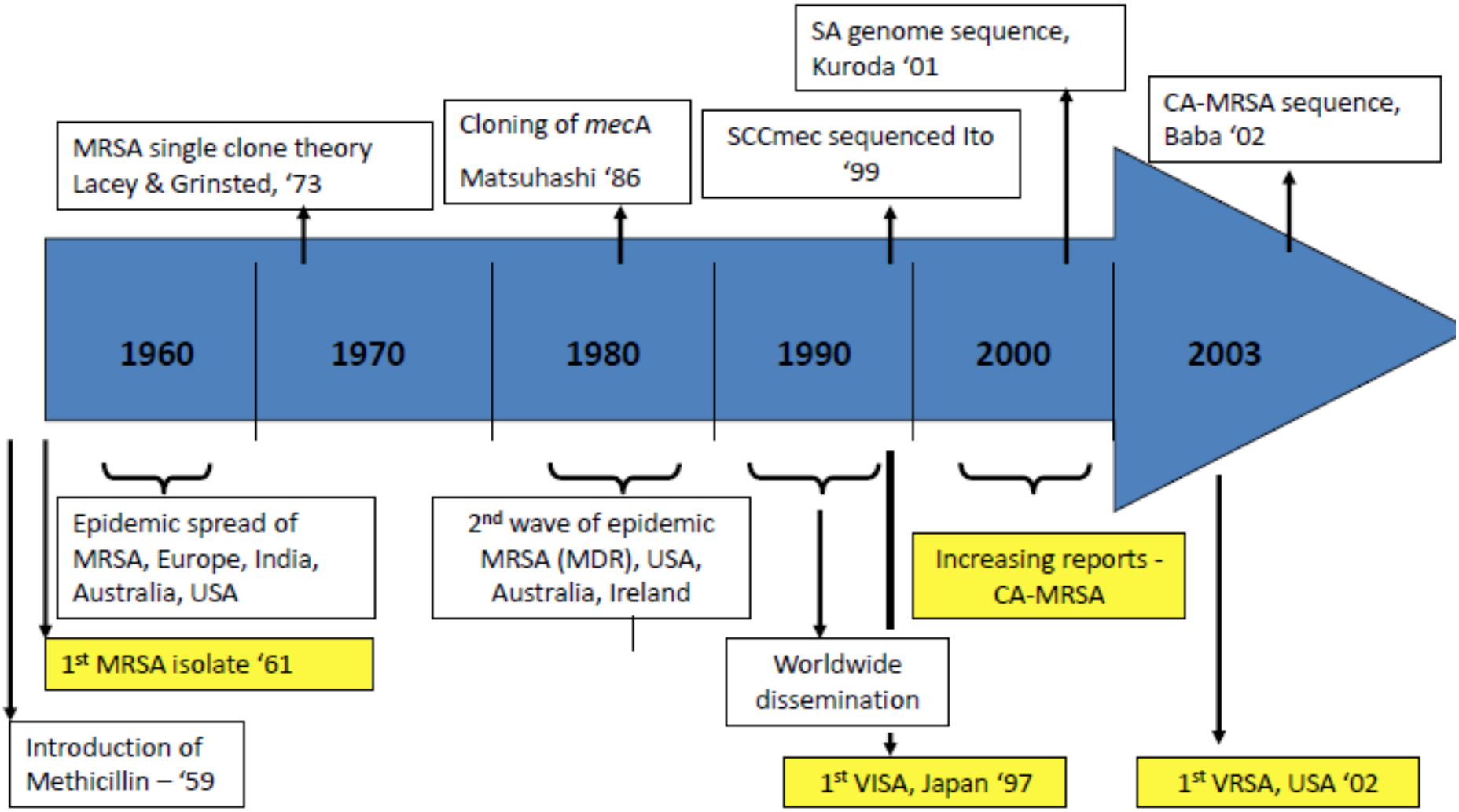
Legend. MRSA: methicillin-resistant *Staphylococcus aureus*; MIC: minimum inhibitory concentration; SSTI: skin soft tissue infection.

European Heart Journal (2015) **36**, 3075–3123
doi:10.1093/eurheartj/ehv319

2015 ESC Guidelines for the management of infective endocarditis

Penicillin-allergic patients[h] or methicillin-resistant staphylococci						
Vancomycin[b] **	30–60 mg/kg/day i.v. in 2–3 doses	4–6	I	B	6,8, 135, 136	**Cephalosporins** (cefazolin 6 g/day or cefotaxime 6 g/day i.v. in 3 doses) are recommended for penicillin-allergic patients with non-anaphylactic reactions with methicillin-susceptible endocarditis
	Paediatric doses:[g] 40 mg/kg/day i.v. in 2–3 equally divided doses					
Alternative therapy:** Daptomycin[c,d]	10 mg/kg/day i.v. once daily	4–6	IIa	C		**Daptomycin** is superior to vancomycin for MSSA and MRSA bacteraemia with vancomycin MIC > 1 mg/L
	Paediatric doses:[g] 10 mg/kg/day i.v. once daily					
Alternative therapy* Cotrimoxazole[a]	Sulfamethoxazole 4800 mg/day and Trimethoprim 960 mg/day (i.v. in 4–6 doses)	1 i.v. + 5 oral intake	IIb	C		*for *Stahylococcus aureus*
with						
Clindamycin	1800mg/day IV in 3 doses	1	IIb	C		

S. aureus - antibiyotik direnç öyküsü



Direnç sorunu....

SUPPLEMENT ARTICLE

Methicillin-Resistant *Staphylococcus aureus*: An Evolving Pathogen

Martin E. Stryjewski[1] and G. Ralph Corey[2,3]

Linezolid[a]	*cfr*	Ribosomal methyltransferase	Methylation of the 23S rRNA that interferes with ribosomal binding	Plasmid
Daptomycin[b]	*mprF*	Lysylphosphatidylglycerol synthetase (LPG) synthetase	Increasing: synthesis of total LPG, outer LPG translocation and positive net charges on cell membrane	Chromosomal

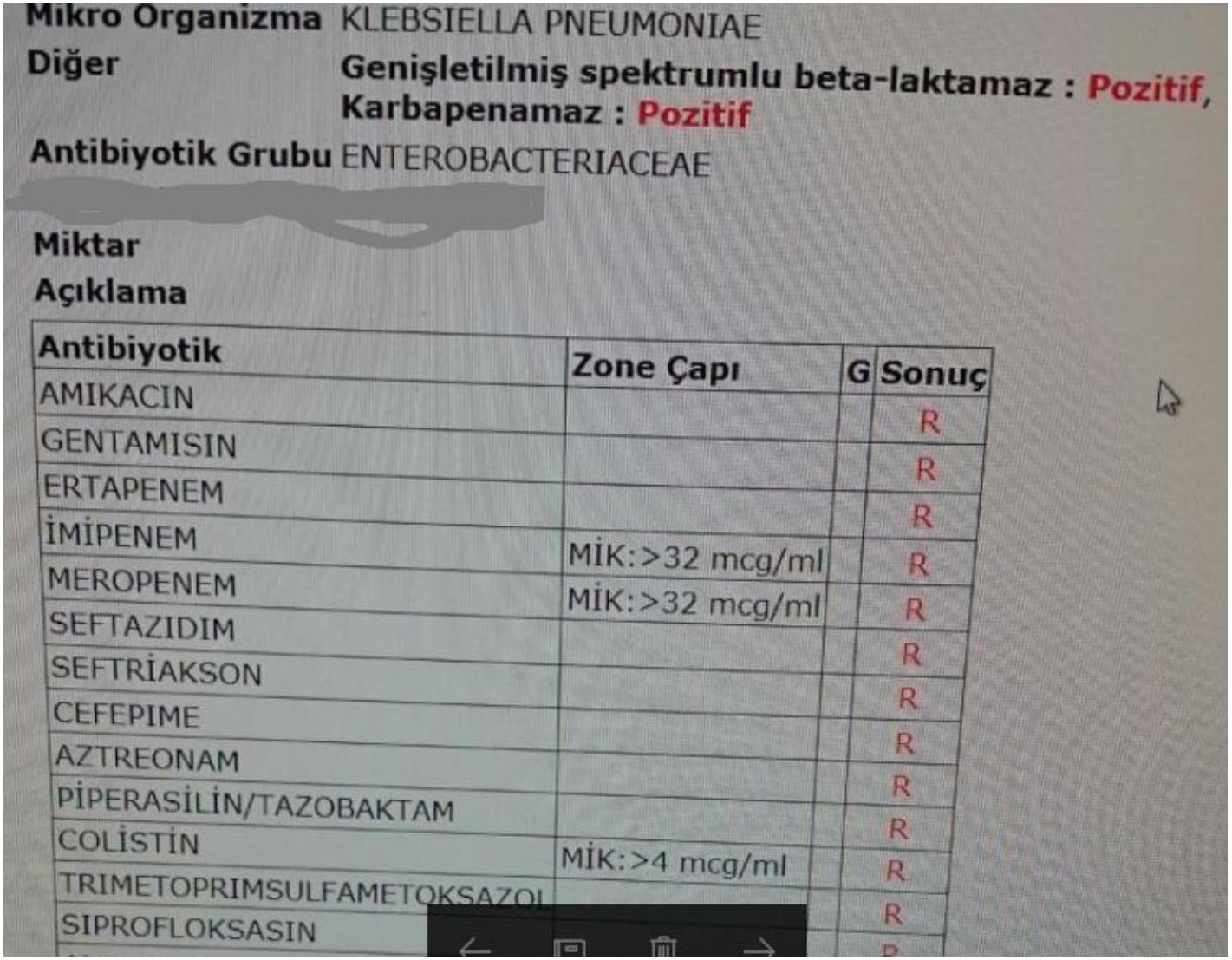
Olgu

- Hastada GD kötü stabil.
- Entübe, MV, SVK, üriner kateter.
- Antibiyotik tedavisi (Daptomisin+İMP)6. gün
- Ateşleri olmuyor. NA infüzyonu kesildi.
- Lökosit 15.000, CRP 210, prokalsitonin 3
- Aniden klinik tablo bozulan hastada hipotansiyon, ateş, solunum parametrelerinde bozulma ve AC grafisinde infiltrasyon.

Olgu

- ETA, HK gönderildi.
- ETA Gram: Bol lökosit, Gram-negatif çomak
- İmipenem kesilerek yerine Kolistin+ Sefaperazon-Sulbaktam başlandı.
- ETA ve HK: Klebsiella pneumoniae üredi

Olgu antibiyogram



Mikro Organizma KLEBSIELLA PNEUMONIAE

Diğer **Genişletilmiş spektrumlu beta-laktamaz : Pozitif, Karbapenamaz : Pozitif**

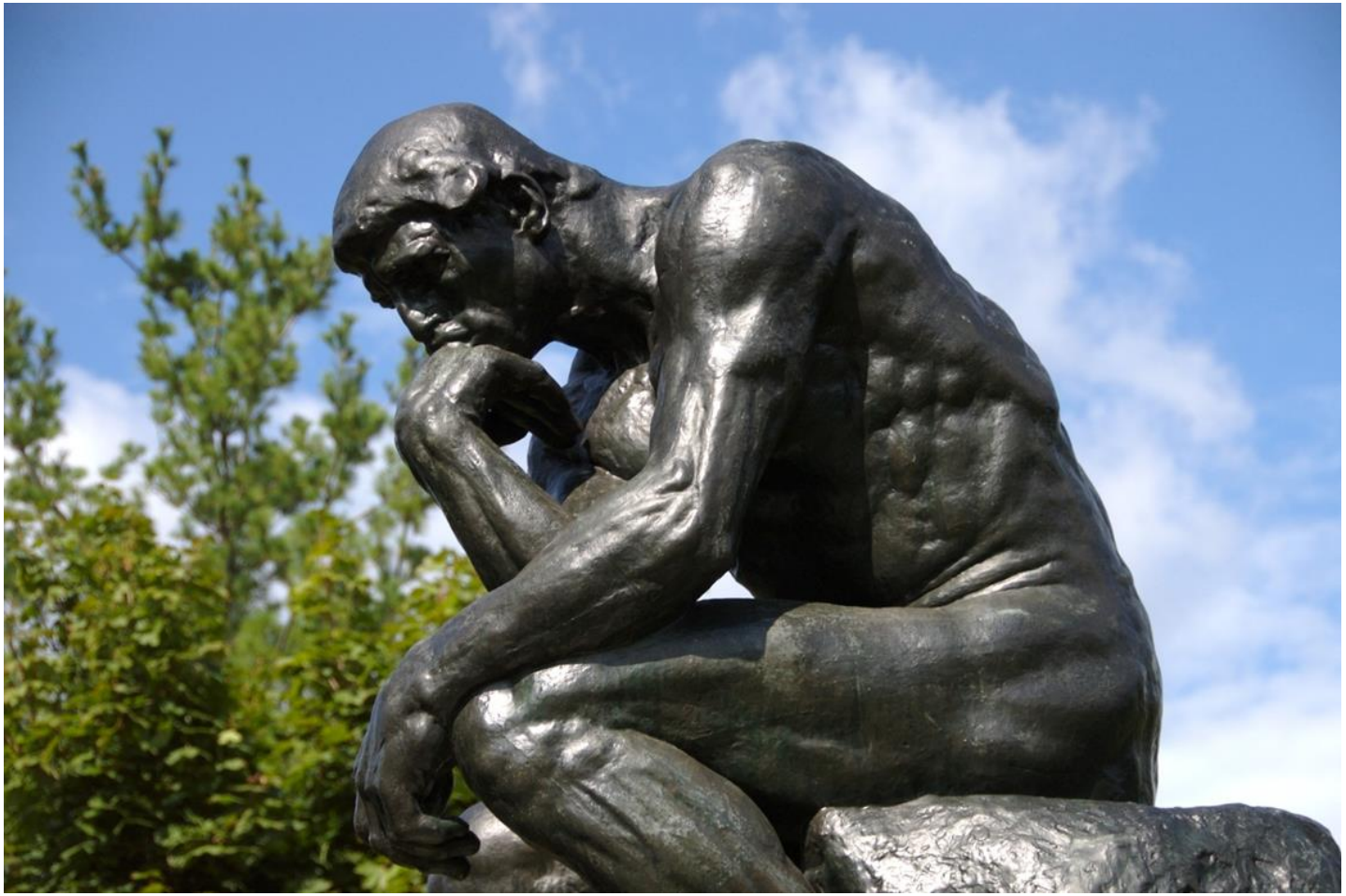
Antibiyotik Grubu ENTEROBACTERIACEAE

Miktar

Açıklama

Antibiyotik	Zone Çapı	G	Sonuç
AMIKACIN			R
GENTAMISIN			R
ERTAPENEM			R
İMİPENEM	MİK:>32 mcg/ml		R
MEROPENEM	MİK:>32 mcg/ml		R
SEFTAZIDIM			R
SEFTRİAKSON			R
CEFEPIME			R
AZTREONAM			R
PİPERASİLİN/TAZOBAKTAM			R
COLİSTİN	MİK:>4 mcg/ml		R
TRIMETOPRIMSULFAMETOKSAZOL			R
SIPROFLOKSASIN			R

Antibiyotik ???



Antibiyotik ???

Karbapenem dirençli enterikler ?

- Kolistin + karbapenem (YD, devamlı inf)
- (+) Tigesiklin
- Fosfomisin İV
- Karbapenem+karbapenem kombinasyonu
- ceftolozane/tazobactam
  ceftazidime/avibactam
- .....
- Disk difüzyonda zonu olanlarla kombinasyon!

Karbapenem+kolistin dirençli ?

AMERICAN SOCIETY FOR MICROBIOLOGY | mBio®

OBSERVATION

Colistin- and Carbapenem-Resistant *Escherichia coli* Harboring *mcr-1* and bla_{NDM-5}, Causing a Complicated Urinary Tract Infection in a Patient from the United States

José R. Mediavilla,[a] Amee Patrawalla,[b] Liang Chen,[a] Kalyan D. Chavda,[a] Barun Mathema,[c] Christopher Vinnard,[a] Lisa L. Dever,[d]

ABSTRACT Colistin is increasingly used as an antibiotic of last resort for the treatment of carbapenem-resistant Gram-negative infections. The plasmid-borne colistin resistance gene *mcr-1* was initially identified in animal and clinical samples from China and subsequently reported worldwide, including in the United States. Of particular concern is the spread of *mcr-1* into carbapenem-resistant bacteria, thereby creating strains that approach pan-resistance. While several reports of *mcr-1* have involved carbapenem-resistant strains, no such isolates have been described in the United States. Here, we report the isolation and identification of an *Escherichia coli* strain harboring both *mcr-1* and carbapenemase gene bla_{NDM-5} from a urine sample in a patient without recent travel outside the United States. The isolate exhibited resistance to both colistin and carbapenems, but was susceptible to amikacin, aztreonam, gentamicin, nitrofurantoin, tigecycline, and trimethoprim-sulfamethoxazole. The *mcr-1*- and bla_{NDM-5}-harboring plasmids were completely sequenced and shown to be highly similar to plasmids previously reported from China. The strain in this report was first isolated in August 2014, highlighting an earlier presence of *mcr-1* within the United States than previously recognized.

IMPORTANCE Colistin has become the last line of defense for the treatment of infections caused by Gram-negative bacteria resistant to multiple classes of antibiotics, in particular carbapenem-resistant *Enterobacteriaceae* (CRE). Resistance to colistin, encoded by the plasmid-borne gene *mcr-1*, was first identified in animal and clinical samples from China in November 2015 and has subsequently been reported from numerous other countries. In April 2016, *mcr-1* was identified in a carbapenem-susceptible *Escherichia coli* strain from a clinical sample in the United States, followed by a second report from a carbapenem-susceptible *E. coli* strain originally isolated in May 2015. We report the isolation and identification of an *E. coli* strain harboring both colistin (*mcr-1*) and carbapenem (bla_{NDM-5}) resistance genes, originally isolated in August 2014 from urine of a patient with recurrent urinary tract infections. To our knowledge, this is the first report in the United States of a clinical bacterial isolate with both colistin and carbapenem resistance, highlighting the importance of active surveillance efforts for colistin- and carbapenem-resistant organisms.

International Journal of Infectious Diseases 33 (2015) 132–134

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Case Report

Therapeutic strategy for pandrug-resistant *Klebsiella pneumoniae* severe infections: short-course treatment with colistin increases the in vivo and in vitro activity of double carbapenem regimen

Alessandra Oliva [a], Maria T. Mascellino [a], Alessia Cipolla [a], Alessandra D'Abramo [a], Annalisa De Rosa [a], Stefano Savinelli [a], Maria Rosa Ciardi [a], Claudio M. Mastroianni [a,b,*], Vincenzo Vullo [a]

ml. Thus, rifampicin was stopped and intravenous therapy with ertapenem 1 g/day and meropenem 2 g every 8 h was started. The following day, intravenous colistin was added (loading dose 6 000 000 IU, then 4 500 000 IU every 12 h). After 48 h of therapy, the patient remained febrile and blood cultures grew PDR *K. pneumoniae*. After 96 h she became afebrile. Laboratory analyses showed a reduction of the ESR and CRP. Blood and urine cultures did not grow any organism. After 7 days of therapy, colistin was stopped because of visual hallucinations, whereas the double carbapenem regimen was continued for an additional 14 days, in the absence of adverse events. The patient was discharged in good condition; she was afebrile with an ESR of 31 mm/h and CRP of 0.9 mg/dl. She was then transferred to the Orthopaedic Department for a new hip prosthesis replacement.

Sorular?

- Çiftli karbapenem+ kolistin
- Dışarıdan ilaç (fosfomisin, yeni betalaktamaz kombnasyonları)
- Ampirik tedaviye devam ederdim (COL+SCF)
- Antibiyotikleri keserdim!

Son dönem hastalara antibiyotik!

Clin Infect Dis. 2001 Nov 15;33(10):1697-705. Epub 2001 Oct 5.

Ethical issues relating to the use of antimicrobial therapy in older adults.

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Abstract

This article aims to review the literature relating to the ethics of antibiotic prescription decisions in older adults and to offer some suggestions as to how one might approach these difficult problems. According to many studies, most patients and their family members wish to receive antibiotics even when they are terminally ill or suffering from advanced dementia. Health care professionals are also frequently reluctant to deny the use of antibiotics in such situations. We suggest that the difficult decisions regarding whether one should withhold treatment can be based on consideration of the ethical principles of autonomy, beneficence, nonmaleficence, and justice. From the public health point of view, one should also take into account the need to avoid the emergence of antimicrobial resistance, keeping in mind the balance between the benefit to the specific patient and the cost to future patients. Infectious diseases consultants should actively participate in these ethical dilemmas.

TEDAVİ DEĞİL; KORUMA ÖNLEMLERİ ÖNCELİĞİMİZ OLMALI