Mevcut Tedavi Algoritmaları Güncel Epidemiyolojiyi Karşılıyor mu?

Prof. Dr. Tuba Turunç

SBÜ Adana Şehir Eğitim ve Araştırma Hastanesi

İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji ABD

İmmünsüprese Olguda Antimikrobiyal Direnç Gerçek Yaşam Verisi….

- Atinalı 26 yaşındaki eczacı Areti, ALL için kemoterapi gördükten sonra, antibiyotik dirençli Klebsiella bakterisinin neden olduğu ciddi bir infeksiyonla karşı karşıya kaldı

- Kanser tedavisi durduruldu ve hayatı riske girdi

Ufukta Güzel Şeyler Var mı?

- İngiltere'de Longitude Ödülü, İsveç'te bir antimikrobiyal direnç testini geliştiren ekibe verildi.
- Testin mucitlerinden Türk bilim insanı Özden Baltekin de ödülü kazanan ekipte.
- Test, idrar yolu infeksiyonlarında, etken bakteriyi tespit ediyor,
- Bakteriye karşı uygulanması gereken doğru antibiyotik tedavisini belirliyor.
- Mevcut geleneksel yöntemlerle sonuçlar yaklaşık 3 günde çıkarken, bu testle 45 dakikada sonuç alınıyor.

Sunum Planı

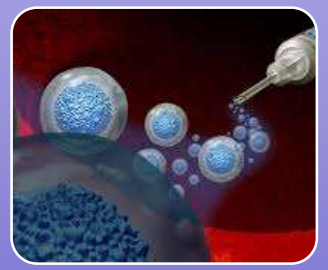
Güncel Epidemiyolojik Veriler Ne Anlatıyor?

Tedavi Algoritmaları Neler Öneriyor?

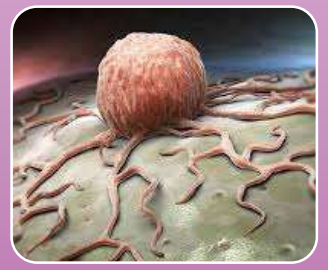
Tedavi Algoritmaları Yeterli mi?

Bu Sunumda Hangi İmmünsüprese Olgular Tartışılacak?

- Solid Organ Nakilli Olgular



- HKHN Uygulanmış Olgular



- Solid ve Hematolojik Kanserli olgular

Hangi Rehberlerin Tedavi Algoritmaları Tartışılacak?

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DOI: 10.1111/ctr.13594

SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
WILEY

Multidrug-resistant Gram-negative bacterial infections in solid organ transplant recipients—Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Stephanie M. Pouch[1] | Gopi Patel[2] | on behalf of the AST Infectious Diseases Community of Practice

İmmünsüprese Olgularda İnfeksiyon Sıklığı Nedir?

ABD

2006-2012

Erişkin Acil Servise başvuran olguların %4.2 kanser olgusu

Hastaneye yatırılan kanser olgularının %60'ında infeksiyon mevcut

En sık İnfeksiyon nedenleri

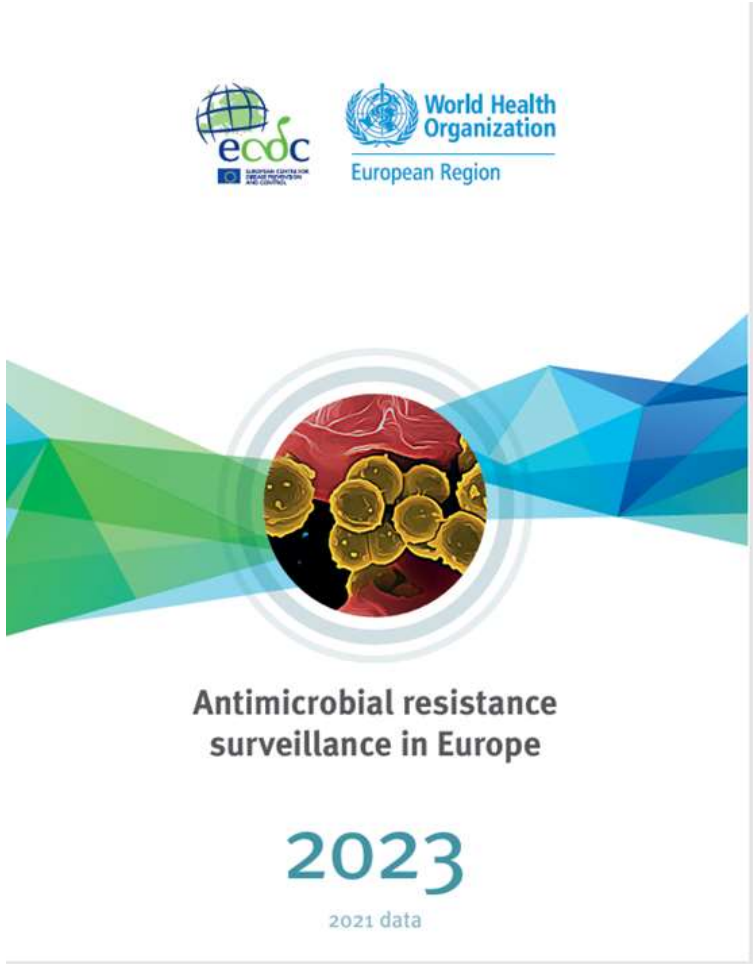
Pnömoni,

ÜSİ

Sepsis

Yang Z, et al. Oncologic emergencies in a cancer center emergency department and in general emergency departments countywide and nationwide. PLoS ONE. 2018;13:

Avrupa Antimikrobiyal Direnç Verileri Ne Diyor?



Bacterial species	Antimicrobial group/agent	Estimated incidence[b] of isolates from bloodstream infections with resistance phenotype (n per 100 000 population)						
		2019 (baseline year)	2020	2021	2022	2023	Trend 2019-2023[c]	Change 2019–2023 (%)[d]
Staphylococcus aureus	Aminoglycoside (gentamicin/netilmicin/tobramycin) resistance[e]	2.38	3.07	4.37	2.92	2.66	-	+11.8
	Combined resistance to carbapenems, fluoroquinolones and aminoglycosides[e]	2.20	2.93	4.17	2.74	2.55	-	+15.9
	MRSA[g]	5.63	4.86	4.41	4.72	4.64	↓	-17.6
Streptococcus pneumoniae	Penicillin non-wild-type[h]	0.72	0.47	0.51	0.63	0.76	-	+5.6
	Macrolide (azithromycin/clarithromycin/erythromycin) resistance	0.92	0.51	0.53	0.74	0.96	-	+4.3
	Combined penicillin non-wild-type and resistance to macrolides[h]	0.41	0.24	0.28	0.34	0.43	-	+4.9
Enterococcus faecalis	High-level gentamicin resistance	2.25	2.59	2.98	2.50	2.36	-	+4.9
Enterococcus faecium	Vancomycin resistance	1.85	2.09	2.57	2.47	2.30	↑	+24.3

NA: not applicable.

[a] For each individual EU Member State, a similar table is available as part of the country summaries.

[b] Incidence was estimated using the EARS-Net data reported to EpiPulse. Each de-duplicated isolate from a blood sample (>99% data) or cerebrospinal fluid sample (<1% data) was considered a proxy for a bloodstream infection.

[c] ↑ and ↓ indicate statistically significant increasing and decreasing trends, respectively; – indicates no statistically significant trend. NA: not applicable indicates that a significant change in data sources occurred during the period.

[d] The 'Council Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach' (2023/C 220/01), includes 2030 EU targets, with 2019 as the baseline year: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOC_2023_220_R_0001

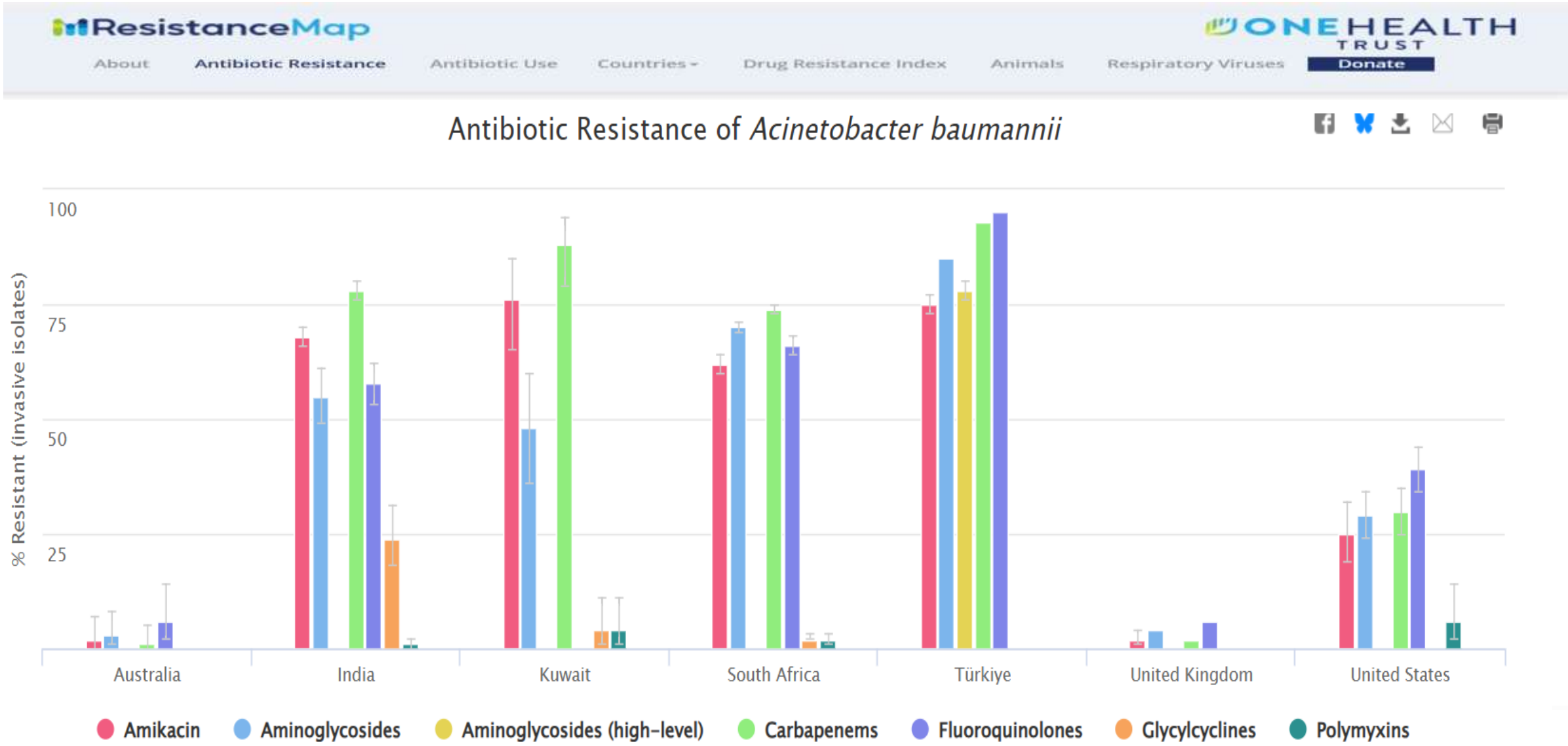
[e] The aminoglycoside group includes only gentamicin and tobramycin from 2020 onwards.

[f] The aminoglycoside group includes only tobramycin from 2020 onwards.

[g] MRSA is based on AST results for cefoxitin or, if unavailable, oxacillin. AST results reported for cloxacillin, dicloxacillin, flucloxacillin or meticillin are accepted as a marker for oxacillin resistance if oxacillin is not reported. If no phenotypic results are available, data from molecular confirmation tests (detection of mecA gene by PCR or a positive PBP2A-agglutination test) are accepted as a marker for MRSA.

[h] Penicillin results are based on penicillin or, if unavailable, oxacillin. For S. pneumoniae, the term penicillin non-wild-type is used in this report, referring to S. pneumoniae isolates reported by local laboratories as susceptible, increased exposure (I) or resistant (R) to penicillin, assuming MIC to benzylpenicillin above those of wild-type isolates (> 0.06 mg/L). The qualitative susceptibility categories (S/I/R) as reported by the laboratory are used, since quantitative susceptibility information is missing for a large part of the data.

Türkiye Verileri Ne Diyor?



HKHN Olgularında Etken Dağılımı ve Direnç Oranları Yıllar İçinde Değişti mi?

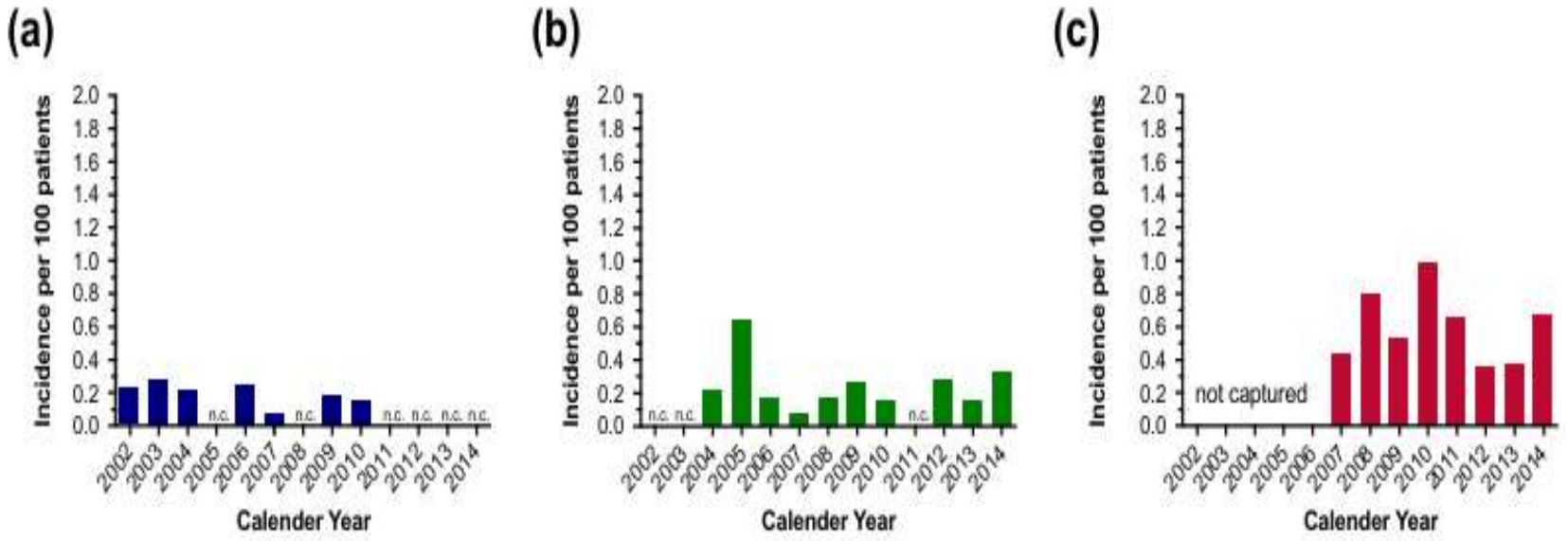
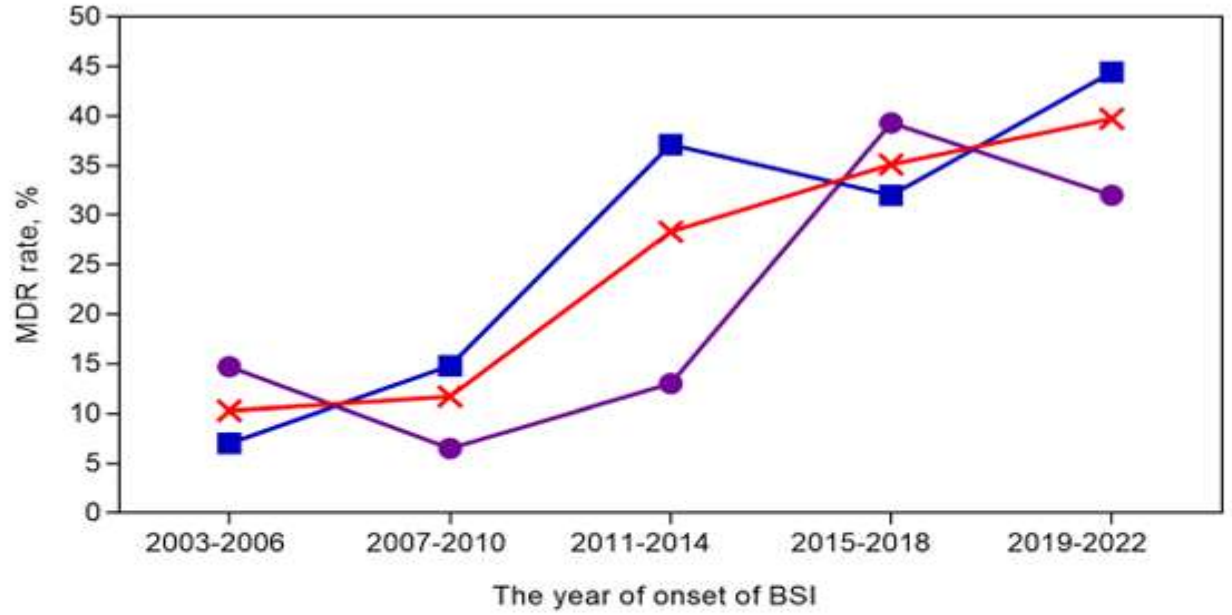


Fig. 3. Bloodstream infections in haematopoietic stem cell transplantation patients infected with multidrug-resistant bacteria. (A) Methicillin-resistant *Staphylococcus aureus*. (B) Vancomycin-resistant enterococci. (C) Extended-spectrum β-lactamase-producing *Enterobacteriacea*. n.c., not cultured.

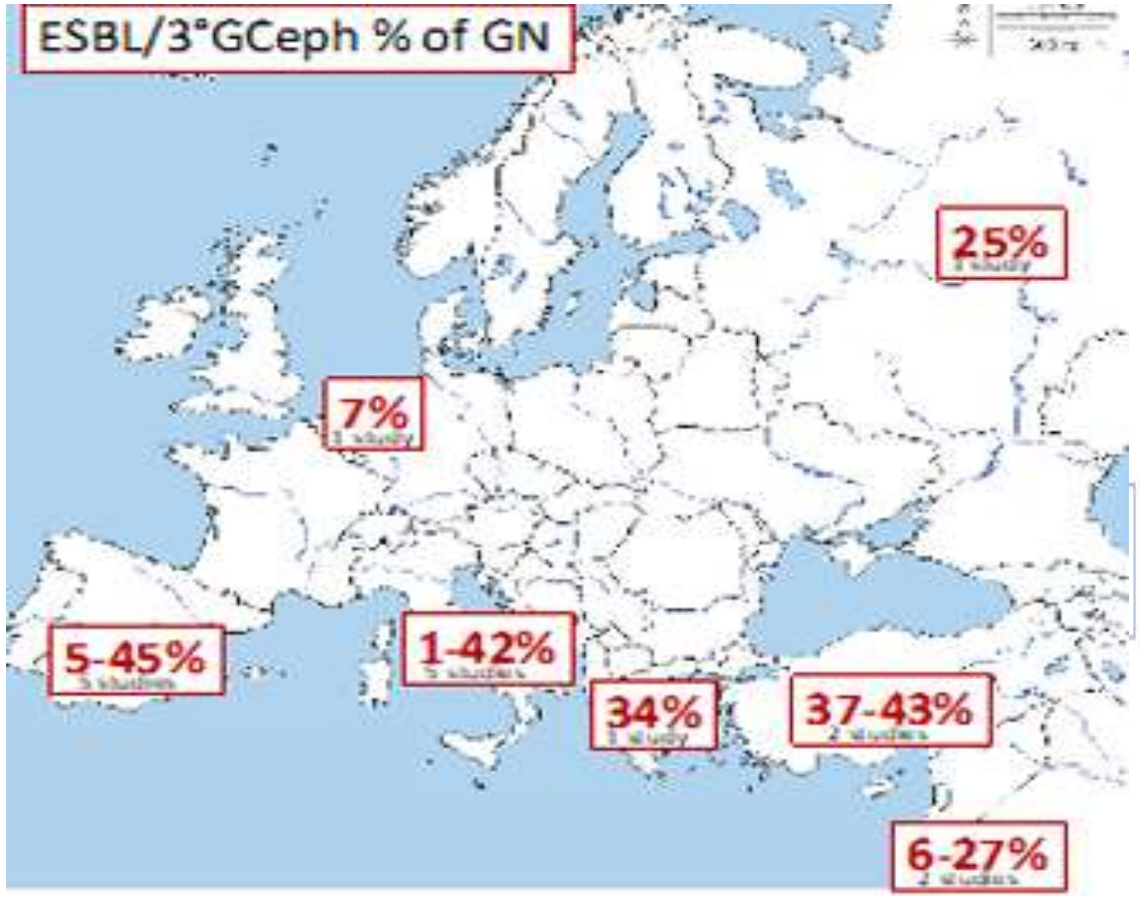
Hematolojik Kanser Olgularında Etken Dağılımı ve Direnç Oranları Yıllar İçinde Değişti mi?

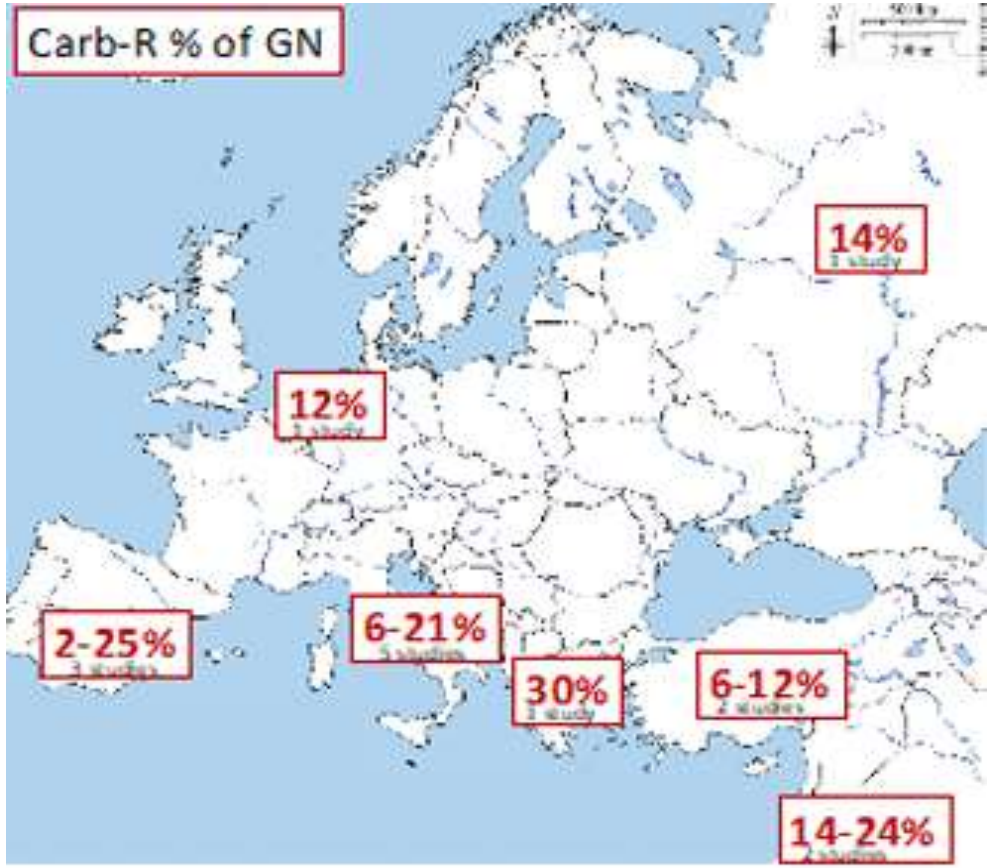


	2003-2006	2007-2010	2011-2014	2015-2018	2019-2022
All organism	10.3% (8/78)	11.7% (7/60)	28.3% (17/60)*	35.1% (20/57)**	39.7% (29/73)***
Gram-positive bacteria	14.7% (5/34)	6.5% (2/31)	13.0% (3/23)	39.3% (11/28)	32.0% (8/25)
Gram-negative bacteria	7.0% (3/43)	14.8% (4/27)	37.1% (13/35)**	32.0% (8/25)*	44.4% (16/36)***

Figure 1. Twenty-year trends in the rates of multidrug resistance (MDR) in bacterial bloodstream infections (BSIs) in patients with hematological cancer. MDR rates during the periods of 2007–2010, 2011–2014, 2015–2018, and 2019–2022 were compared with those during the period of 2003–2006. The statistical significance was displayed using the following notation: $^{*}P<0.05$, $^{**}P<0.01$, and $^{***}P<0.001$.

HKHN Olgularında Etken Dağılımı ve Direnç Oranları Yıllar İçinde Değişti mi?





Ülkemizde HKHN Olgularında Bakteremi Etkenlerinin Değişimi Nasıl?

RESEARCH ARTICLE

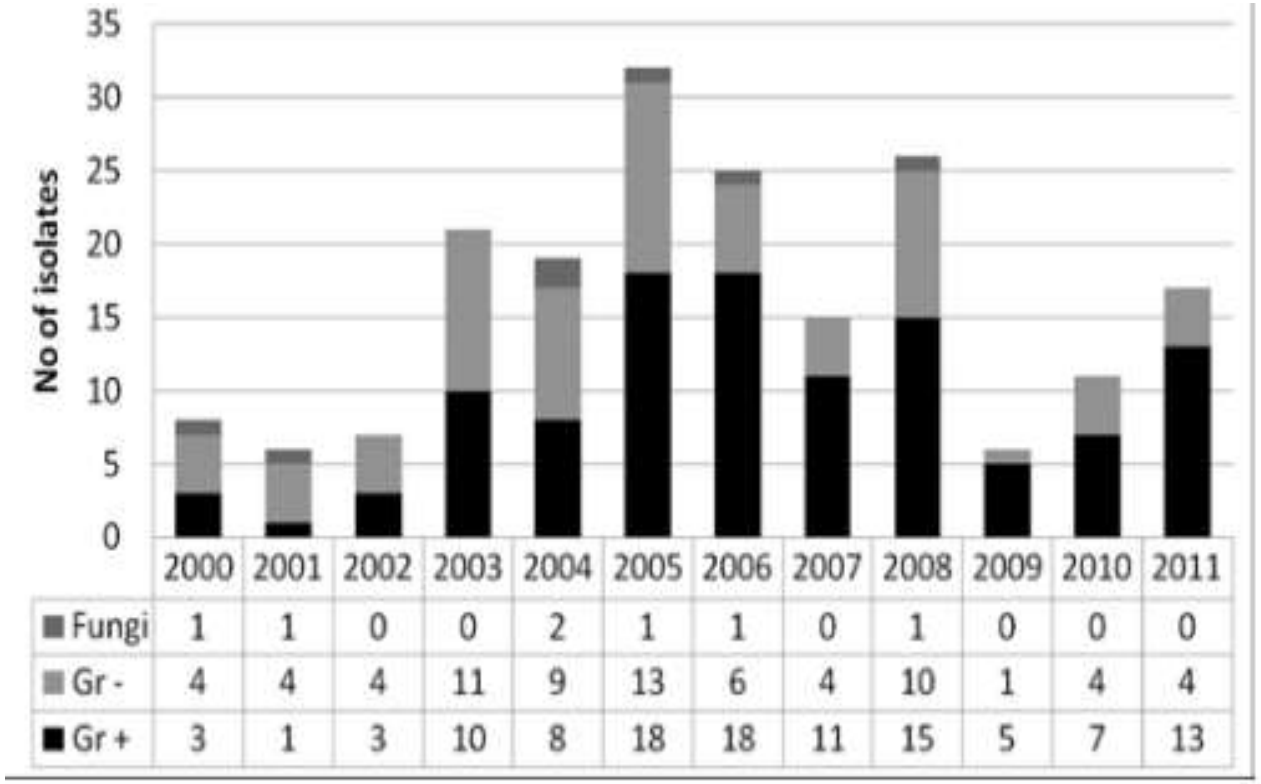
DOI: 10.4274/tjh.2014.0378
Turk J Hematol 2016;33:216-222

The Changing Epidemiology of Bloodstream Infections and Resistance in Hematopoietic Stem Cell Transplantation Recipients

Hematopoetik Kök Hücre Nakli Alıcılarında Kan Akım Enfeksiyonu ve Direnç Epidemiyolojisindeki Değişim

Mücahit Yemişen[1], İlker İnanç Balkan[1], Ayşe Salihoğlu[2], Ahmet Emre Eşkazan[2], Bilgül Mete[1], M. Cem Ar[2], Şeniz Öngören[2], Zafer Başlar[2], Reşat Özaras[1], Neşe Saltoğlu[1], Ali Mert[1], Burhan Ferhanoğlu[3], Recep Öztürk[1], Fehmi Tabak[1], Teoman Soysal[2]

[1]İstanbul University Cerrahpaşa Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey
[2]İstanbul University Cerrahpaşa Faculty of Medicine, Department of Internal Medicine, Division of Heamatology, İstanbul, Turkey
[3]Koç University Faculty of Medicine, American Hospital, Clinic of Internal Medicine, Division of Heamatology, İstanbul, Turkey



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Fungi	1	1	0	0	2	1	1	0	1	0	0	0
Gr -	4	4	4	11	9	13	6	4	10	1	4	4
Gr +	3	1	3	10	8	18	18	11	15	5	7	13

Figure 1. Evolution of bloodstream infection etiology.

Kliniğimizin Verileri

Mikroorganizma	Antimikrobiyal duyarlılık paterni, (%)
Escherichia coli	ESBL (+); 62.1 Karbapenem dirençli; 14
Klebsiella pneumonia	Karbapenem dirençli; 58.6
Acinetobacter baumannii	Karbapenem dirençli; 100
Pseudomonas aeruginosa	Karbapenem dirençli; 27.7
Staphylococcus haemoliticus	Metisilin dirençli; 100
E. faecium	Vankomisin dirençli; 57.6
Staphylococcus hominis	Metisilin dirençli; 100
Staphylococcus epidermidis	Metisilin dirençli; 100
Staphylococcus aureus	Metisilin dirençli; 64.7

SOT Olgularında Epidemiyolojik Veriler Değişiklik Gösterdi mi?

Table 2. Organism groups and associated antimicrobial resistance causing BSIs in the year after SOT

	SOT type					
Organism	Overall ($n=323$)	Kidney ($n=87$)	Liver ($n=133$)	Heart ($n=26$)	Multi-organ ($n=77$)	P^a
Enterobacterales	155 (48.0)	53 (60.9)	48 (36.1)	12 (46.2)	42 (54.5)	0.002
ESBL (% of all organisms)	52 (16.1)	23 (26.4)	14 (10.5)	3 (11.5)	12 (15.6)	0.02
ESBL (% of Enterobacterales)	52 (33.6)	23 (43.4)	14 (29.2)	3 (25.0)	12 (28.6)	0.31
CRE (% of all organisms)	20 (6.2)	0 (0)	13 (9.8)	1 (3.9)	6 (7.8)	0.03
CRE (% of Enterobacterales)	20 (12.9)	0 (0)	13 (27.1)	1 (8.3)	6 (14.3)	<0.001
Enterococcus spp.	67 (20.7)	3 (3.4)	43 (32.3)	7 (26.9)	14 (18.2)	<0.001
VRE (% of all organisms)	45 (13.9)	0 (0)	30 (22.6)	3 (11.5)	12 (15.6)	<0.001
VRE (% of *Enterococcus*)	45 (67.2)	0 (0)	30 (69.8)	3 (42.9)	12 (85.7)	0.02
P. aeruginosa	27 (8.4)	7 (8.0)	13 (9.8)	5 (19.2)	2 (2.6)	0.05
CNSPA (% of all organisms)	12 (3.7)	1 (1.1)	8 (6.0)	1 (3.9)	2 (2.6)	0.28
CNSPA (% of *Pseudomonas*)	12 (44.4)	1 (14.3)	8 (61.5)	1 (20)	2 (100)	0.05
S. aureus	21 (6.5)	11 (12.6)	6 (4.5)	1 (3.8)	3 (3.9)	0.06
MRSA (% of all organisms)	8 (2.5)	4 (4.6)	2 (1.5)	0 (0)	2 (2.6)	0.42
MRSA (% of *S. aureus*)	8 (38.1)	4 (36.4)	2 (33.3)	0 (0)	2 (66.7)	0.63
Candida spp.	16 (5.0)	3 (3.4)	6 (4.5)	0 (0)	7 (9.1)	0.20
ARC (% of all organisms)	10 (3.1)	2 (2.3)	4 (3.0)	0 (0)	4 (5.2)	0.54
ARC (% of *Candida*)	10 (62.5)	2 (66.7)	4 (66.7)	0 (0)	4 (57.1)	0.93
Any MDRO[b]	147 (45.5)	30 (34.5)	71 (53.4)	8 (30.8)	38 (49.4)	0.02
Other organisms	37 (11.5)	10 (11.5)	17 (12.8)	1 (3.8)	9 (11.7)	0.63

[a]*P* value (determined by χ^2 or ANOVA) is comparison between different organ transplant types.
[b]Any organism that was either ESBL-producing (ESBL), CRE, VRE, CNSPA, MRSA or ARC was counted as an MDRO.

Ülkemizdeki Veriler Farklı mı?

Table 2. Clinical characteristics of the bacteremia episodes.

Table 3. The distribution of isolated bacteria according to transplanted organ.

Type of transplantation	Most common	2nd most common	3rd most common	4th most common
Liver (n = 98)	*K. pneumoniae* (46.9%)	*A. baumannii* (40.8%)	*P. aeruginosa* (8.2%)	*E. coli* (4.1%)
Kidney (n = 48)	*K. pneumoniae* (37.5%)	*E. coli* (25 %)	*A. baumannii* (18.8%)	*P. aeruginosa* (14.6%)
Heart (n = 14)	*A. baumannii* (64.3%)	*E. coli* (21.4 %)	*K. pneumoniae* (7.1%)	*P. aeruginosa* (7.1%)
Lung (n = 11)	*K. pneumoniae* (36.4%)	*Enterobacter spp.* (27.3%)	*P. aeruginosa* (18.2%)	*E. coli* (9.1%)

Hastanemiz Verileri Farklı mı?

- ✓ 2018-2024 tarihleri arasında
- ✓108 hastanın 29’u (%27) çalışmaya dahil edildi.
- ✓ Yaş ortalaması 54.5 yıl (18-68 yıl), % 65’i kadın (n=18)
- ✓ Kadaverik donör %31
- ✓ Ort. bakteriyemi atak sayısı 2.2
- ✓ Mortalite %41 (n=12)

Hastanemiz Verileri Farklı mı?

- 29 hastada 51 bakteriyemi atağı
- 55 etken izole edildi.

	Bakteriyemi atağı
Nakil süresi	
Erken dönem	16 (%31)
Orta dönem	**26 (%51)**
Geç dönem	9 (%18)
Etken dağılımı	
Gram (+) bakteriler	9 (%16)
Gram (-) bakteriler	**35 (%64)**
Mantar	11 (%20)
Monobakteriyel	47 (%92)
Ba**kteriyemi kaynak**	
İntraabdominal	**37 (%72)**
Kateter	10 (%20)
Pnömoni	4 (%8)

Hastanemiz Verileri Farklı mı?

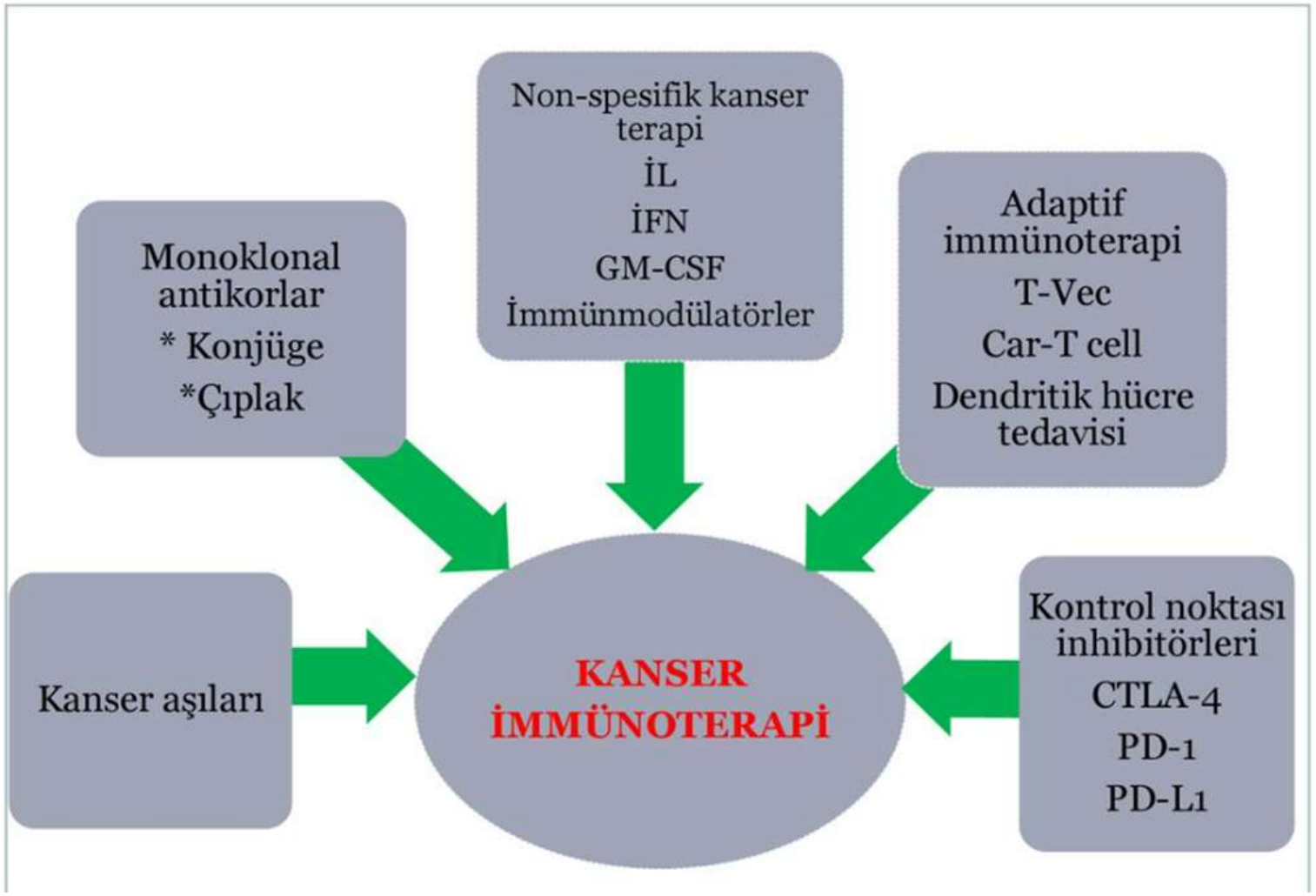
Gram-negatif enterik basillerde (GNEB) ESBL oranı: %69

Kinolon direnci:%61

Karbapenem direnci:%30

A. baumanii ve *P. aeruginosa* karbapenem direnci: %92 olarak saptandı.

Değişen Sadece Epidemiyoloji mi?



Kanser Tedavisinde İmmünoterapi

Science dergisi,2013 yılın en önemli gelişmesi

Tümörü değil immünsistemi hedefler

Kanser tedavisinde farklı bir yoldur

IDSA GUIDELINES

Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America

Alison G. Freifeld,[1] Eric J. Bow,[9] Kent A. Sepkowitz,[2] Michael J. Boeckh,[4] James I. Ito,[5] Craig A. Mullen,[3] Issam I. Raad,[6] Kenneth V. Rolston,[6] Jo-Anne H. Young,[7] and John R. Wingard[8]

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Tedavi Algoritmaları Epidemiyoloji İle Uyumlu mu?

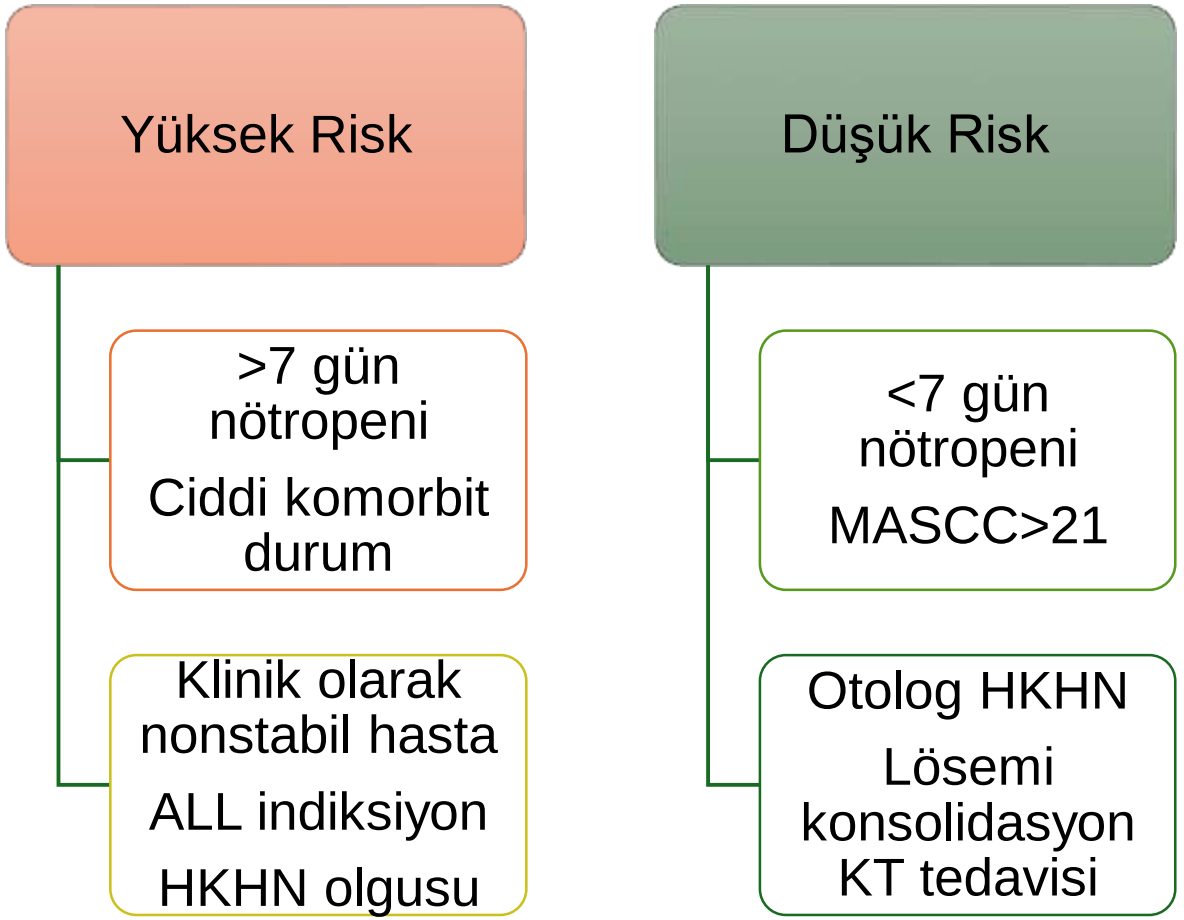

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Table 3. The Multinational Association for Supportive Care in Cancer Risk-Index Score

Characteristic	Weight
Burden of febrile neutropenia with no or mild symptoms[a]	5
No hypotension (systolic blood pressure >90 mmHg)	5
No chronic obstructive pulmonary disease[b]	4
Solid tumor or hematologic malignancy with no previous fungal infection[c]	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms[a]	3
Outpatient status	3
Age <60 years	2

NOTE. The maximum value of the score is 26. Adapted from [43]. Reproduced with permission of the American Society for Clinical Oncology.

[a] Burden of febrile neutropenia refers to the general clinical status of the patient as influenced by the febrile neutropenic episode. It should be evaluated on the following scale: no or mild symptoms (score of 5); moderate symptoms (score of 3); and severe symptoms or moribund (score of 0). Scores of 3 and 5 are not cumulative.

[b] Chronic obstructive pulmonary disease means active chronic bronchitis, emphysema, decrease in forced expiratory volumes, need for oxygen therapy and/or steroids and/or bronchodilators requiring treatment at the presentation of the febrile neutropenic episode.

[c] Previous fungal infection means demonstrated fungal infection or empirically treated suspected fungal infection.

- ✓ MASCC sistemiyle ilgili ana sıkıntı "febril nötropeninin şiddeti" şeklinde belirtilen kriterin yorumlanması ile ilgili
- ✓ Bu kriter hastanın ne kadar hasta olduğu şeklinde belirtilebilir
- ✓ Ancak belirli bir standardizasyon yok
- ✓ Bu kriterin yorumlanması kafa karıştırıcı olabilmektedir.

Risk Skorlama Sistemleri Yerine Yapay Zeka Kullanılabilir mi?

- MDR-GNB enfeksiyonu ile ilişkili bağımsız faktörler şunlardı:
  - 45 yaş üstü olmak
  - Önceki antibiyotik kullanımı
  - Bu hastanede ilk kez FN atağının görülmesi
  - Önceki FN nedeniyle hastaneye yatışlar
  - En az 15 kez hastane ziyareti geçmişi
  - Yüksek riskli hematolojik hastalıklar
  - Daha önce MDR-GNB izolasyonu yapılan bir hastanın kaldığı odada yatış

Febril Nötropenik Hastalarda , Hangi Ampirik Antibiyotik Tedavisi Uygundur ve Hangi Durumlarda Kullanılmalıdır?

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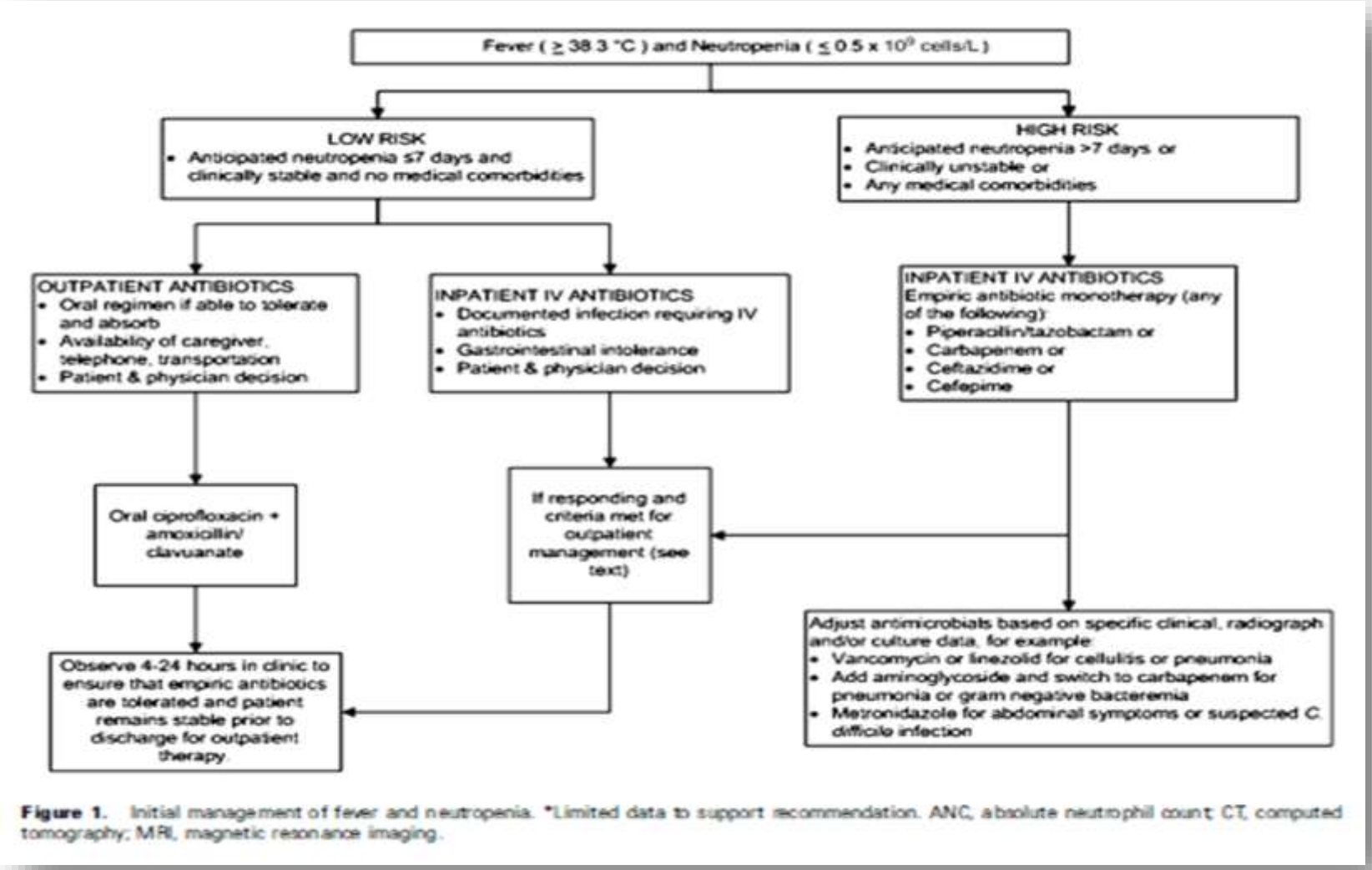
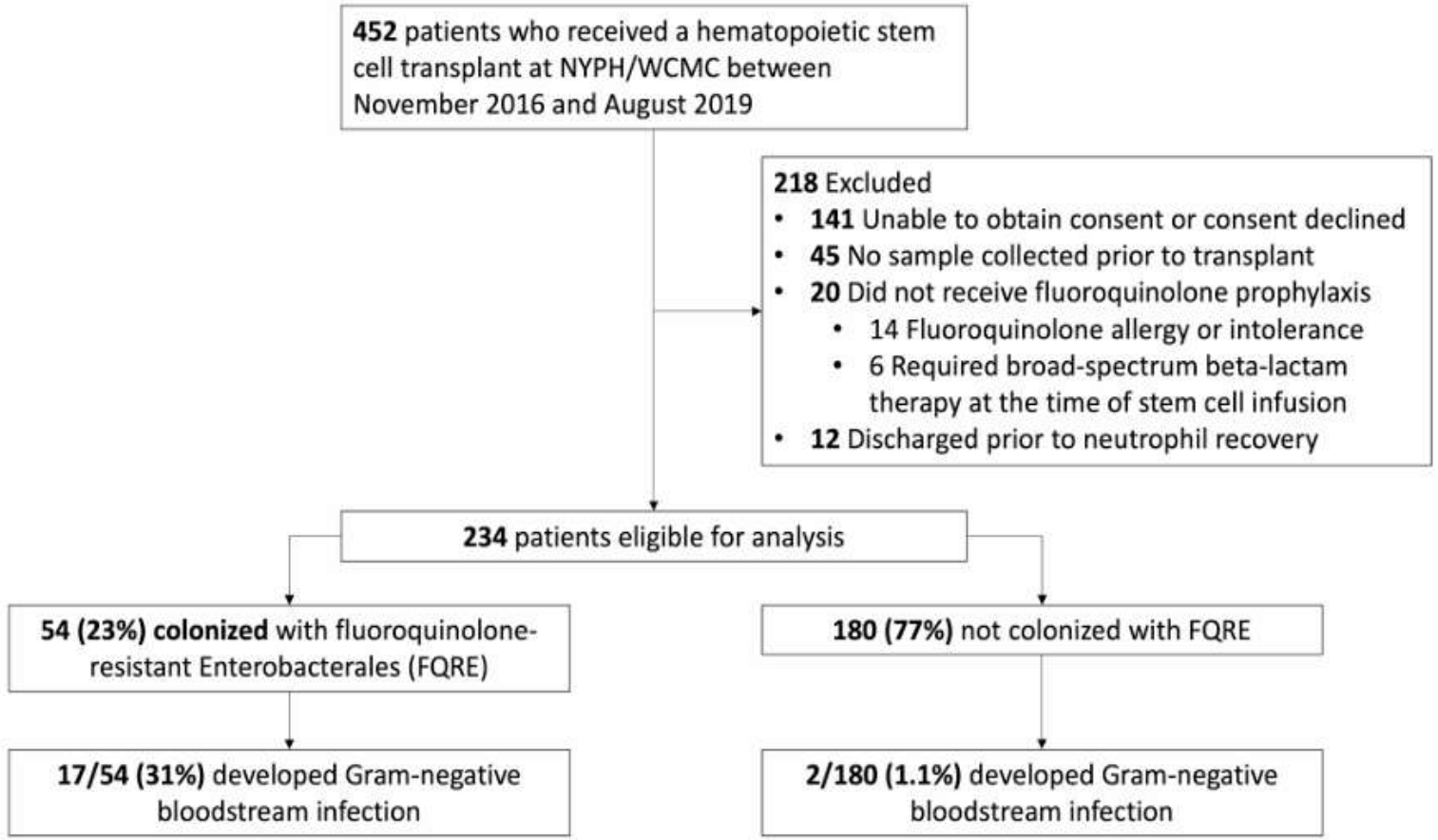


Figure 1. Initial management of fever and neutropenia. *Limited data to support recommendation. ANC, absolute neutrophil count; CT, computed tomography; MRI, magnetic resonance imaging.

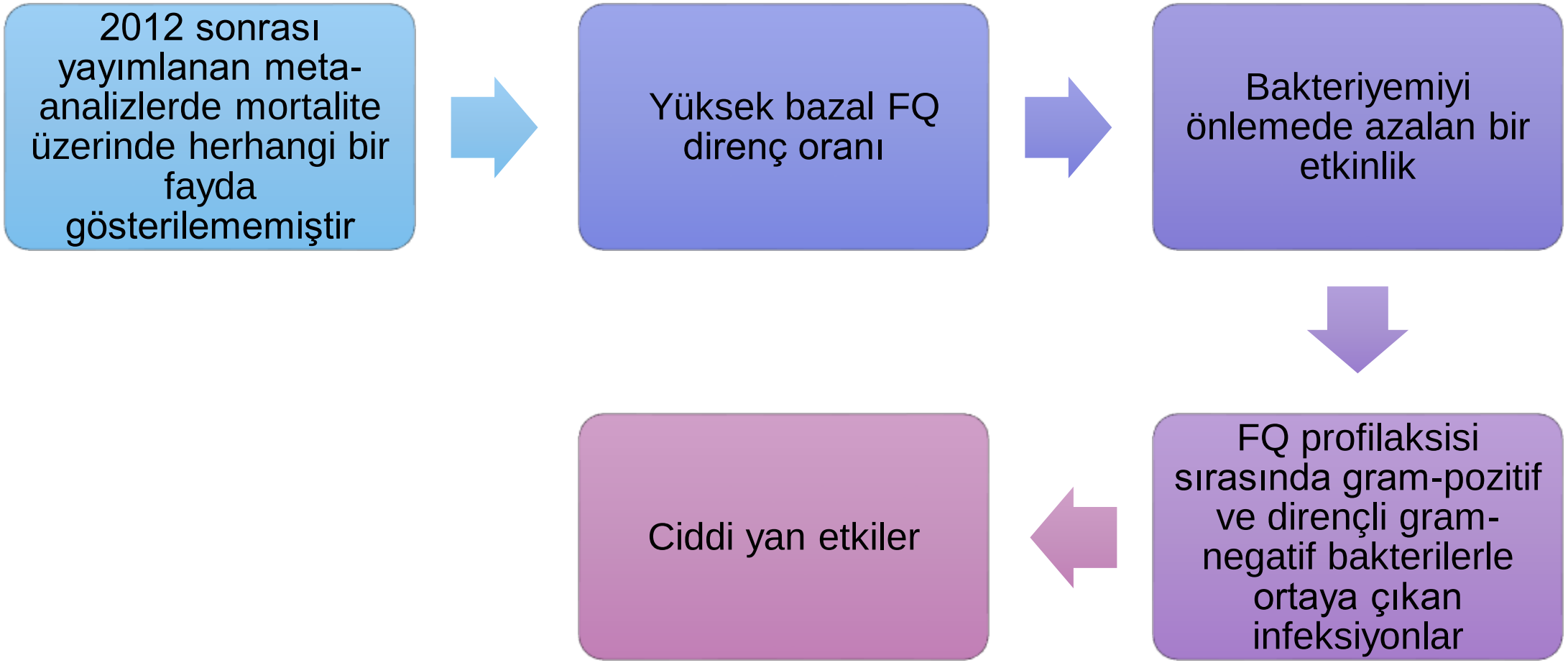
Clinical Infectious Diseases
MAJOR ARTICLE

Colonization With Fluoroquinolone-Resistant Enterobacterales Decreases the Effectiveness of Fluoroquinolone Prophylaxis in Hematopoietic Cell Transplant Recipients

Michael J. Satlin,[1,2] Liang Chen,[3,4] Claire Douglass,[1,5] Michael Hovan,[1,6] Emily Davidson,[1,7] Rosemary Soave,[1] Marisa La Spina,[8] Alexandra Gomez-Arteaga,[9] Koen van Besien,[9] Sebastian Mayer,[9] Adrienne Phillips,[9] Jing-Mei Hsu,[9] Rianna Malherbe,[10] Catherine B. Small,[1] Stephen G. Jenkins,[1,2] Lars F. Westblade,[1,2] Barry N. Kreiswirth,[3,4] and Thomas J. Walsh[1]



Kinolon Profilaksisi Gerekli mi?



IDSA GUIDELINES

Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America

Alison G. Freifeld,[1] Eric J. Bow,[9] Kent A. Sepkowitz,[2] Michael J. Boeckh,[4] James I. Ito,[5] Craig A. Mullen,[3] Issam I. Raad,[6] Kenneth V. Rolston,[6] Jo-Anne H. Young,[7] and John R. Wingard[8]

Downl

Güncel Epidemiyolojik Veriler ve Tedavi Algoritmasının Uygunluğu

Özellikle karbapenem dirençli Enterobacteriaceae ve Pseudomonas aeruginosa gibi patojenlerde görülme sıklığı artış söz konusu

2010 kılavuzunda önerilen empirik tedavi rejimlerinin etkinliği azalmış

Güncellenmiş tedavi stratejilerine ihtiyaç var

SOT Olgularında ATS Rehberi Güncel Epidemiyojiye Uygun mu?

MDR and XDR *Pseudomonas aeruginosa*	Preferred regimens:	
	• High-dose continuous or extended-infusion antipseudomonal β-lactam	Strong, moderate
	• Ceftolozane/tazobactam	Strong, moderate
	• Ceftazidime/avibactam	Strong, moderate
	Alternative regimens:	Strong, moderate
	• Individualized combination regimen with two of the following: o High-dose continuous or extended-infusion antipseudomonal β-lactam o Aminoglycoside o Colistin or polymyxin B o Ciprofloxacin or levofloxacin	
	• Adjunctive aerosolized colistin or tobramycin for pneumonia	Weak, low
PDR *Pseudomonas aeruginosa*	Individualized combination regimen with three of the following:	
	• High-dose continuous or extended-infusion antipseudomonal β-lactam	Strong, moderate
	• Colistin or polymyxin B	
	• Aminoglycosides	
	• Adjunctive aerosolized colistin or tobramycin for pneumonia	Weak, low
Carbapenem-resistant *Acinetobacter baumannii*	Preferred regimen:	
	• Combination therapy with a carbapenem plus colistin or polymyxin B	Strong, moderate
	Alternate regimens:	
	Monotherapy with:	Strong, moderate
	• Ampicillin/sulbactam if susceptible[a] (sulbactam dose ≥9 g daily, dose adjusted for creatinine clearance)	Weak, low
	• Minocycline	
MDR *Stenotrophomonas maltophilia*	Preferred regimen:	
	• High-dose SXT (15 mg/kg/d trimethoprim, dose adjusted for creatinine clearance)	Strong, moderate
	Alternatives (combination therapy if SXT-resistant recommended):	
	• Ceftazidime	Strong, low
	• Minocycline	Strong, low
	• Levofloxacin	Strong, low
	• Ceftazidime/avibactam plus aztreonam	Weak, low

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SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

Clinical TRANSPLANTATION WILEY

Multidrug-resistant Gram-negative bacterial infections in solid organ transplant recipients—Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Stephanie M. Pouch[1] | Gopi Patel[2] | on behalf of the AST Infectious Diseases Community of Practice

Bakteriyemik donörlerden veya nakledilen allotransplantın kolonizasyonu veya infeksiyonu varsa organ alan kişiler en az 7 gün hedefli antimikrobiyal tedavi almalıdır

SOT alıcıları ve adayları için dirençli mikroorganizmalarla kolonize olmaları durumunda barsak dekolonizasyonu önerilmez

İnfekte olmuş veya kolonize olmuş donörlerden alınan organlar

nakilden hariç tutulmamalıdır.

İnfeksiyonu olan donörler, organ alımından

24-48 saat önce etkili antimikrobiyal tedavi almalıdır

Received: 6 May 2019 | Accepted: 11 May 2019
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Guidelines

ESCMID/EUCIC clinical practice guidelines on perioperative antibiotic prophylaxis in patients colonized by multidrug-resistant Gram-negative bacteria before surgery

ECIL-10

Part I
Empirical therapy in febrile neutropenia

Francesco Baccelli, Carolina Garcia Vidal, Murat Akova, Thierry Calandra, Dina Averbuch

10th EUROPEAN CONFERENCE on INFECTIONS in LEUKAEMIA

▶ CONFERENCE
From September
19th to 21st, 2024

▶ Golden Tulip Sophia Antipolis
Nice, France

Background for the changes of recommendations on empirical antibiotic therapy choice based on colonizing bacteria

Key questions	Answers
1) Is there an increased risk of subsequent BSI due to resistant bacteria in patients colonized with resistant bacteria?	**Yes** for GN (289/1607; 18.0% vs 116/9772; 1.2%; 33 studies) **Yes** for GP (VRE, MRSA) (208/1584; 13.1% vs 50/5549; 0.9%; 16 non-RCT, 1 metaanalysis)
2) Is there a correlation between inappropriate empirical antibiotic therapy and mortality due to resistant bacteria?	**Yes** for GN (92/417; 22.1% vs 104/1070; 9.7%; 27 studies, in 16 studies correlation was statistically significant; others did not reach significance, low numbers) **No** for VRE (24/183; 13.1%; 6 studies vs. 6/41; 14.6%; 3 studies) **No** for VGS (limited data, 2 studies) **No data** for MRSA in HM/HCT patients (data from other patients` population demonstrate correlation between delay in appropriate therapy and mortality in 5/9 non-RCT, 1 metaanalysis)
3) Does decolonization (with fecal microbiota transplantation or pharmacological agents) **prevent** subsequent BSI due to resistant GN in patients colonized with resistant bacteria?	**No** evidence that pharmacological decolonization prevents subsequent BSI with resistant bacteria in colonized patients (11 studies; 2 vs control – 1 no reduction, 1 early reduction, late no difference) **Limited evidence** suggests that FMT prevents BSI with resistant bacteria in colonized patients (6 studies; 1 non-RCT– significant reduction vs control)
4) Shall novel beta-lactams be used empirically in FN patients colonized with resistant Gram-negative bacteria?	Limited data showed good efficacy of empirical ceftazidime/avibactam *(2 non-RCT, 1 higher efficacy in KPC-colonized pts vs colistin-based combinations),* ceftolozane/tazobactam *(1 RCT FN higher clinical cure rates vs other BLs, 1 case-control MDR PsA lower mortality with CT vs controls, CT used as empirical/targeted, 1 non-RCT in colonized pts, 0 mortality);* and imipenem/cilastatin/relebactam *(1 RCT FN, higher clinical response vs comparator)* (total 6 studies, 2 RCT), **only 1 in colonized patients**

Revision of recommendations for empirical antibiotic therapy: escalation approach

	Escalation approach ECIL 4	Escalation approach ECIL 10
Indication **B-II for all**	1) Uncomplicated presentation; 2) No known colonization with resistant bacteria; 3) No previous infection with resistant bacteria; 4) In centers where infections due to resistant pathogens are rarely seen at the onset of febrile neutropenia	**No change**
Options for initial antibiotic therapy	1) Anti-pseudomonal cephalosporin (cefepime*, ceftazidime*) **AI** 2) Piperacillin-tazobactam **AI** 3) Other possible options include: • Ticarcillin-clavulanate • Cefoperazone-sulbactam • Piperacillin + gentamicin	1) Anti-pseudomonal cephalosporin (cefepime*, ceftazidime*) **AI** 2) Piperacillin-tazobactam **AI** 3) Other possible options include: • Cefoperazone-sulbactam • Piperacillin + gentamicin

Revision of recommendations for empirical antibiotic therapy: de-escalation approach (in red changes vs ECIL4)

	De-escalation approach ECIL 4	De-escalation approach ECIL 10
Indication	1) Complicated presentations **BII** 2) Known colonization with resistant bacteria **BII** 3) Previous infection with resistant bacteria **BII** 4) In centers where resistant pathogens are regularly seen at the onset of febrile neutropenia **BII**	1) Sepsis/Septic shock 2) Known colonization with resistant bacteria; 3) Previous infection with resistant bacteria; 4) In centers where resistant pathogens are regularly seen at the onset of febrile neutropenia.
Options for initial antibiotic therapy	1) Carbapenem monotherapy **BII** 2) Combination of anti-pseudomonal beta-lactam + aminoglycoside or quinolone (with carbapenem as the beta- lactam in seriously ill-patients) **BIII** 3) Colistin + beta-lactam +/- rifampicin (for PsA, AB, SM) **BIII** 4) Early coverage of resistant-Gram-positives with a glycopeptide or newer agent (If risk factors for Gram-positives present) **CIII**	1) Carbapenem monotherapy 2) Combination of anti-pseudomonal beta-lactam + aminoglycoside 3) Beta lactam targeting the suspected colonizing pathogen based on susceptibility testing 4) Early coverage of resistant-Gram-positives with a glycopeptide or newer agent if risk factors for Gram-positives present

Revision of recommendations for empirical antibiotic therapy: Specific situations for de-escalation approach

Situations for which carbapenems are indicated as empirical regimen

(in red changes vs ECIL4)

ECIL-4	ECIL-10
1. Seriously-ill patients e.g. presentation with septic shock BII	1. Critically-ill patients e.g. presentation with sepsis/septic shock **and no known colonization or previous infection with carbapenem-resistant bacteria AIIu** *(based on increase in resistant bacteria including 3dGCephalosporin resistant Enterobacterales in community and in hospitals and increased mortality with IEAT)*
2. Known colonization or previous infection with: BII **a. ESBL-producing enterobacteriaceae** **b. Gram-negatives resistant to narrower-spectrum beta-lactams**	2. Known colonization or previous infection with: **AIIu** *(based on increased risk of BSI in colonised patients and increased mortality with IEAT)* a. ESBL-producing Enterobacterales b. Gram-negatives resistant to narrower-spectrum beta-lactams
3. Centres with a high prevalence of infections due to ESBL-producers at the onset of febrile neutropenia BIII	3. Centres with a high prevalence of infections due to ESBL-producers at the onset of febrile neutropenia **AIIu** *(based on increased mortality with IEAT)*

Situations for which novel anti-Gram-negative beta-lactams are indicated as the empirical regimen (not covered by ECIL-4)

In patients colonized or previously infected with <u>carbapenem-resistant Gram-negative bacteria</u>:

KPC-producers	ceftazidime-avibactam **(AIIu),** meropenem-vaborbactam **(BIItu),** imipenem-cilastatin-relebactam **(CIIt),** cefiderocol **(CIII)**
OXA-48 -producers	ceftazidime avibactam **(AIItu),** cefiderocol **(CIII)**
MBL- producers	ceftazidime-avibactam plus aztreonam **AIItu ,** cefiderocol **(CIII);**

In patients colonized or previously infected with DTR *<u>Pseudomonas aeruginosa</u>*:

High dose ceftolozane tazobactam (**AIItu),** ceftazidime-avibactam **(AIItu),**

imipenem/cilastatin/relebactam **(BIIt),** cefiderocol (**CIII**);

*Coverage against invasive streptococcal infections should be considered if antibiotics with limited activity against Gram-positive organisms are used (e.g., ceftazidime with or without avibactam or cefiderocol), especially in patients with severe mucositis (**CIII**).

** screening for resistant bacteria should be performed in high-risk setting

The strength of recommendations is based on: 1) on the experience with specific compounds (such as ceftazidime, carbapenems, cefiderocol) in FN in general; 2) Experience in the targeted treatment of patients known to have bacteremia with these resistant bacteria; 3) Experience as empirical therapy in patients colonized with resistant bacteria

Carbapenem-resistant *Acinetobacter baumanii* (CRAB)
ECIL-10 treatment recommendations

We recommend combination therapy for CRAB **A II t**

AB	RCTs	Observational data in HM/HSCT/IC	Proposed grading
Sulbactam-durlobactam* + high-dose imipenem	Not inferior to comparator	Not available	**A II t**
High-dose sulbactam (≥ 9gr/day) + other drug[1, 2]	Good efficacy in general populations	No data in HM/HSCT Data in general population	**B II t**
Other combinations[3]	Data on cefiderocol[4], tigecycline [5]	Some data on cefiderocol[4] in HM; Some data on fosfomycin, tigecycline[5] minocycline[6] in general population	**B II t**

***durlobactam not EMA approved**

(1) In case sulbactam-durlobactam is not available

(2) In combination: colistin is preferred. If colistin cannot be used, considered addition of one of cefiderocol [4] , tigecycline [5], minocycline [6].

(3) If sulbactam MIC>16 (resistance): consider combination of any of the following: colistin, cefiderocol, tigecycline/minocycline, fosfomycin.

(4) Although cefiderocol **monotherapy** has been associated with increased mortality in RCT, cefiderocol-based **combinations** have been associated with improved clinical outcomes in meta-analyses and retrospective studies. It can be favored if sulbactam-R isolates and/or when colistin cannot be used.

(5) Tigecycline studied as mono- and combination therapy with variable outcomes. High-dose tigecycline can be used if tolerated. Should be avoided in cases of bacteremia, pneumonia or urinary tract infections; or if MIC>2.

(6) Minocycline: limited clinical data on CRAB. Based on MIC and PK/PD data, high-dose minocycline IV/PO may be an alternative to tigecycline

Ülkemizde Güncel Rehber Önerileri Uygulanabilir mi?

Ülkemizde sadece Seftazidim/Avibaktam mevcut

Diğer ceftolazon/tazobactam, meropenem/vaborbaktam vs mevcut değil

Seftazidim/avibaktam YBÜ'nde izlenilen olgularda ödeniyor

Sonuç Olarak

Doktorlar; az bildikleri ilaçları daha az bildikleri vücudumuza vererek,

hiç bilmedikleri hastalıkları tedavi ederler