

Acinetobacter baumannii

Dr. Oral ONCUL

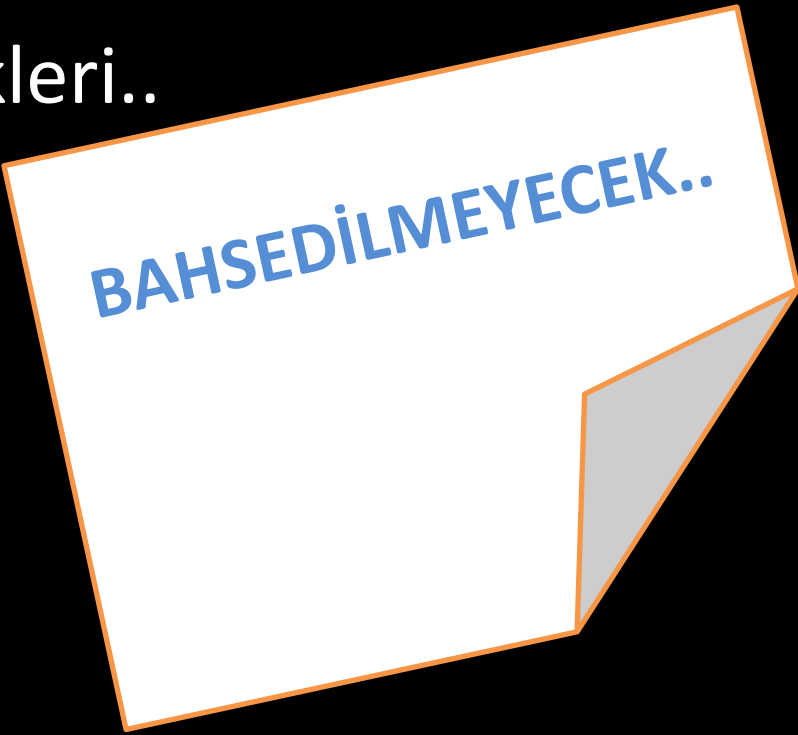
GATA Haydarpaşa Eğitim Hastanesi

Enf. Hst. Kl. Mik. Srv. Istanbul

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Konu Başlıkları ve Gündem..

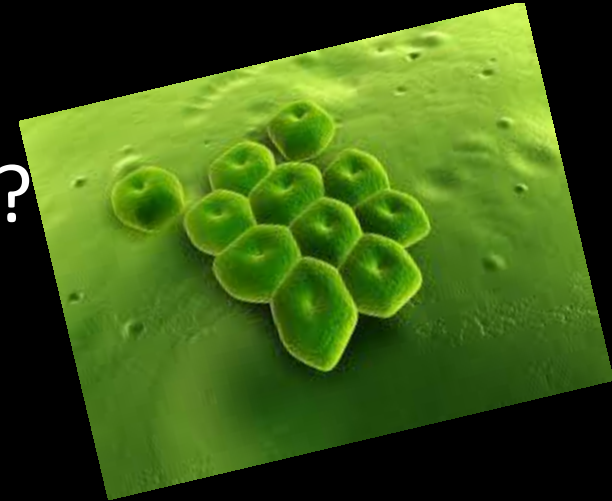
- Mikrobiyolojik özellikleri..
- Patogenez
- Epidemiyoloji
- Klinik özellikleri
- Antibiyotik direnci
- Tedavi ..



BAHSEDİLMEMEYECİK..

Cevap Aranacak Sorular..

- *A.baumannii* neden sorunlu bir bakteri?
- Diğer bakterilerden neden farklı?
- Neden bu kadar dirençli?
- Son dönemde *A.baumannii* ile ilgili önemli gelişmeler?
- MDR / PDR Nasıl tedavi edebiliriz?
- YBU'lerimizi nasıl kurtarabiliriz?



Hospital-acquired infections following the 1999 Marmara earthquake

O. Öncül*, Ö. Keskin†, H. V. Acar‡, Y. Küçükardalı§, R. Evrenkaya¶, E. M. Atasoyu¶, C. Top§, S. Nalbant§, S. Özkan‡, G. Emekdaş||, Ş. Çavuşlu*, M. H. Us**, A. Pahsa*, M. Gökben‡

Table III Data related with microbiologic evaluation of 4 patients with HAI

		Rate (%)
Culture specimens		
Blood		67.8
Wound		8
Urine		8.4
Catheter		3.5
Bronchoalveolar lavage		3.5
Number of agents isolated		
<i>A. baumannii</i>		31.2
MRSA	9	18.7
<i>P. aeruginosa</i>	7	14.6
<i>E. coli</i>	6	12.5
<i>K. pneumoniae</i>	6	12.5
<i>S. maltophilia</i>	2	4.2
Other <i>Pseudomonas</i> spp.	3	6.3

Yaygın AB kullanımı
YBU Kolonizasyonu..



ABD Askeri Personeli ve *Acinetobacter* spp.



- Mart 2003'de ilk olgu
- Landstuhl Regional Medical Center (Almanya)
- Walter Reed Army Medical Center (ABD)
- İnfeksiyonlar kabul edildiğinde ya da sonradan ortaya çıktı.

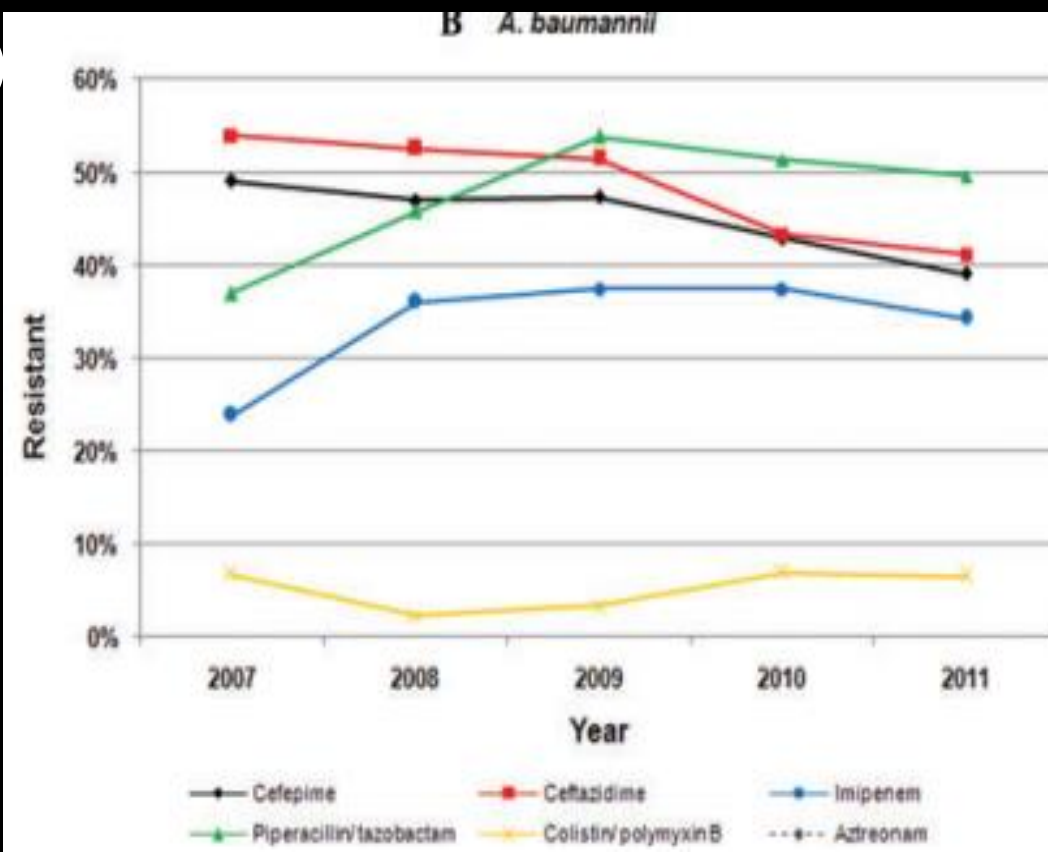
Recent trends in resistance to cell envelope–active antibacterial agents among key bacterial pathogens

Ronald N. Master,¹ Jennifer Deane,² Carol Opiela,² and Daniel F. Sahm²

¹Quest Diagnostics, Chantilly, Virginia. ²Eurofins Medinet, Chantilly, Virginia

Address for correspondence: Carol Opiela, Eurofins Medinet–Microbiology, 14100 Park Meadow Dr., Chantilly, VA 20151. carolopiela@eurofins.com

- The Surveillance Network (USA)
- 217 farklı bölge laboratuvarı
- 108.747 tanımlanmış izolat
- 2007-2011 arasında;
- IMP % 23.9'dan %34.3'e
- PIPTAZ %37'den %49.7'e





Review

Emergence of resistance to carbapenems in *Acinetobacter baumannii* in Europe: clinical impact and therapeutic options

Marie Kempf, Jean-Marc Rolain*

Aix-Marseille University, URMITE CNRS-IRD, UMR 6236, Faculté de Médecine et de Pharmacie, Université de la Méditerranée, 27 Bd. Jean Moulin, 13385 Marseille cedex 05, France

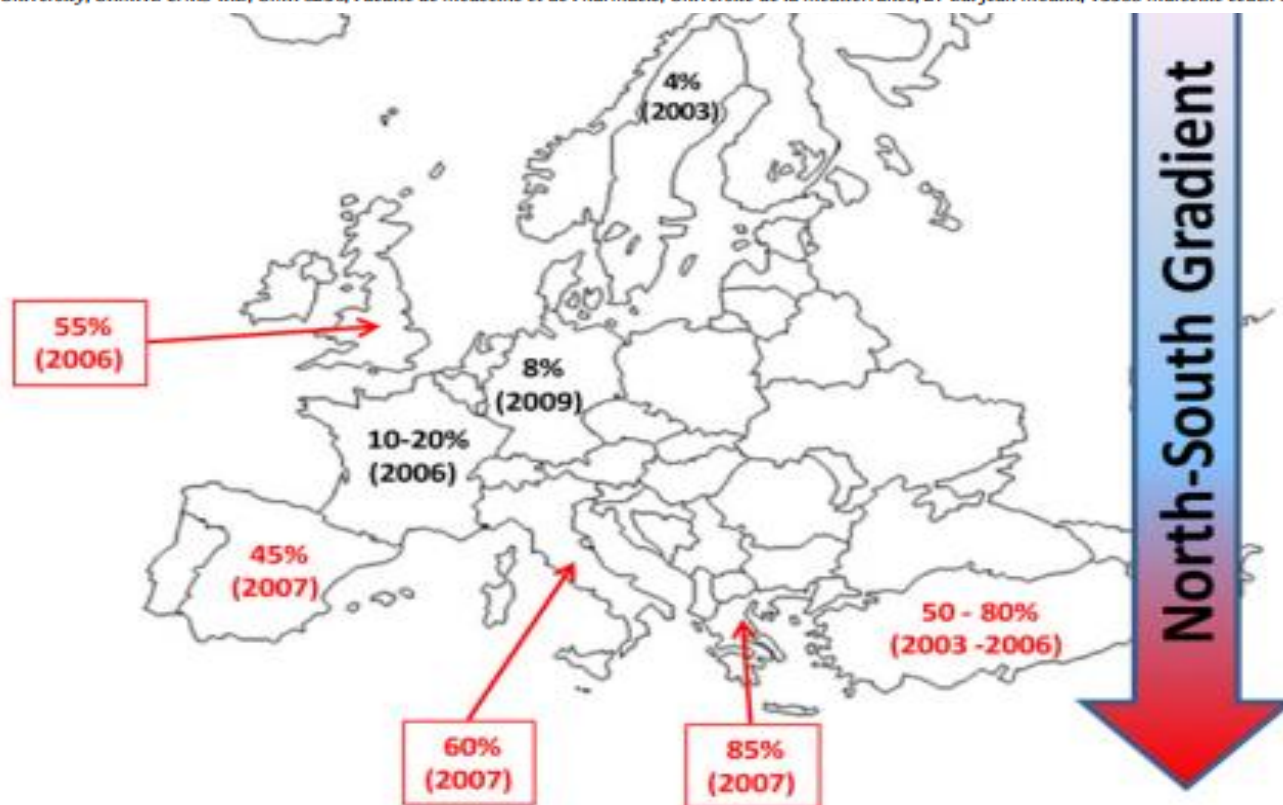
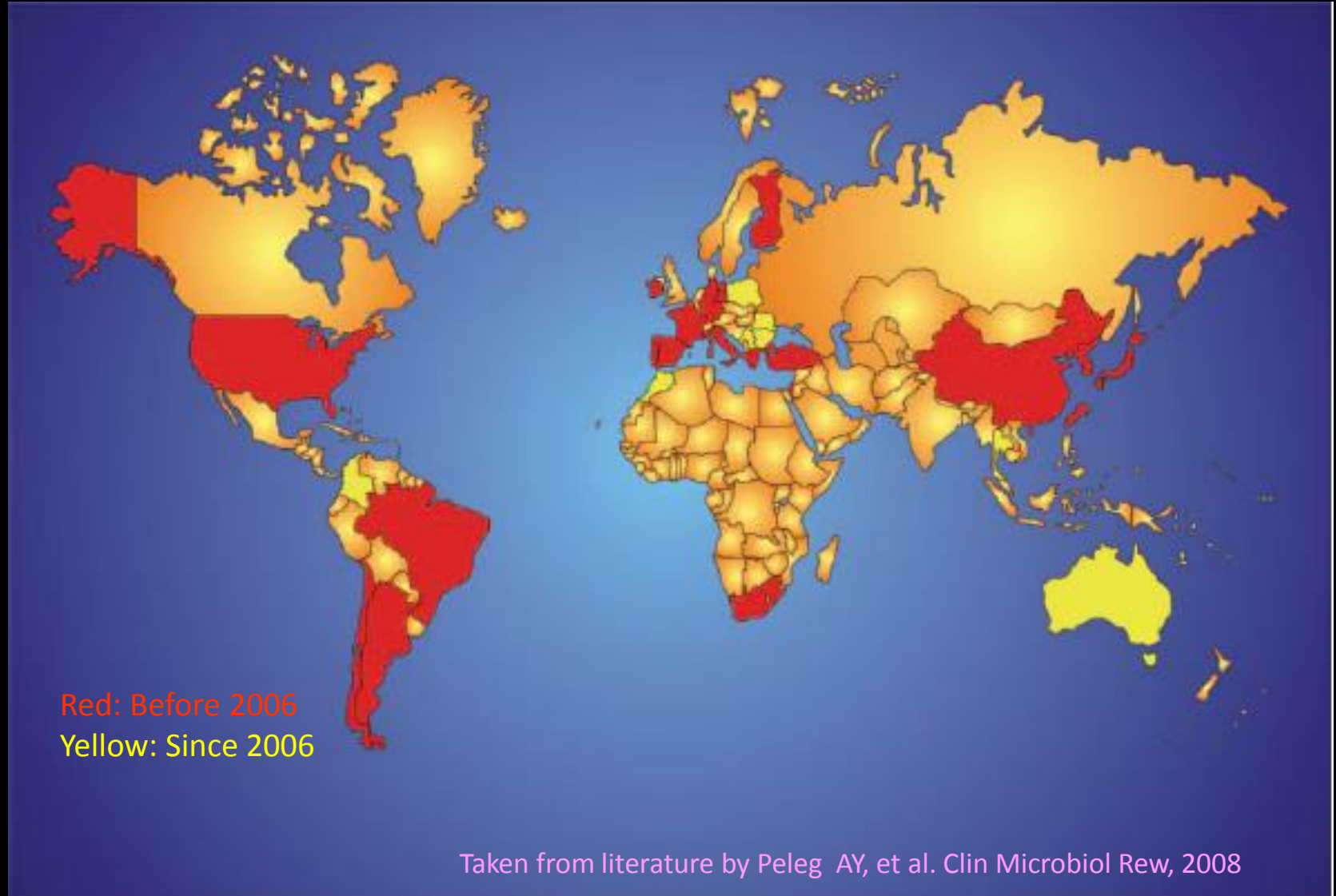


Fig. 3. The north to south gradient of prevalence of resistance to carbapenems in *Acinetobacter baumannii* in Europe (1997–2008)

Dünyada Karbapeneme Dirençli *A.baumannii* Dağılımı



Acinetobacter baumannii ile İlgili Klinik Çalışmaların Seyri

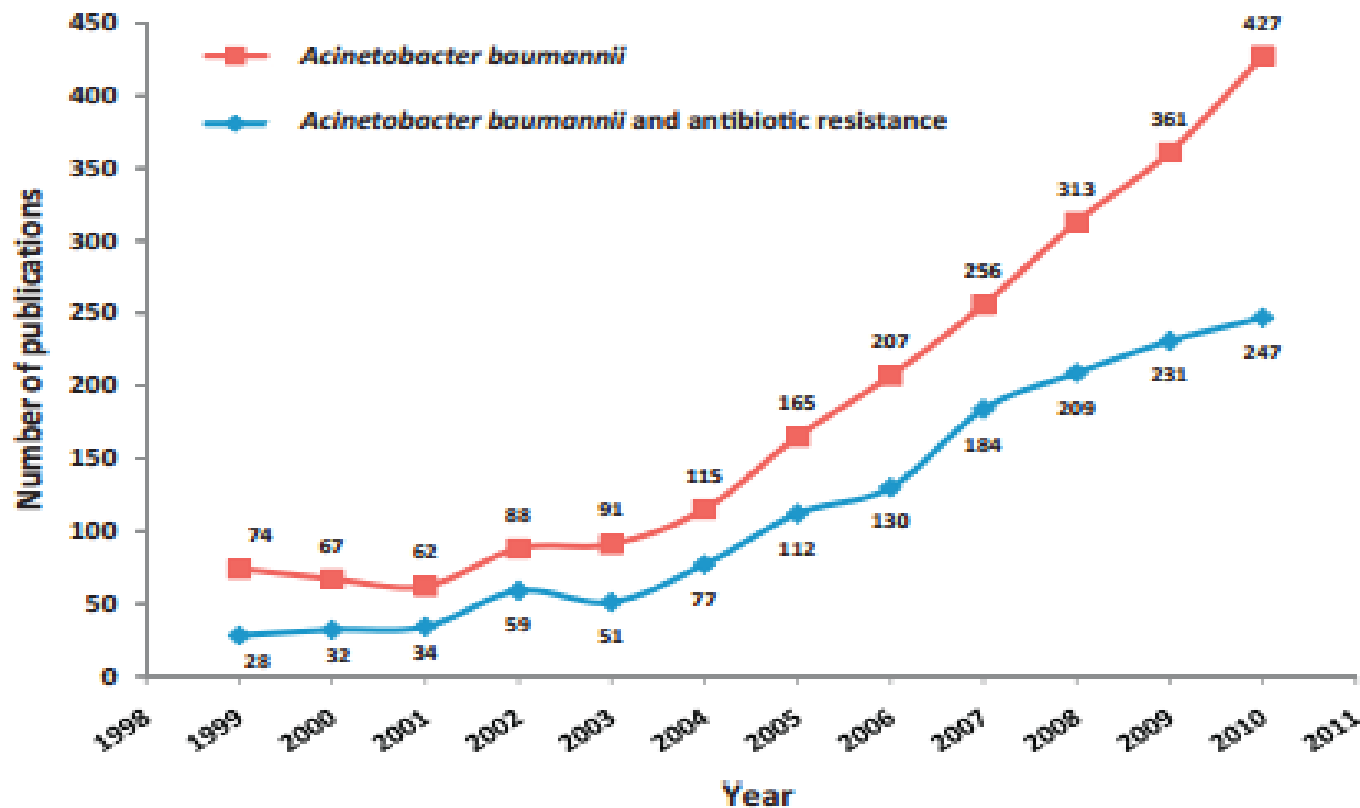
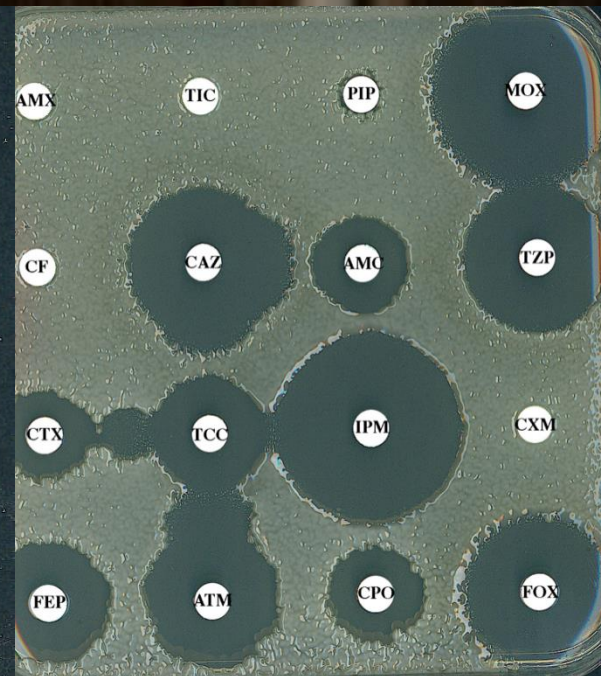
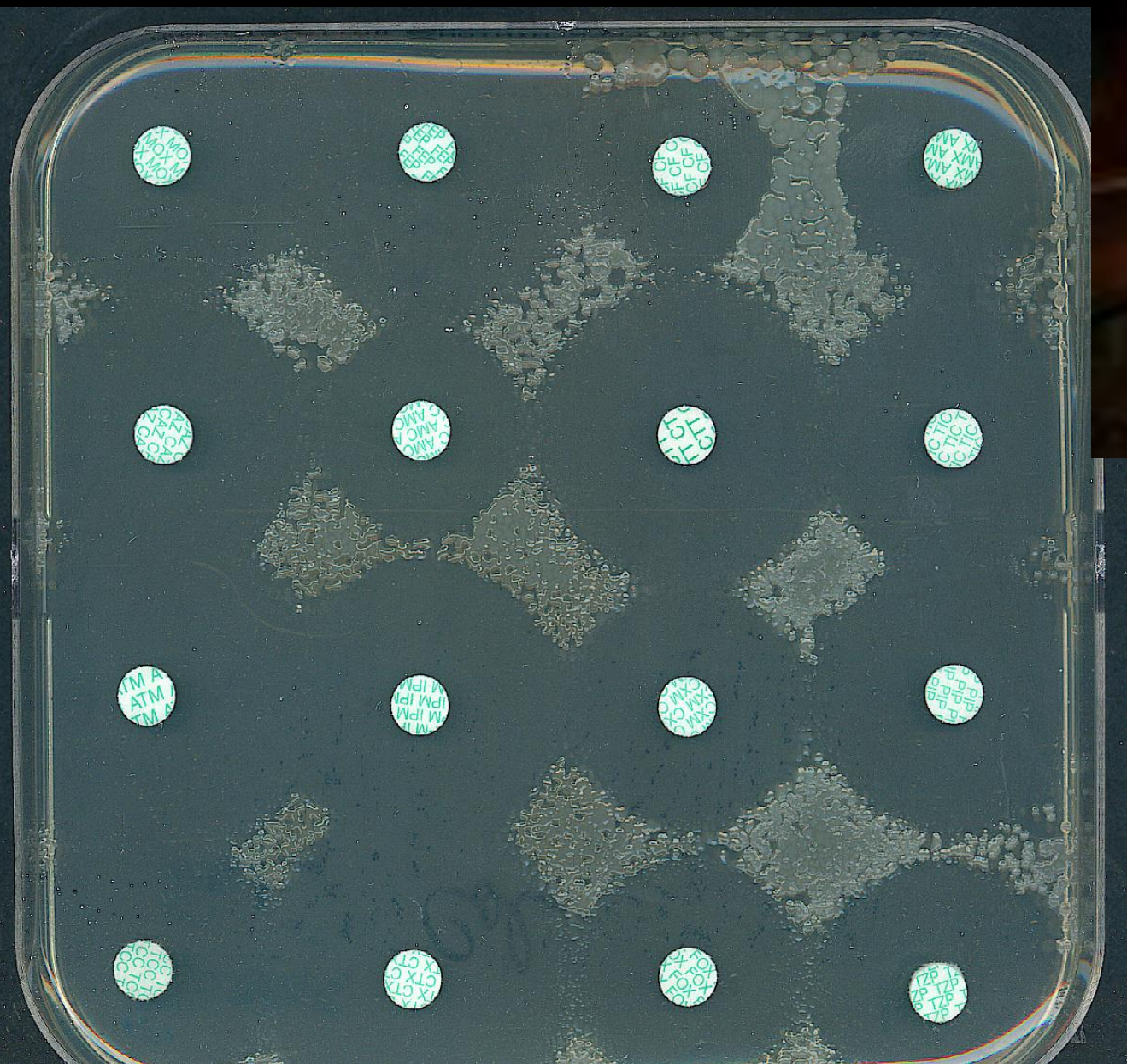
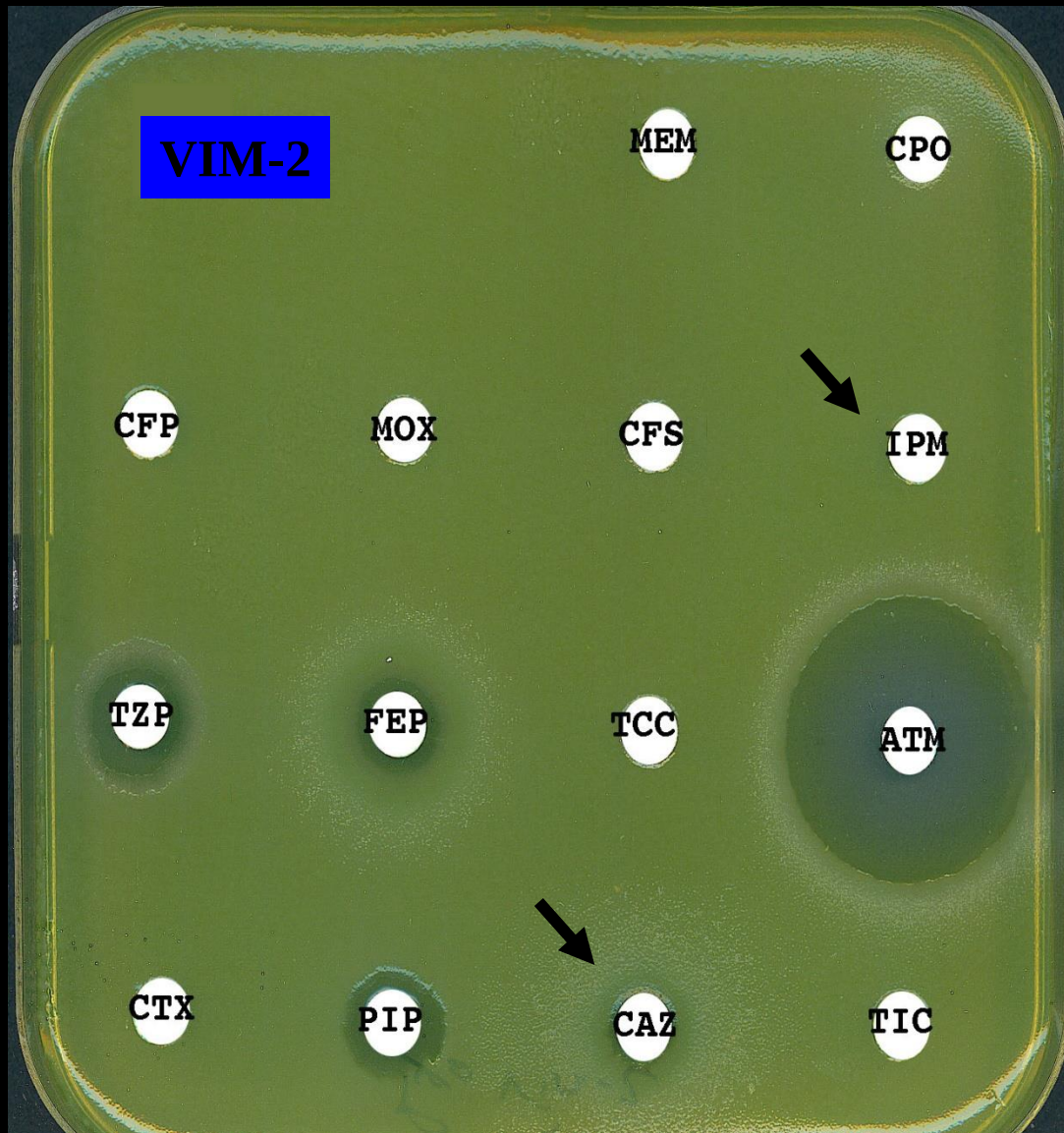


Fig. 1. Number of citations found in PubMed from 1999 to the end of 2010 using either '*Acinetobacter baumannii*' or '*Acinetobacter baumannii* and antibiotic resistance'.



Metallo- β -lactamases



- Spectrum
- Genetic background; plasmids, transposons, integrons...
- Associated resistance





ScienceDirect



Review

Emergence of *Staphylococcus aureus* clinical impact

Marie Kempf, Jean-Marc Rolain

Aix-Marseille University, URM106, Marseille, France

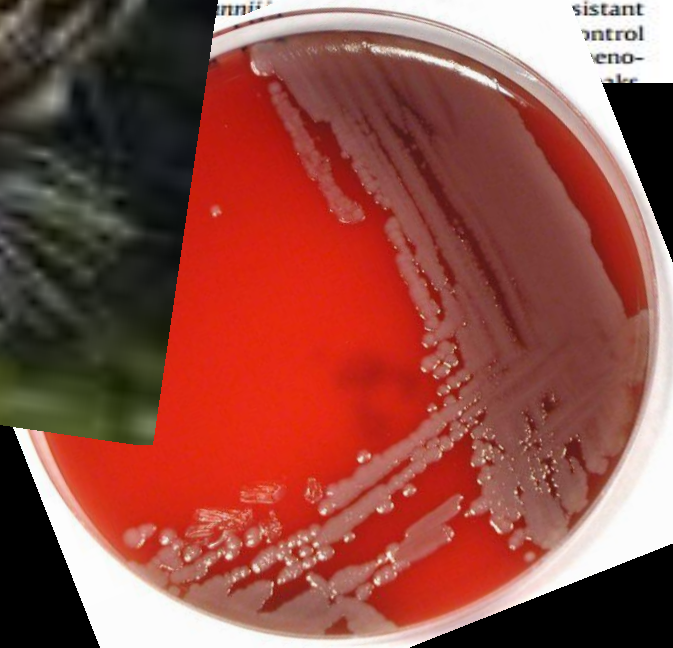
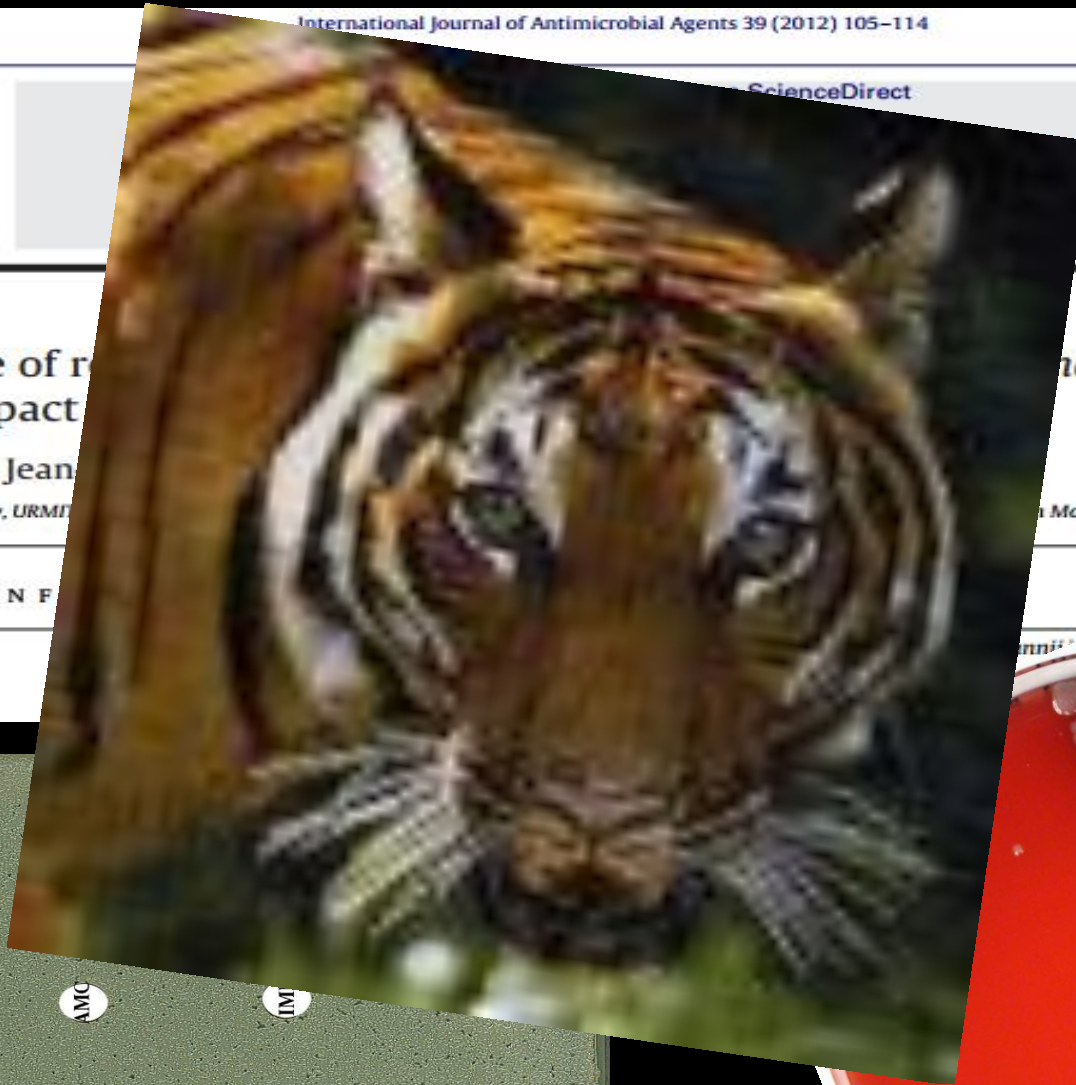
Staphylococcus aureus in Europe:

in Moulin, 13385 Marseille cedex 05, France

ARTICLE INFO

Keywords:
Colistin
Carbapenemase
Fitness cost

Resistant
control
veno-
sclerosis



ESKAPE Patojenler

- *Enterococcus faecium*
- *Staphylococcus aureus*
- *Klebsiella pneumoniae*
- *Acinetobacter baumannii*
- *Pseudomonas aeruginosa*
- *Enterobacter spp.*



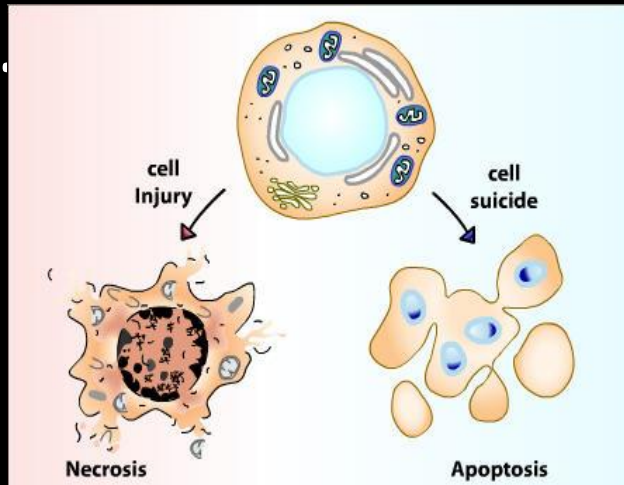
NEDEN ?

A.baumannii Patogenezinde Yenilikler

- Pathogen-Associated Molecular Pattern (PAMPs)
 - Proinflammatuar aktivite (NF- κ B ve MAPK pathway)
 - Macrophage Inflammatory Protein-2 (MIP-2)
 - Monocyte Chemoattractant Protein (MCP-1)
 - Keratinocyte-Derived Chemokines (KC/IL-8)
 - TNF-alfa, IL-1 beta, IL-6
- Lipopolisakkarid
 - Lipid A
 - Core Polysaccharide
 - O antigen
- TLR2 ve Antiinflammatuar etkinlik

Acinetobacter baumannii ve Yüksek İnvazyon Kapasitesi

- Farklı hücre tiplerine adezyon özelliği
- Türlerle ve hücre tipine göre farklılık
- Doku hücrelerinde sitotoksik etki
- Caspase-3, 8, 9 ve poly(ADP-ribose) polymerase
- Apoptoz ..



Microreview

Host–microbe interactions that shape the pathogenesis of *Acinetobacter baumannii* infection

Brittany L. Mortensen and Eric P. Skaar*

Department of Pathology, Microbiology and Immunology, Vanderbilt University School of Medicine, Nashville, TN 37232, USA.

Contributing to the fortitude of *A. baumannii* is its propensity to form biofilms on a number of abiotic surfaces, including catheters, ventilators, and other medical devices, enhancing bacterial transmission (Vidal *et al.*,

Patogenezin
Önemli
Ursu

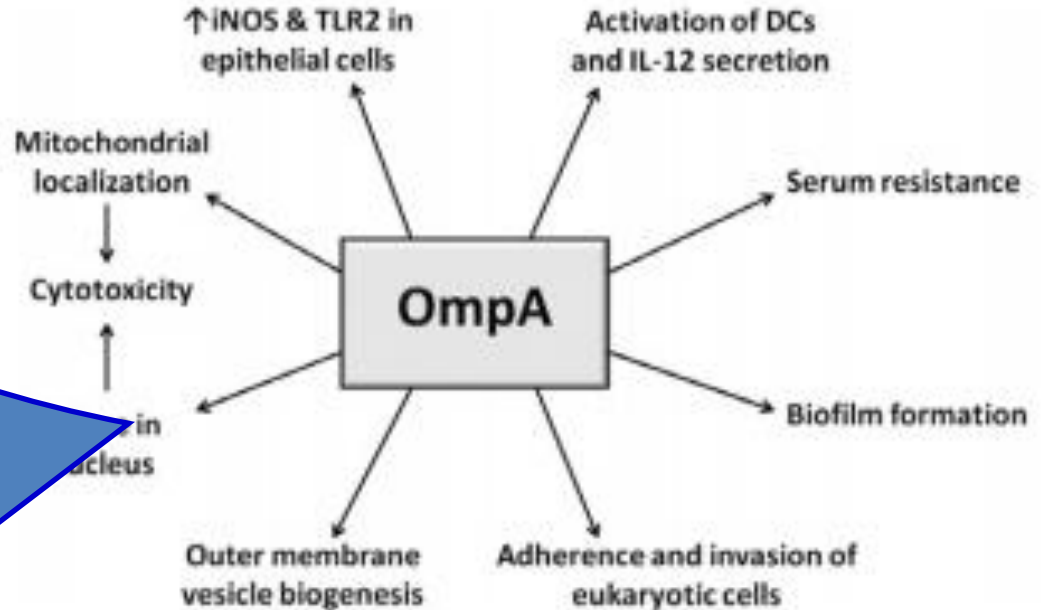
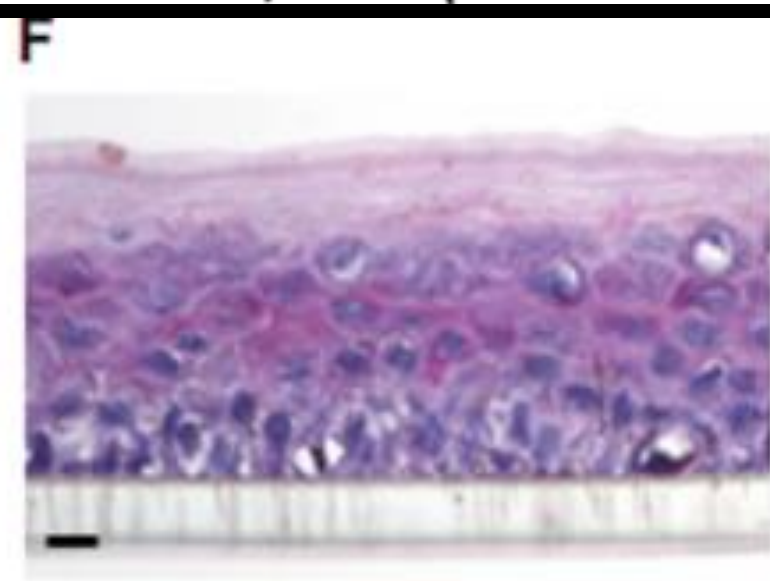
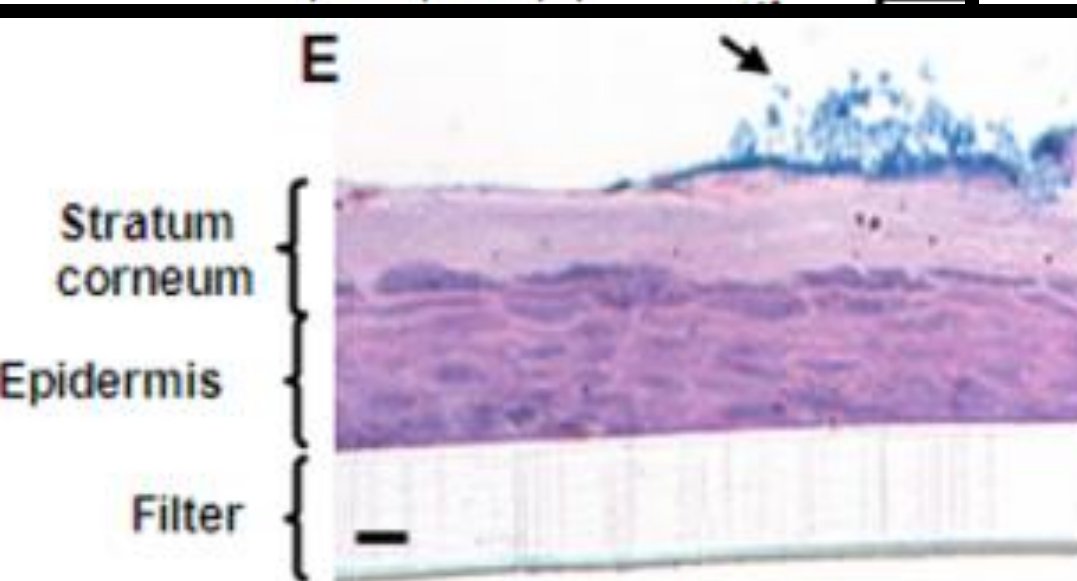
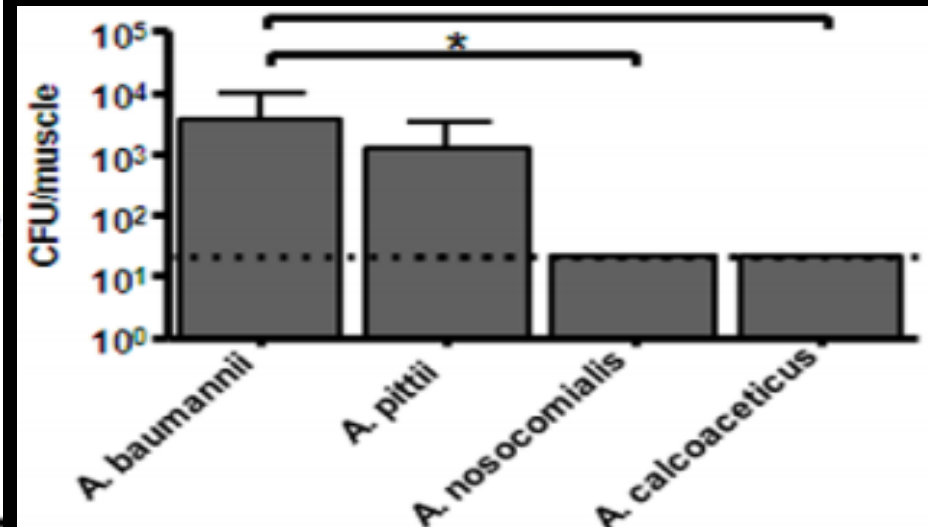
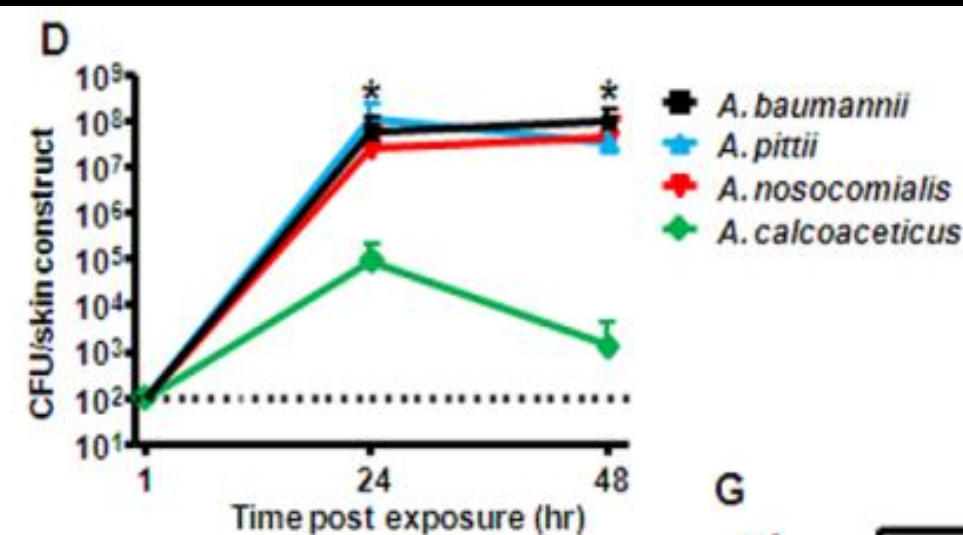


Fig. 1. Outline of the multiple contributions of *A. baumannii* OmpA to pathogenesis.

Acinetobacterlerde Virulans Kapasitesi



Acinetobacterlerde Virulans Kapasitesi

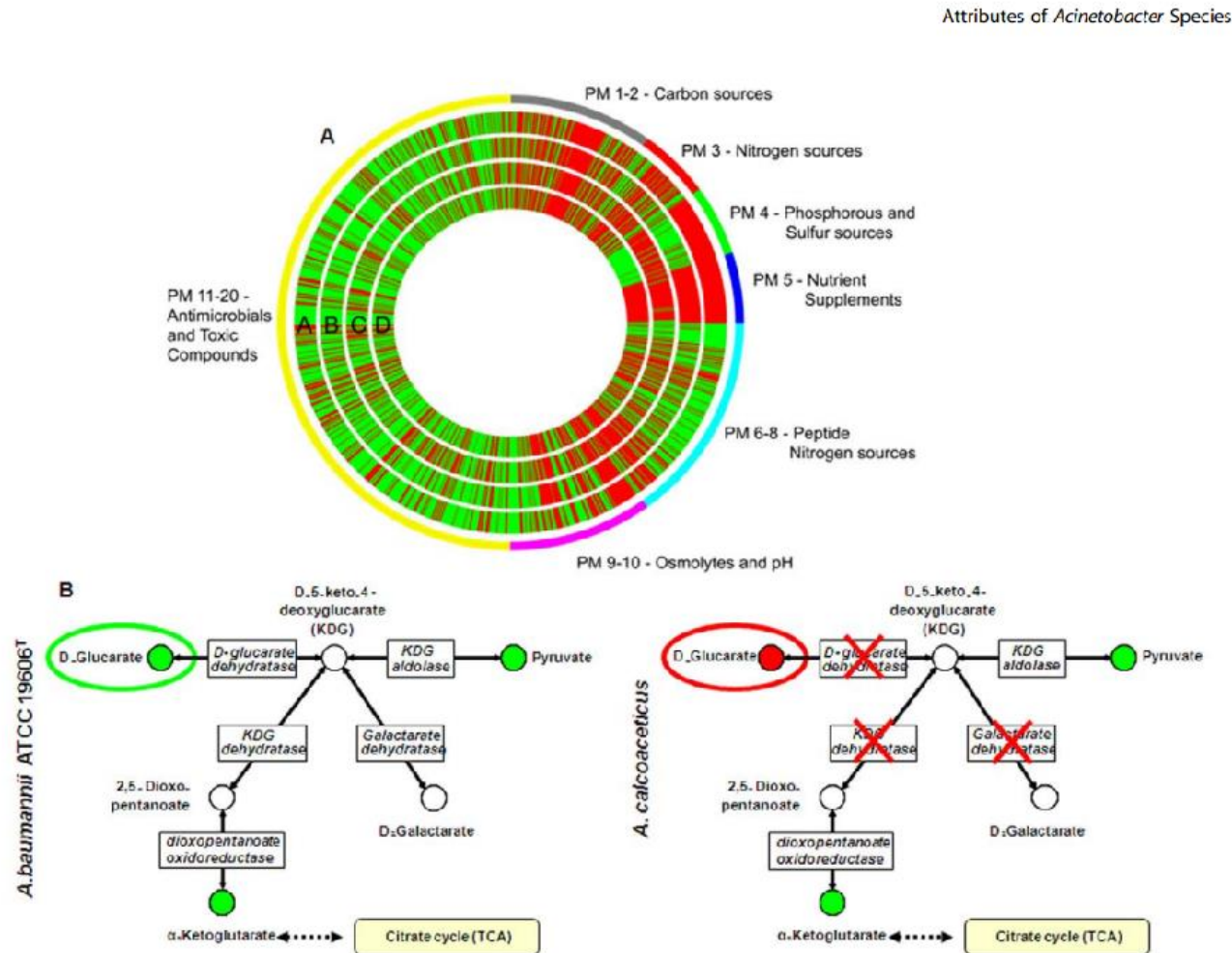


Figure 4. Metabolic diversity of specific strains of the *A. calcoaceticus* – *A. baumannii* complex. (A) Phenotype Microarray (PM) comparative results showing the number of compounds used (green) or not used (red) by *A. baumannii* ATCC 19606^T [A], *A. nosocomialis* [B], *A. pittii* [C] and *A.*

Acinetobacter baumannii ve Direnç

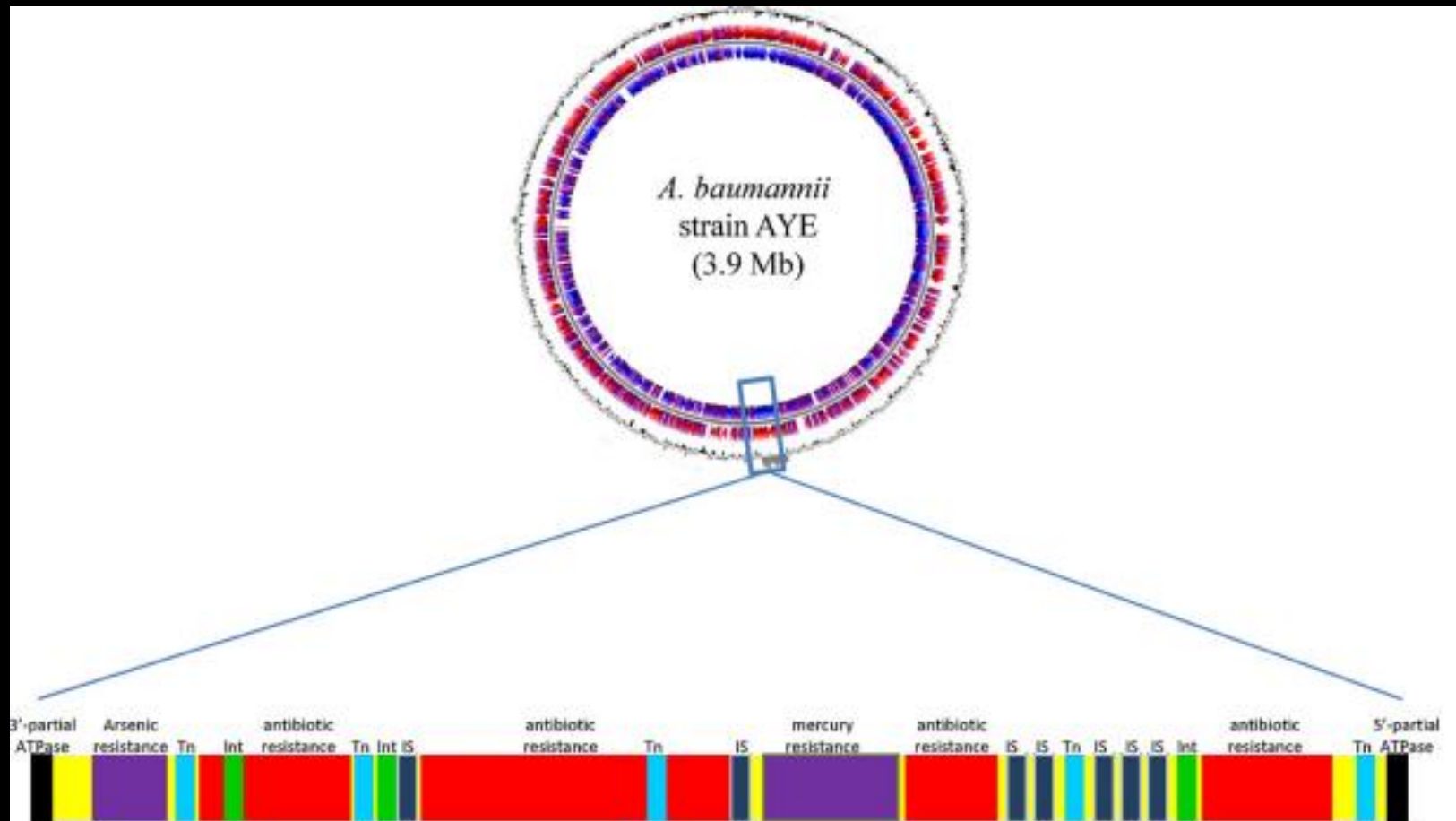
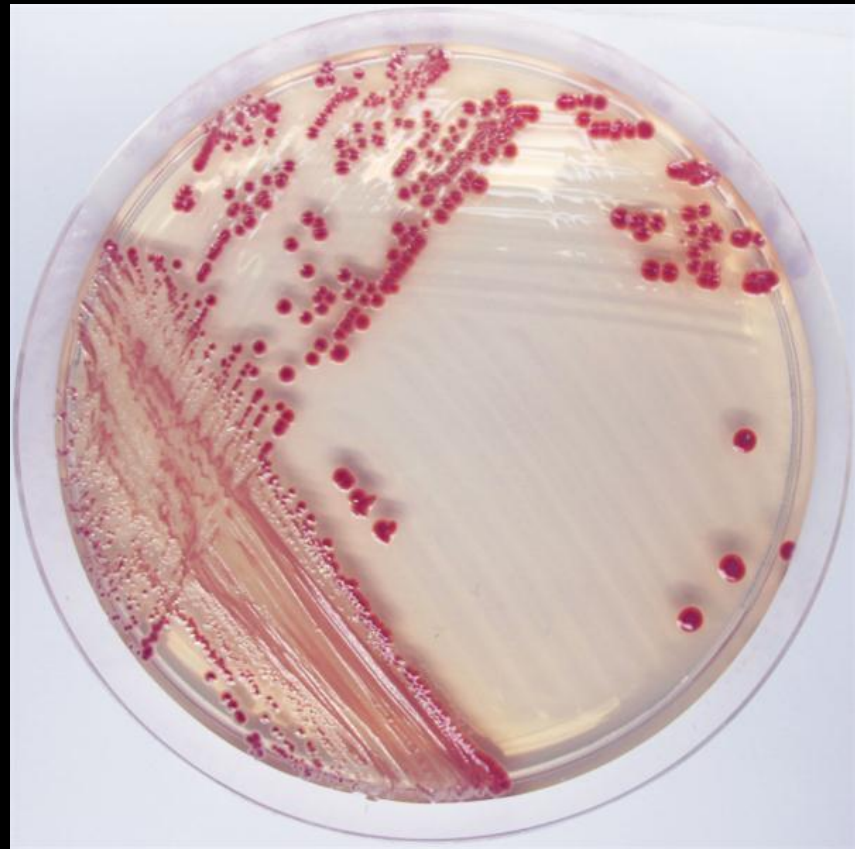


Fig. 2. Genetic context of the 86-kb resistance island in *Acinetobacter baumannii* strain AYE. Tn, transposase; Int, integrase; IS, insertion sequence.

A.baumannii'de Tanımlanmış Karbapenem Direnci ile İlişkili Genler

- OXA-23
- OXA-24
- OXA-51
- OXA-235
- OXA 236..
- OXA-58
- imp
- vim
- adeB





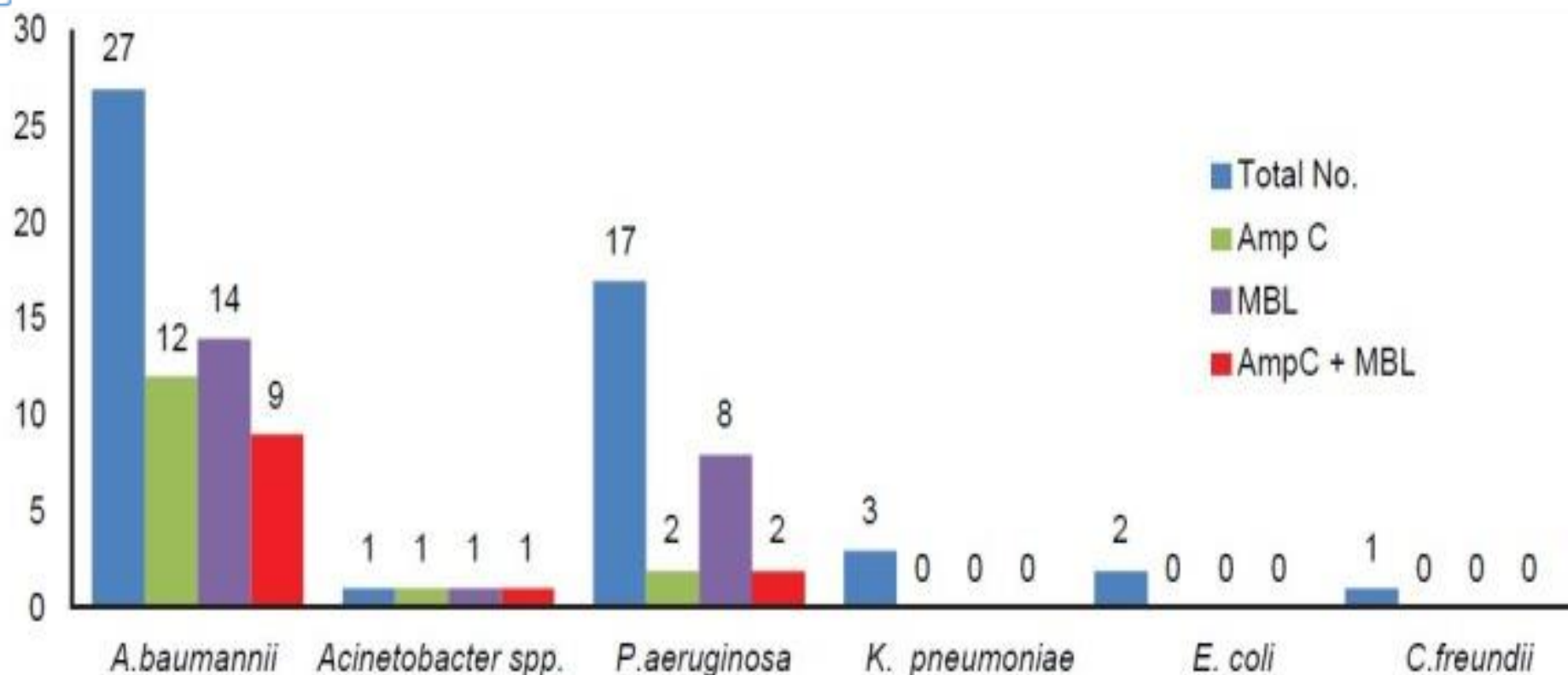
Indian J Anaesth. 2012 Nov-Dec; 56(6): 558–562.

doi: [10.4103/0019-5049.104575](https://doi.org/10.4103/0019-5049.104575)

PMCID: PMC3546243

Ventilator associated pneumonia in a medical intensive care unit: Microbial aetiology, susceptibility patterns of isolated microorganisms and outcome

[Varun Goel](#), [Sumati A Hogade](#), and [SG Karadesai](#)





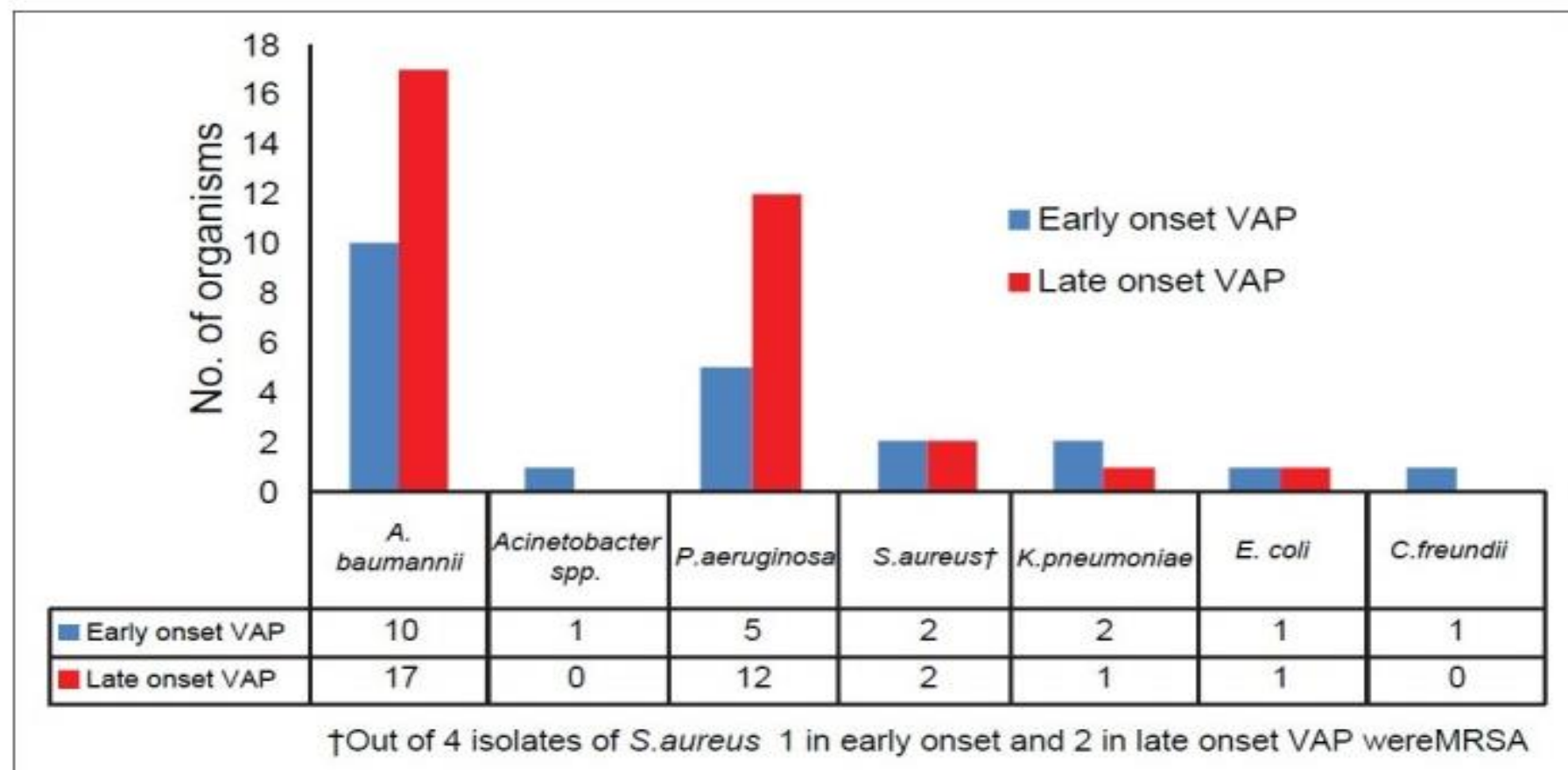
Indian J Anaesth. 2012 Nov-Dec; 56(6): 558–562.
doi: [10.4103/0019-5049.104575](https://doi.org/10.4103/0019-5049.104575)

PMCID: PMC3546243

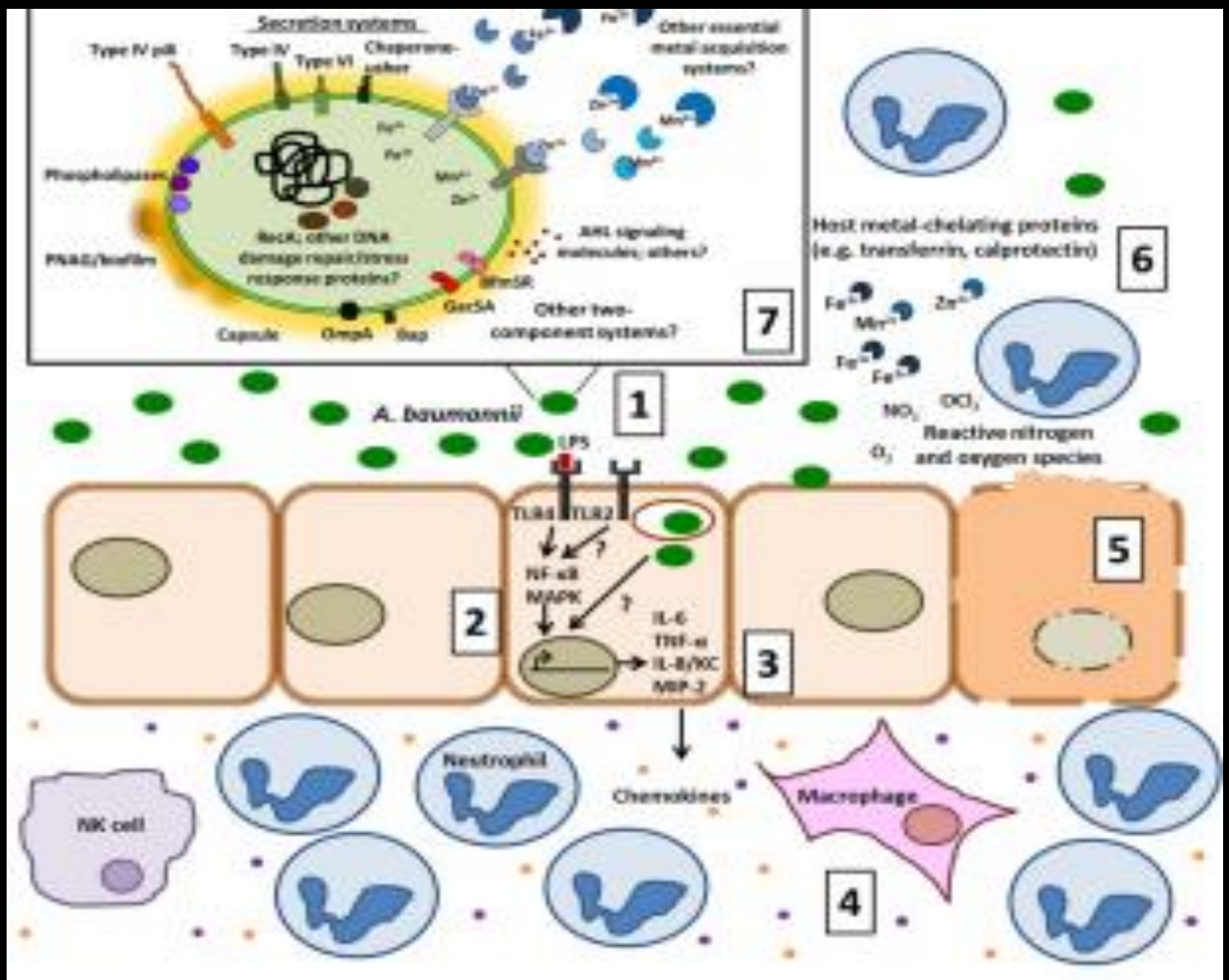
Ventilator associated pneumonia in a medical intensive care unit: Microbial aetiology, susceptibility patterns of isolated microorganisms and outcome

Varun Goel, Sumati A Hogade, and SG Karadesai

Figure 1

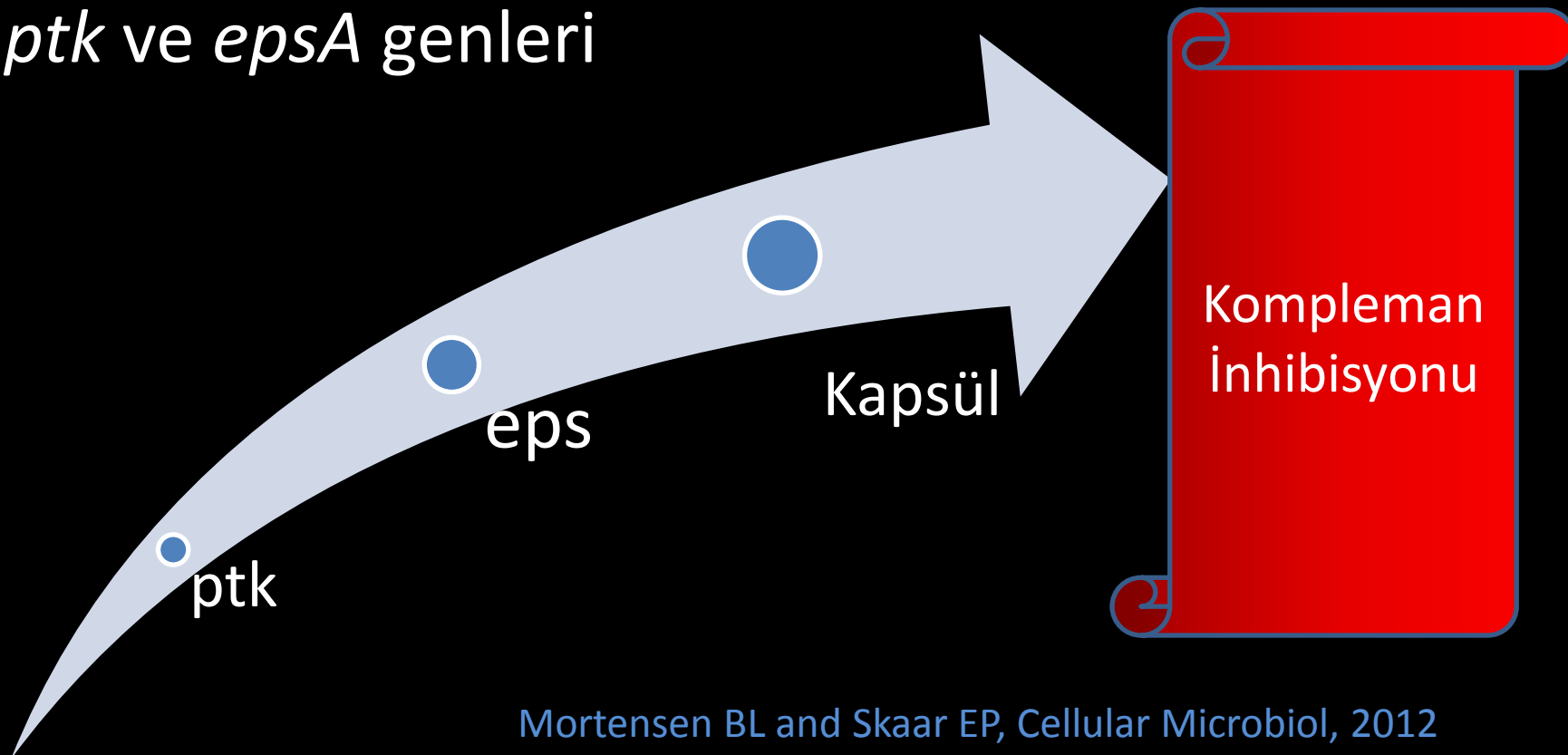


Organisms causing VAP (Early and late onset VAP)

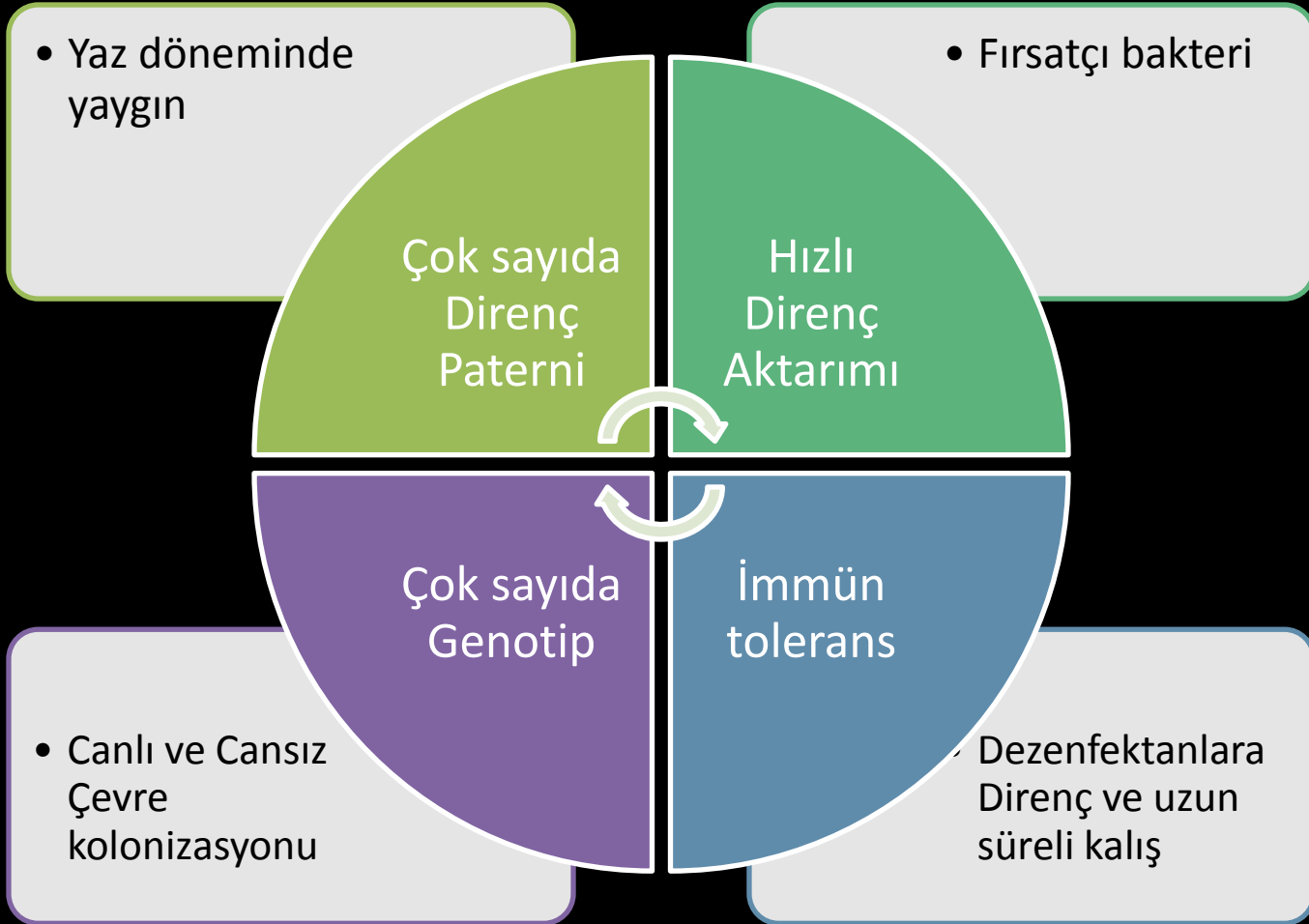


A.baumannii ve Kompleman Sistemi

- Alternatif Yolun inhibisyonu (Faktör H)
- *ptk* ve *epsA* genleri



Epidemiyoloji



Seasonal Variation of Acinetobacter Infections: 1987–1996

L. Clifford McDonald,^a Shailen N. Banerjee,
William R. Jarvis, and the National Nosocomial
Infections Surveillance System

From the Centers for Disease Control and Prevention, Public Health
Service, US Department of Health and Human Services,
Atlanta, Georgia

To determine whether nosocomial infections due to *Acinetobacter* species have increased over the past 10 years and whether infections continue to have a pronounced seasonal variation, we analyzed infections reported by hospitals in the National Nosocomial Infections Surveillance System that performed adult and pediatric intensive care unit surveillance from

- 3447 *Acinetobacter* infeksiyonu (1987-1996)
- Yaz aylarında *Acinetobacter* infeksiyonlarında artış..
- Daha sıcak ve nemli ortam ısısı..

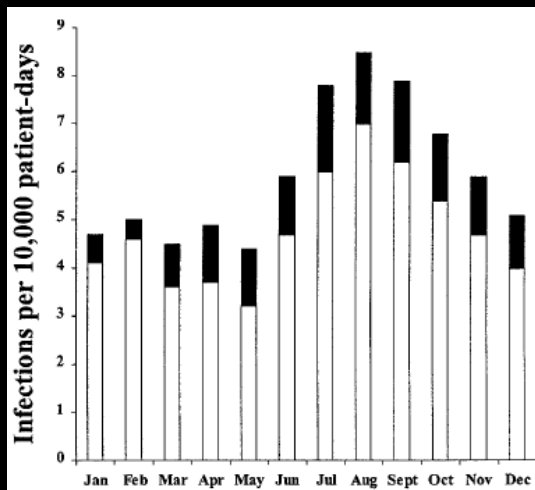


Figure 2. Monthly incidence density of acinetobacter infections: intensive care unit surveillance component, National Nosocomial Infection Surveillance System, 1987–1996 (white bars, *A. baumannii*; black bars, all other *Acinetobacter* species).

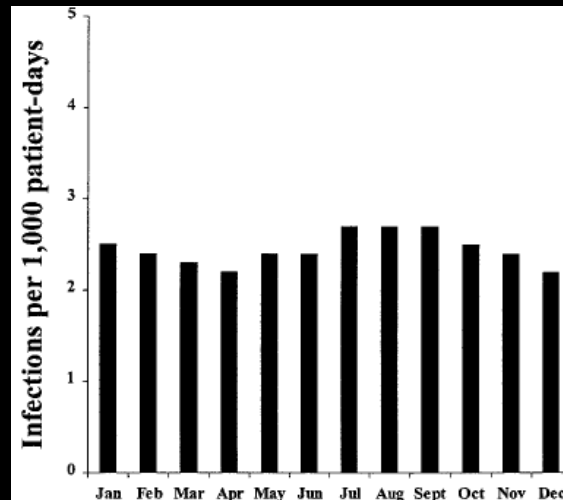
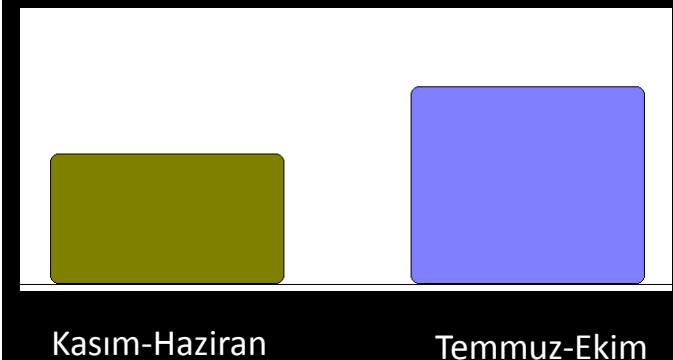


Figure 5. Monthly incidence density of *Pseudomonas aeruginosa* infections: intensive care unit surveillance component, National Nosocomial Infection Surveillance System, 1987–1996.

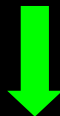


Surveillance Cultures and Duration of Carriage of Multidrug-Resistant *Acinetobacter baumannii*[∇]

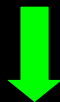
Dror Marchaim,^{1*} Shiri Navon-Venezia,¹ David Schwartz,² Jalal Tarabeia,¹ Iris Fefer,¹
Mitchell J. Schwaber,¹ and Yehuda Carmeli¹

*Division of Epidemiology, Tel-Aviv Sourasky Medical Center, 6 Weizmann St., Tel-Aviv 64239, Israel,¹ and
Clinical Microbiology Laboratory, Tel-Aviv Sourasky Medical Center, 6 Weizmann St., Tel-Aviv 64239, Israel²*

- Uzamış kolonizasyon..



- 42 ay
- Hastaların %17'si



- *Acinetobacter* sp. ENDEMİK KAREKTER

Toplum Kaynaklı A.baumannii Pnömonileri

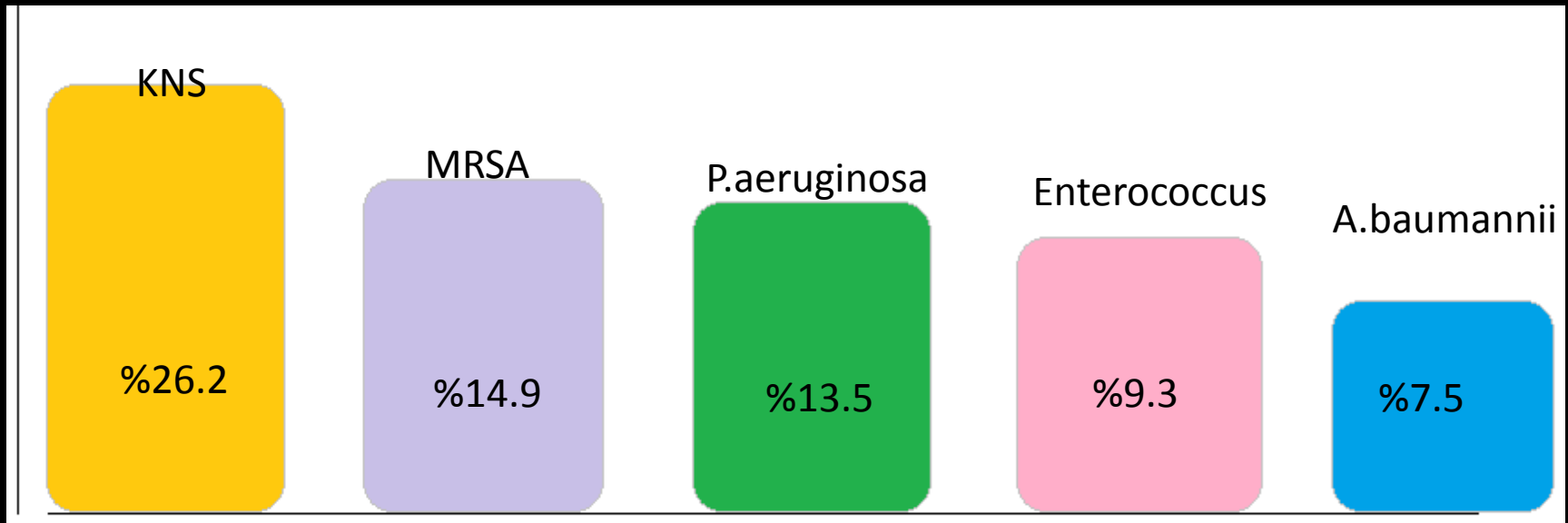
- Ani başlangıçlı, hızlı seyirli,
- Solunum yetmezliği ve hemodinamik bozukluk
- Septik şok olguların yaklaşık 1/3'ünde
- Güneydoğu Asya'da daha yaygın
- Alkolik ve immünsupressiflerde daha yaygın
- AB direnç geliştirme potansiyelleri çok yüksek

MDR Patojenler ve Maliyet..

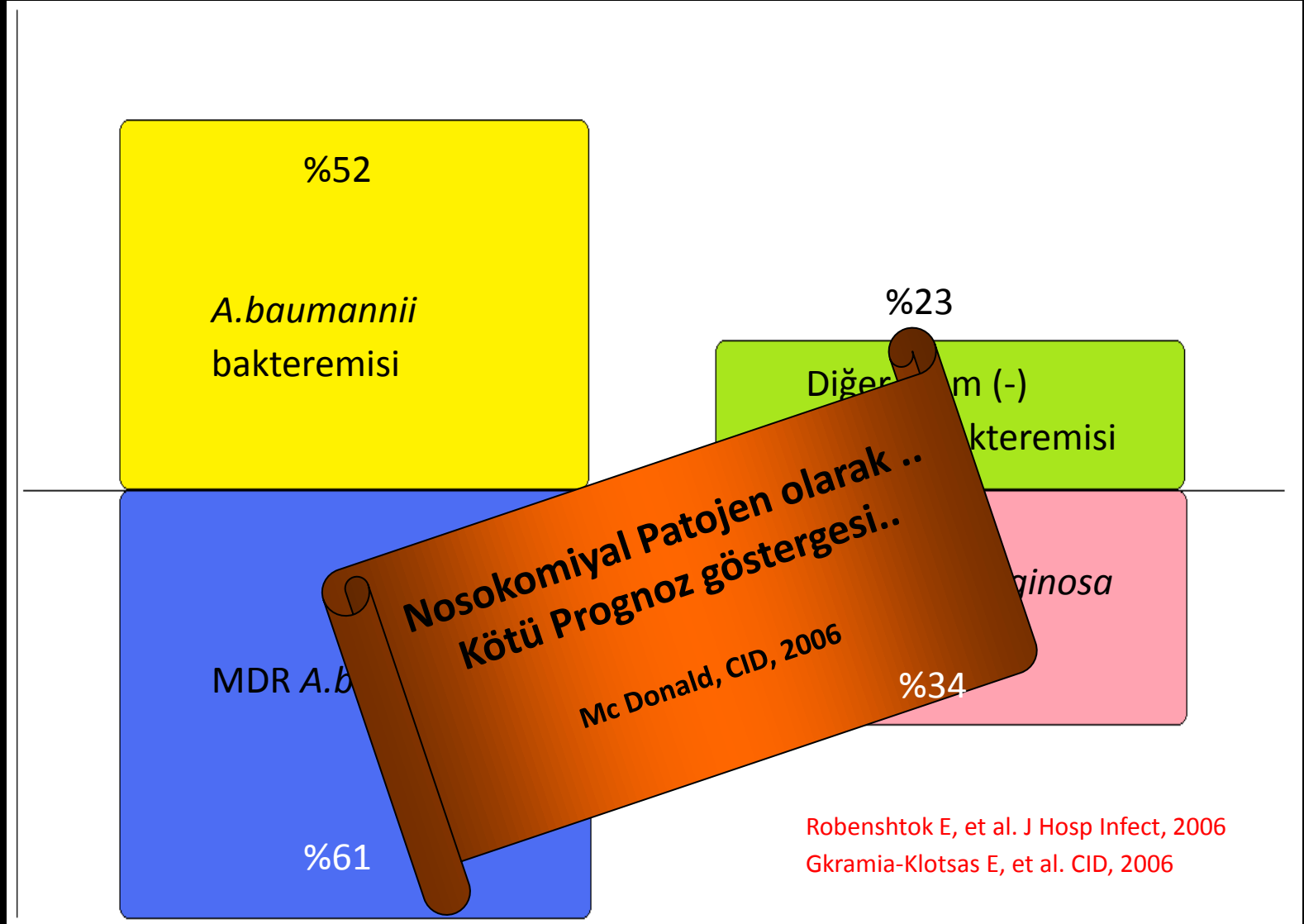
MDR Patojen	Çalışma Sayısı	Ortalama Maliyet (USD)
<i>A.baumannii</i>	24	58.457 – 85.299
GSBL (+) Enterik bakteri	8	1584-30.093
MRSA	12	1014-40.090

Acinetobacter baumannii ve Mortalite

- Kan dolaşım sistemi enfeksiyonları,
- 8 yıllık prospektif YBU çalışması
- 1741 hastada tarandı, 167 olguda 203 KDE
- Mortalite en fazla Ab suşlarında (%37.5) ve Candida sp. (%30)



Acinetobacter infeksiyonları Niçin Daha Tehlikelidir?



Risk Factors for Mortality in Patients with Carbapenem-Resistant *Acinetobacter baumannii* Bacteremia: Impact of Appropriate Antimicrobial Therapy

Table 3. Risk factors associated with 14-day mortality in patients with *Acinetobacter baumannii* bacteremia

Risk factors	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Age ≥ 60 yr	1.48	0.61-3.6	0.38			
Diabetes mellitus	2.45	0.90-6.66	0.07			
Malignancy	1.72	0.72-4.13	0.21			
Mechanical ventilator	5.77	2.22-15.0	< 0.001	1.59	0.39-6.41	0.51
Central venous catheter	4.02	1.37-11.8	0.01	3.53	0.68-18.2	0.13
APACHE II score ≥ 14	4.01	1.39-11.4	0.01	1.67	0.36-7.79	0.5
Septic shock	5.61	2.13-14.7	< 0.001	10.5	1.93-57.4	0.006
CR	9.14	2.86-29.2	< 0.001	7.29	1.57-33.8	0.01
Pneumonia as a source of bacteremia	5.05	1.94-13.0	0.001	5.29	1.07-26.1	0.04
Inappropriate antibiotic therapy	6.58	2.53-17.1	< 0.001	8.05	1.65-39.2	0.009

OR, odds ratio; CI, confidential interval; CR, carbapenem-resistance.

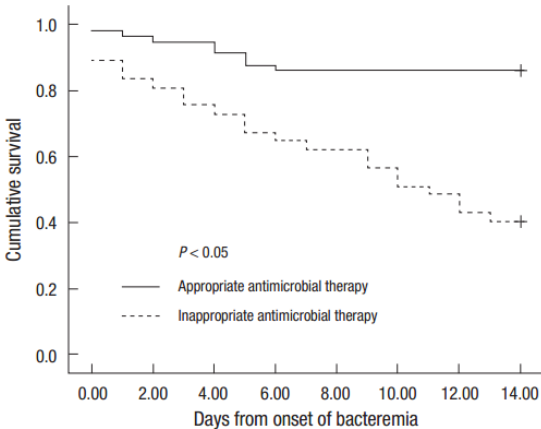


Fig. 1. Survival curve according to the appropriateness of antimicrobial therapy.

MDR Acinetobacter ve Mortalite ile ilişkili Risk Faktörleri

- Pub Med Veri Tabanı
- Key words: Risk factors, mortality, acinetobacter
- 2012 ve 2013 yılında yapılmış 31 klinik çalışma
- Multivariate Logistic Regression Analysis

MDR A.baumannii Enfeksiyonlarında Mortalite ile İlişkili Risk Faktörleri	Çalışma Sayısı	OR (Max-min)
Septik Şok	28	9.6-1.4
Önceden antibiyotik kullanımı	27	7.7-0.8
Mekanik ventilasyon	13	15.2-1.4
APACHE II Skoru >21	7	5.6-0.9
Uygunsuz antibiyotik kullanımı	5	8.1-1.6

Karbapenem Kullanımı *A.baumannii*'de Antibiyotik Direnç Artırıyor mu?

- Karbapenem kullanımı ile antibiyotik direnç
- Günlük tanımlanmış (DDD), 2001-2009
- WHO Therapeutic Chemical Classification Index

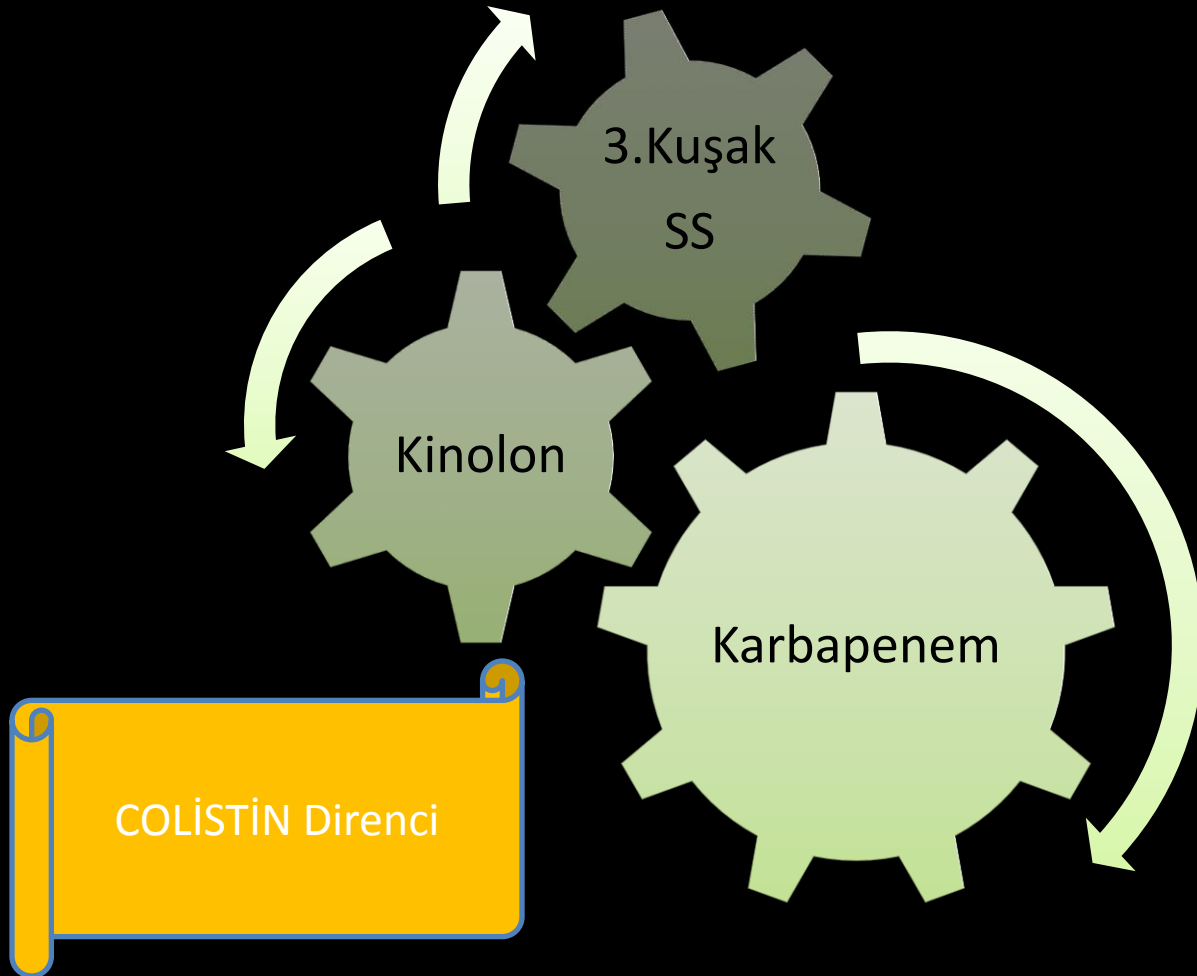
**MULTIDRUG
RESISTANCE**

IMP, MEM ve Total Karbapenem Kullanımı

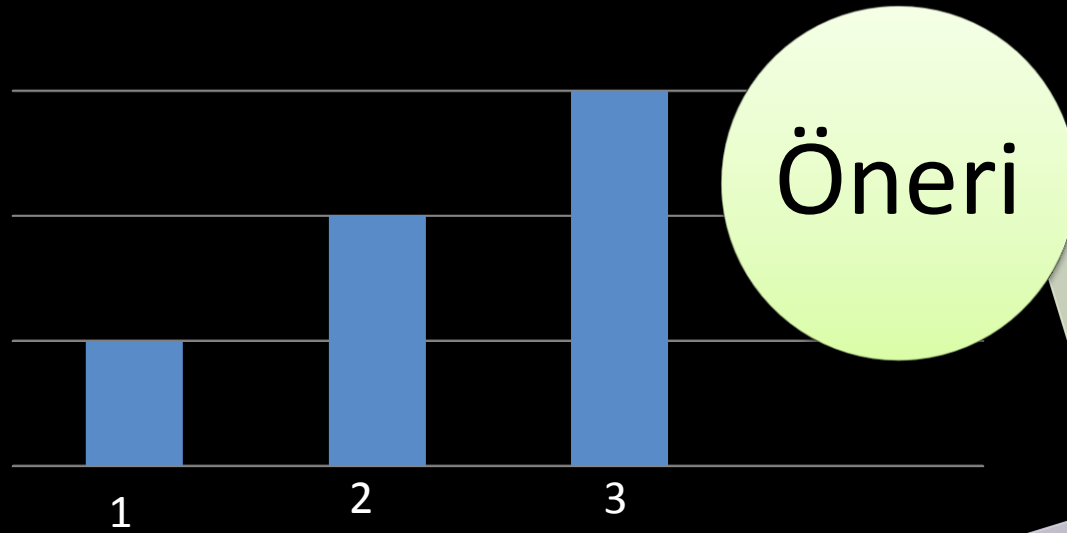
IMP Direnci ($r=0.818$), MEM Direnci ($r=0.900$)

PIP/TAZ, Ceftazidim, Cefepim, Amikasin,
Levofloksasin

Acinetobacter baumannii ve Antibiyotik Direnci



Colistin Dirençli A.baumannii Suşlarını Nasıl Tedavi Etmeliyiz?



Öneri

Col+VA

Col+Dor+VA

Fractional Inhibitory
Concentration (FIC) Index
 <0.5

O'Hara JA, et al. Antimicrob Agents Chemother, 2013

RESEARCH ARTICLE

Open Access

Comparative activity of carbapenem testing (the COMPACT study) in Turkey

Hakan Leblebicioglu^{1*}, Nedim Cakir², Mustafa Celen³, Halil Kurt⁴, Hakan Baris⁵ and Joerg Laeuffer⁶, for Turkish COMPACT Study Group

- 2008 yılında çok merkezli
- 596 klinik izolat
- Karbapenem duyarlılıkları

**AMPIİRİK TEDAVİDE
KARBAPENEM
KULLANIMI
NE KADAR GÜVENİLİR?**

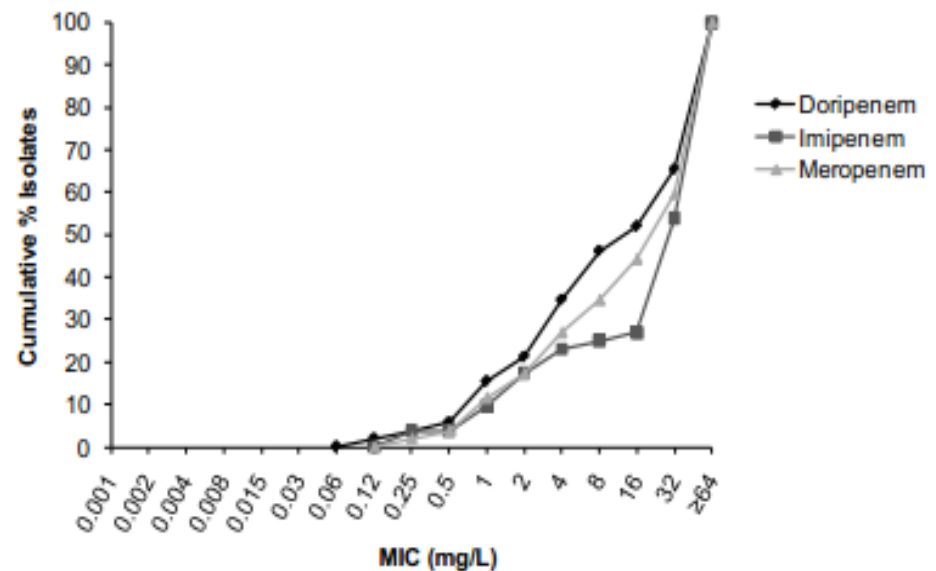
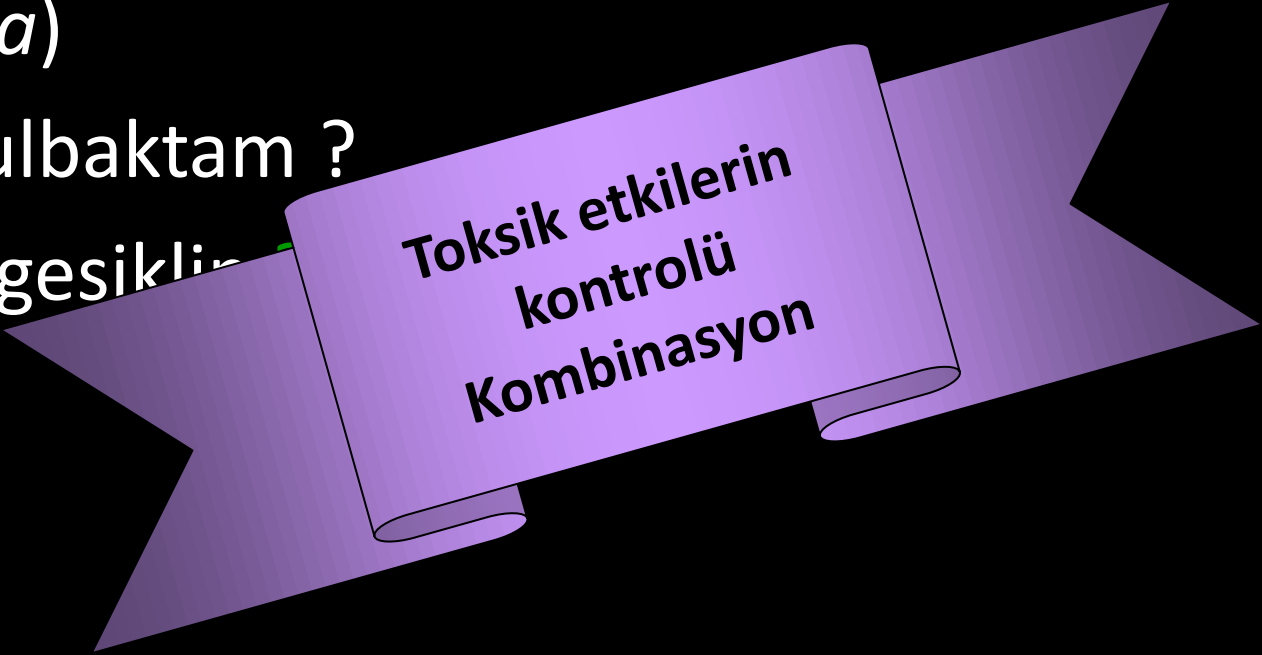


Figure 3 Cumulative% minimum inhibitory concentration (MIC) distributions against *Acinetobacter baumannii* (N = 53).



Sinerjik Etki

- Colistin + Rifampisin (MDR Acinetobacter)
- Colistin + Minosiklin (IMP-R Acinetobacter)
- Colistin + Meropenem (*A.baumannii*, *P.aeruginosa*)
- Colistin + Sulbaktam ?
- Colistin + Tigesiklin



Toksik etkilerin
kontrolü
Kombinasyon

In vitro effect of minocycline and colistin combinations on imipenem-resistant *Acinetobacter baumannii* clinical isolates

Thean Yen Tan^{1*}, Lily Siew Yong Ng¹, Eugene Tan² and Gary Huang²

¹Laboratory Medicine Services, Changi General Hospital, 2 Simei Street 3, Singapore 529889;

²Ngee Ann Polytechnic, 535 Clementi Road, Singapore 599489

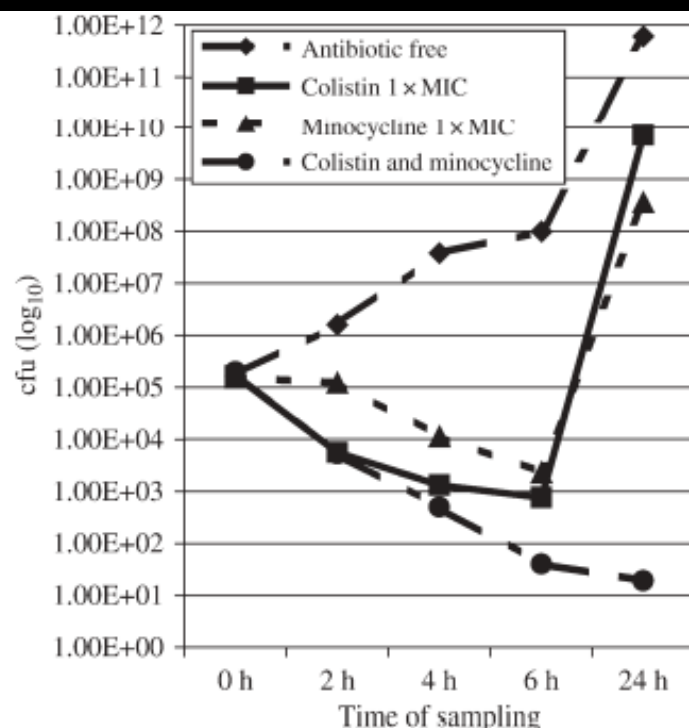
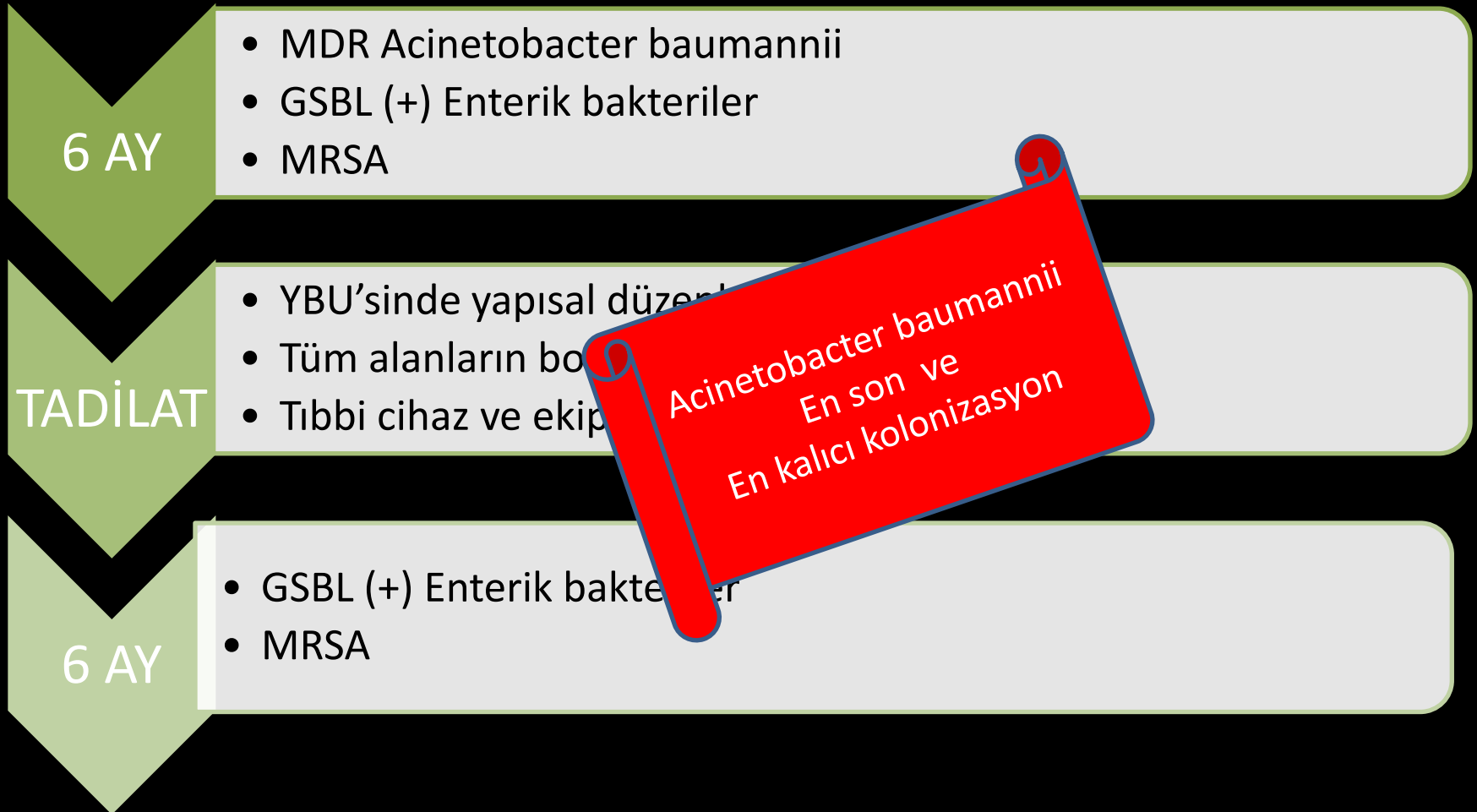


Figure 1. Time-kill curves of representative study isolate.

Table 1. Bacterial counts and synergy interpretation by time-kill methods

Antibiotic		Time of sampling after incubation			
		2 h	4 h	6 h	24 h
Colistin	average change in cfu (log ₁₀)	-0.7	-1.1	-1.0	+4.1
Minocycline	average change in cfu (log ₁₀)	-0.7	-0.7	-0.3	+3.4
Colistin and minocycline	average change in cfu (log ₁₀)	-2.2	-2.8	-3.1	-3.2
	no. (%) of isolates showing bactericidal activity	4 (31%)	7 (54%)	7 (54%)	9 (69%)
	no. (%) of isolates showing synergy	1 (8%)	2 (15%)	2 (15%)	12 (92%)

YBU'nde Yapısal Düzenleme MDR Patojenleri Ortadan Kaldırabilir mi?



Yeni Tedavi Stratejileri

- Bakteriyofaj Tedavisi
- Şelasyon ve Galyum esaslı tedaviler
- Antimikrobiyal Peptidler
- Proflaktik Aşılar ve Pasif immünizasyon
- Fotodinamik Tedaviler
- NO-bazlı Tedaviler

Faj Tedavisi

- A.baumannii için litik faj bildirimi AB1, AB2 (2010)
 - Lin NT, et al. Res Microbiol, 2010
- Phage AP22 Ab suşlarının 89/130 (%68) etkinlik gösterdi (2012)
 - Popova AV, et al. FEMS Microbiol Let, 2012
- AB7-IBBI ve AB7-ABB2 biyofilm aktivitesi ve %75 etkinlik
 - Yele AB, et al. Arch Virol, 2012



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- Faj karşıtı non-Ab türleri tarafından çabuk klirens



?

- Dirençli suşlar ve inflamasyon hücrelerin etkisi?

- Ortam ve Ab türlerine göre değişen etkinlik..

Galyum Tedavisi



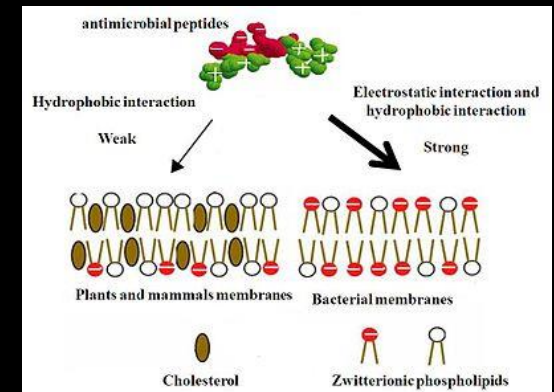
- Aynı metabolik yolak için Fe ile yarışır
- Oksidasyon-redüksiyon döngüsüne girmez
- Bakteri komponentinde inhibitör etkinlik sağlar
- Deneysel fare Ab kaynaklı pnömonilerde invivo etki
- Colistin D/R Ab'de Colistin+Galyum tedavisi (invitro)



•Standardizasyon ve in vivo çalışma gerekliliği....

Antimikrobial Peptid

- İmmün sistemin antimikrobik etkili anahtar elementleri
- Bakteri membranı ve intraselüler mekanizmalara etki
- Cecropin A-melittin hybrid peptid (PDR Ab üzerine in vitro etki)
 - Vila-Farres X, et al. Curr Med Chem, 2012
- A3-APO (MIK: >64 mg/L) Ab'de in vivo ortamda IMP'den daha güçlü etkinlik
 - Ostorhazi E, et al. Biopolymers, 2011



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- .Sürdürülebilir etkisi az, yarı ömrü kısa

Proflaktik Aşı ve Pasif İmmünizasyon

- İnaktive tam hücre aşısı, yüksek immün etki
- Aşılılarda doku bakteri yükü 5 log 10 daha düşük
- Proinflamatuvar ve postinflamatuvar sitokin düzeyi daha düşük

– McConnell MJ, et al. Infect Immun, 2011

- Pan-resistant suşlara karşı koruyucu etkinlik
- Farelerde kullanıldı, insan deneyimi yok, LPS fazla..
- Biofilm-associated protein Bap aşısı..

– Fattahian Y, et al. Microbiol Pathog, 2011

- OmpA aşısı, yüksek immünojenite ve güçlü etki.

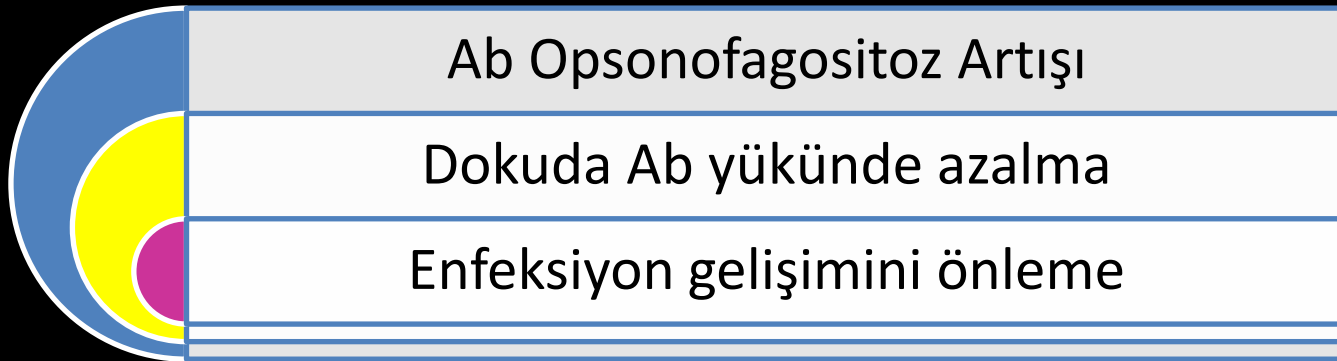
– Luo G, et al. PLoS ONET, 2012



- .Sürdürülebilir etkisi az, yarı ömrü kısa

Pasif İmmünizasyon

- Bakteri Dış Membran Transport Antikorları
- The membrane polysacharide poly-N-acetyl b (1-6 Glucosamine)

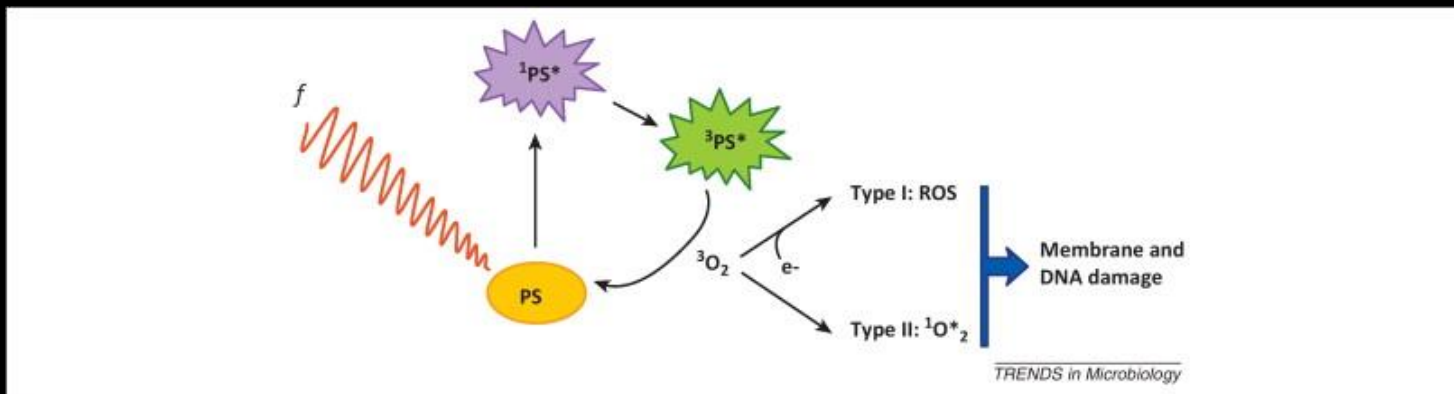


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- .Uygun antijen seçimi, sürdürülebilir immünite

Fotodinamik Tedavi

- Kanser ve oftalmolojik tedavide kullanılıyor
- MDR patojenlere karşı kullanımı yeni..
- Oksijen, görünür infrared ışık ve fotosensitizer
- Yüksek enerjili foton salımı, serbest O₂ birikimi
- Membran ve DNA hasarı, hedef hücre ölümü



NO Tedavisi

- NO hidrofobik serbest radikal özellikli yöntemdir
- Biyolojik zarla, intra ve ekstraselüler yapılara bağlanır
- Lipid peroksidasyonu ile membran harabiyeti
- NO-nanopartikül ile in vivo etkinlik, DNA hasarı



- .Tek problem topikal olarak kullanılması

Acinetobacter Kurtuluş Reçetesi ve Sonuç..

- ESKAPE bakteri sürveyansı
- Hasta izolasyonu
- Ortam temizliği
- El Yıkama

**BAŞARIYA GİDEN YOL KARARLI
ADIMLARI GEREKTİRİR..**



- Anesteziden ananımından kaçınma
- Anestezisiz hasta yatışının kaldırılması
- Fizyoterapi e MV'den erken ayırma..
- Kararlılık..

Teşekkürler....