

MSS İnfeksiyonları Menenjit- Ventrikülit Tedavi

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UÜTF-Enf Hast ve Kl Mik AD

KLİMİK-2018

Nozokomiyal Menenjit-Ventrikülit

- Travma ya da invazif işlemler sonucunda olabilir
- Klinik semptomlar hastanede yatarken ya da taburculuk sonrası veya yıllar sonra gelişebilir

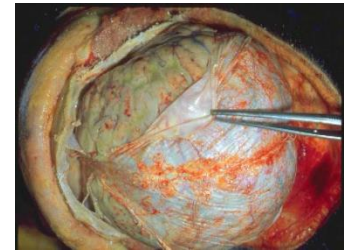
Sağlık Bakımıyla İlişkili Menenjit-Ventrikülit

=

AKUT BAKTERİYEL MENENJİTTİR

SBi MSS infeksiyonları

- Kraniyotomi %0,8-1,5
 - 1/3 ilk hafta; 1/3 2. hafta, 1/3 haftalar aylar...
- İntraventriküler katater %4-17
- EVDS %8
 - 5. günden sonra risk yüksek
- Eksternal lomber katater ~%5
- Kafa travması %2-11 (kafa tabanı?
Açık kırık)
- Lomber ponksiyon 1/50.000



Nozokomiyal menenjit

Sorular

Sorunlar

Her ateş SSS
infeksiyonu mu?

Her BOS da üreme SSS infeksiyonu
mu?
Kontaminasyon?
Kolonizasyon?
Etken??

Her pleositoz SSS
infeksiyonu mu?

Yanıt bazen
yok





BOS'da pleositoz

- Serebellar köşe tümörü
- Operasyon (kan, kemik parçaları, cerrahi manüpilasyon)
- Tümör operasyonu
- Ratke's cleft kist operasyonu (kist duvarındaki kolesterol kristalleri)
- Posterior Fossa Sendromu
- İntratekal ilaç uygulamaları
- Jeneralize nöbet ($<80/ \text{mm}^3$)
- Adipoz doku ya da fasiya greft uygulamaları*

Ateş

- Santral ateş (infeksiyon dışı)

MIB olmayabilir
Çoğu sedatize
Uyutuluyor

Akut faz????
CRP, PCT?, lökositöz??

Steroid alımı

Şuur durumu !!!!



Şüphe durumunda

Tedavi

BOS/kan kültürü alınmalı
hemen tedavi başlanmalı

- Tedavi ampirik başlanır
- Kombine verilir (Antipseudomonal + antistafilokoksik)
 - En sık olası etkenler düşünülmeli
- Lokal direnç göz önünde bulundurulmalı
- İlaçlar nöbet eşiğini düşürmemeli???

G(-) basiller ile mortalite daha yüksek ($p=0,0034$)
Kurtaran B et al Türk Neurosurg 2017; 1-7

Empirical Combination Antibiotic Therapy Improves the Outcome of Nosocomial Meningitis or Ventriculitis in Neuro-Critical Care Unit Patients

Zhiqi Li, Xing Wu, Jian Yu, Xuehai Wu, Zhuoying Du, Yirui Chen, et al.

Abstract

Background: Nosocomial meningitis and ventriculitis (MEN) are serious unit (NCCU) patients. Few data are available on the risk factors and management of these disorders caused by multi-drug-resistant (MDR) pathogens. Our

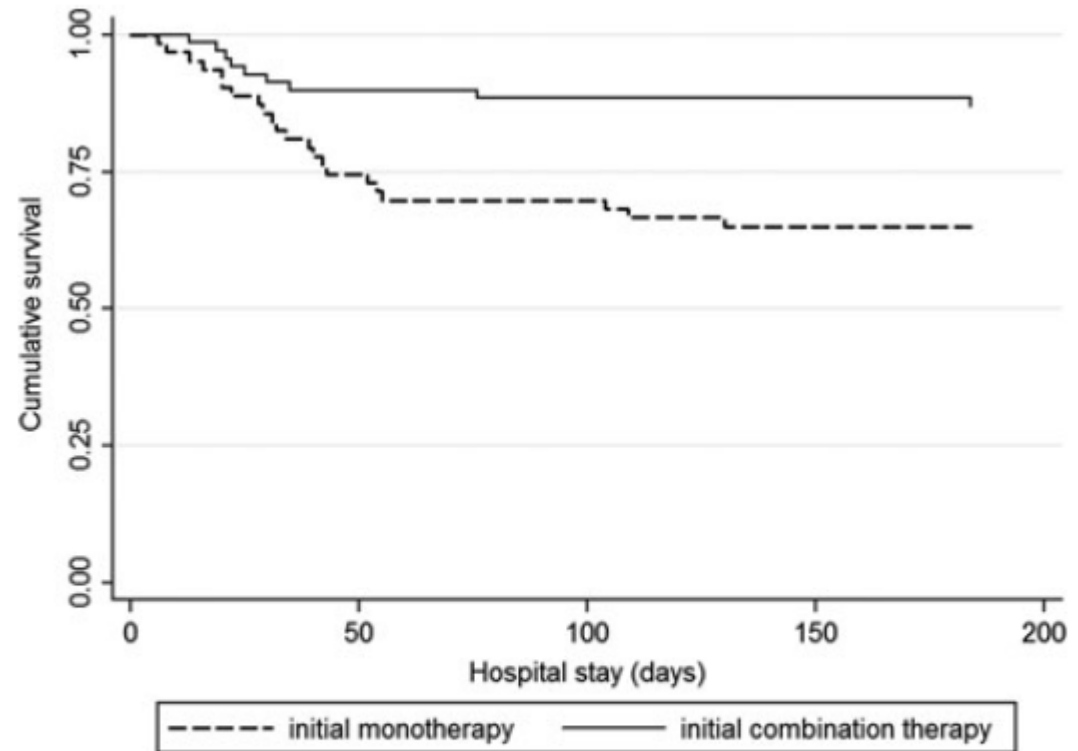


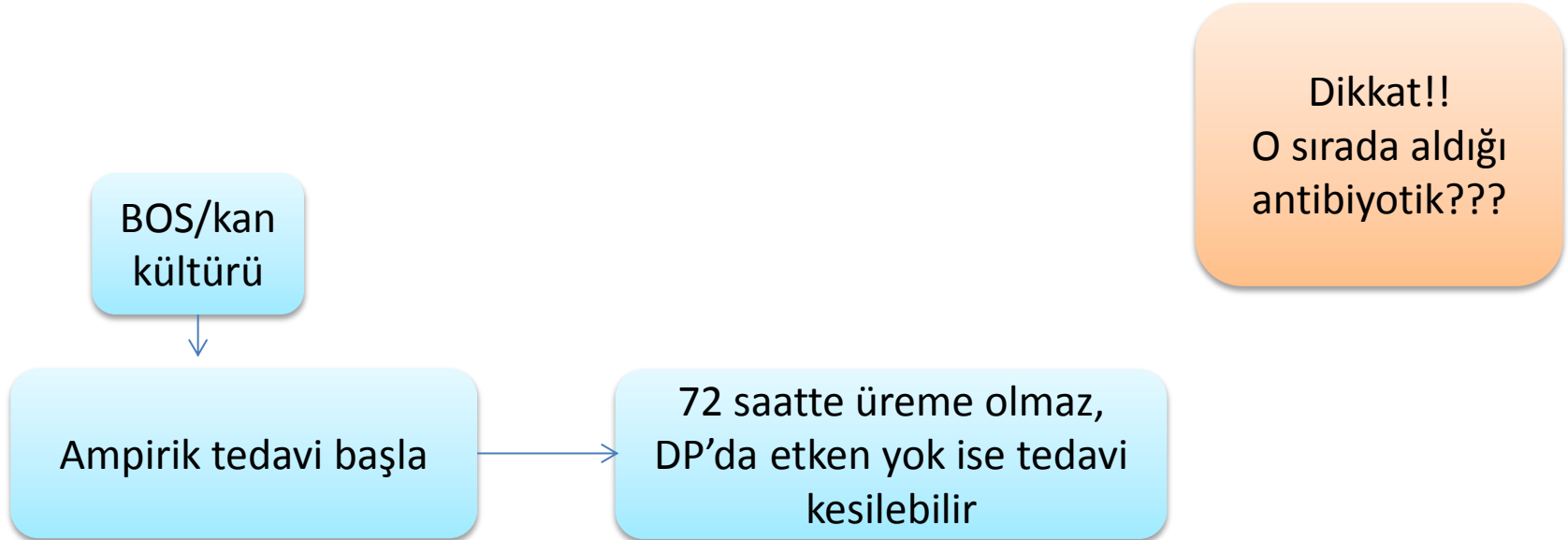
FIG. 2. Cumulative survival curves of patients receiving combined antibiotic therapy compared with patients having monotherapy in the empiric phase of treatment. (Log-rank test, $p = 0.0035$.)

Tedavide Genel Yaklaşım

- BOS'a iyi geçen
- BOS'da yeterli konsantrasyonda olacak şekilde uygun dozda
- Bakterisidal etkili olmalı
- Şant/katater biofilm???

Randomize kontrollü çalışma yok
Olgu sunumları yada olgu serileri
Retrospektif çalışmalar

Ampirik Tedavi



Van de Beek D et al NEJM 2010; 362: 146-54

- Stafilokoklar SBI menenjitlerde en sık etkenler arasında
 - Vankomisin 1. seçenek ancak BOS'da yeterli konsantrasyonda olabilmesi için serum düzeyi 15-20 µg/mL olmalı
 - MIC değeri ≥ 1 ise alternatif tedavi düşünülmeli
- Beta laktam alerjisi varsa (anafilaksi)
 - Aztreonam ya da siprofloksasin yüksek dozda verilmeli

2017 Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis^{*}

Allan R. Tunkel,¹ Rodrigo Hasbun,² Adarsh Bhimraj,³ Karin Byers,⁴ Sheldon L. Kaplan,⁵ W. Michael Scheld,⁶ Diederik van de Beek,⁷ Thomas P. Bleck,⁸ Hugh J. L. Garton,⁹ and Joseph R. Zunt¹⁰

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Table 1. Recommended Antimicrobial Therapy in Patients With Healthcare-Associated Ventriculitis and Meningitis Based on Isolated Pathogen and In Vitro Susceptibility Testing

Microorganism	Standard Therapy	Alternative Therapies
Staphylococci ^a		
Methicillin sensitive	Nafcillin or oxacillin	Vancomycin
Methicillin resistant	Vancomycin	Daptomycin, trimethoprim-sulfamethoxazole, or linezolid
<i>Propionibacterium acnes</i>	Penicillin G	Third-generation cephalosporin, ^b vancomycin, daptomycin, or linezolid
<i>Streptococcus pneumoniae</i>		
Penicillin MIC ≤0.06 µg/mL	Penicillin G	Third-generation cephalosporin ^b
Penicillin MIC ≥0.12 µg/mL		
Cefotaxime or ceftriaxone MIC <1.0 µg/mL	Third-generation cephalosporin ^b	Cefepime or meropenem
Cefotaxime or ceftriaxone MIC ≥1.0 µg/mL	Vancomycin plus a third-generation cephalosporin ^{b,c}	Moxifloxacin ^d
<i>Pseudomonas aeruginosa</i>	Cefepime, ceftazidime, or meropenem	Aztreonam or ciprofloxacin
<i>Haemophilus influenzae</i>		
β-lactamase negative	Ampicillin	Third-generation cephalosporin, ^b cefepime, or a fluoroquinolone
β-lactamase positive	Third-generation cephalosporin ^b	Cefepime, aztreonam, or a fluoroquinolone
Extended spectrum β-lactamase-producing gram-negative bacilli	Meropenem	Cefepime or a fluoroquinolone
<i>Acinetobacter baumannii</i>	Meropenem	Colistin (usually formulated as colistimethate sodium) ^e or polymyxin B ^e
Other Enterobacteriaceae ^f	Third-generation cephalosporin ^b	Meropenem, aztreonam, trimethoprim-sulfamethoxazole, or ciprofloxacin
<i>Candida</i> species ^g	Lipid formulation of amphotericin B ± flucytosine	Fluconazole or voriconazole
<i>Aspergillus</i> species	Voriconazole	Lipid formulation of amphotericin B or posaconazole

Table 2. Recommended Dosages of Antimicrobial Agents in Infants and Children and in Adults With Normal Renal and Hepatic Function

Antimicrobial Agent	Total Daily Dose (Dosing Interval in Hours)	
	Infants and Children	Adults
Amikacin ^a	22.5 mg/kg (8)	15 mg/kg (8)
Amphotericin B lipid complex	5 mg/kg (24)	5 mg/kg (24)
Ampicillin	300–400 mg/kg (6)	12 g (4)
Aztreonam	120 mg/kg (6–8)	6–8 g (6–8)
Cefepime	150 mg/kg (8)	6 g (8)
Cefotaxime	300 mg/kg (6–8)	8–12 g (4–6)
Ceftazidime	200 mg/kg (8)	6 g (8)
Ceftriaxone	100 mg/kg (12–24)	4 g (12)
Ciprofloxacin	30 mg/kg (8–12)	800–1200 mg (8–12)
Daptomycin	Dose not established ^b	6–10 mg/kg (24)
Fluconazole	12 mg/kg (24)	400–800 mg (24)
Gentamicin ^a	7.5 mg/kg (8)	5 mg/kg (8)
Linezolid	Age <12 years: 30 mg/kg (8) ^c Age ≥12 years: 20 mg/kg (12) ^c	1200 mg (12)
Liposomal amphotericin B	3–5 mg/kg (24)	3–5 mg/kg (24) ^d
Meropenem	120 mg/kg (8)	6 g (8)
Moxifloxacin ^e	Dose not established	400 mg (24)
Nafcillin	200 mg/kg (6)	12 g (4)
Oxacillin	200 mg/kg (6)	12 g (4)
Penicillin G	300 000 units/kg (4–6)	24 million units (4)
Posaconazole	—	800 mg (6–12) ^f
Rifampin	20 mg/kg (24) ^g	600 mg (24)
Tobramycin ^a	7.5 mg/kg (8)	5 mg/kg (8)
Trimethoprim-sulfamethoxazole ^h	10–20 mg/kg (6–12)	10–20 mg/kg (6–12)
Vancomycin ⁱ	60 mg/kg (6)	30–60 mg/kg (8–12)
Voriconazole	16 mg/kg (12) ^{j,k,l}	8 mg/kg (12) ^{j,k}

REVIEW ARTICLE

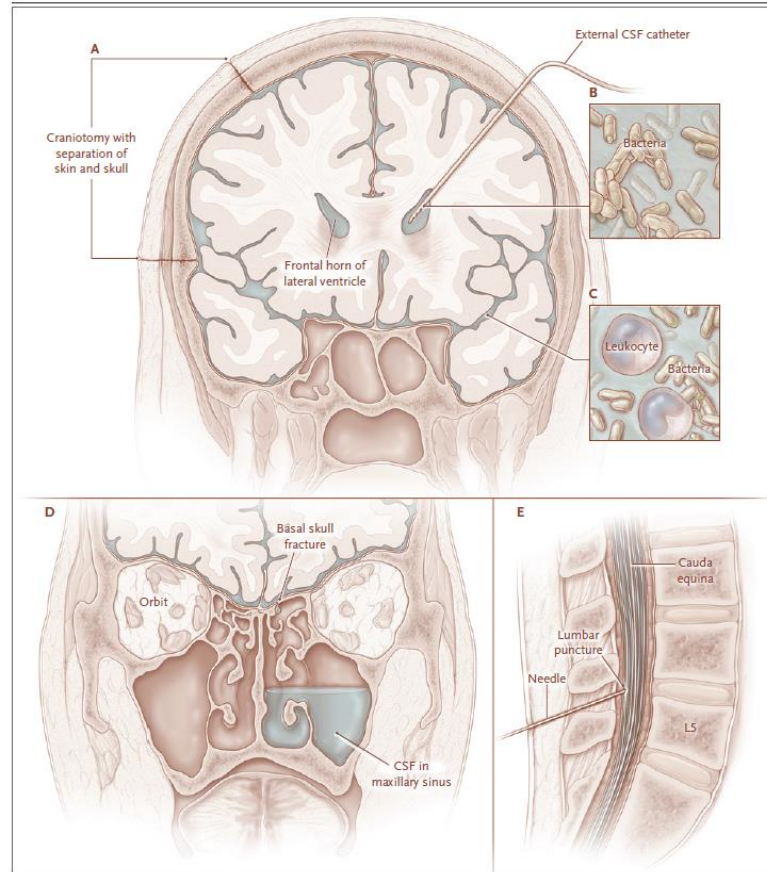
CURRENT CONCEPTS

Nosocomial Bacterial Meningitis

Diederik van de Beek, M.D., Ph.D., James M. Drake, M.B., B.Ch.,
and Allan R. Tunkel, M.D., Ph.D.

From the Department of Neurology, Center of Infection and Immunity Amsterdam, Academic Medical Center, University of Amsterdam, Amsterdam (D.B.); the Division of Neurosurgery, Department of Surgery, Hospital for Sick Children, University of Toronto, Toronto (J.M.D.); and the Department of Medicine, Monmouth

NOSOCOMIAL BACTERIAL MENINGITIS MAY RESULT FROM INVASIVE PROCEDURES (e.g., craniotomy, placement of internal or external ventricular catheters, lumbar puncture, intrathecal infusions of medications, or spinal anesthesia), complicated head trauma, or in rare cases, metastatic infection in patients with a differentiating, and





Nosocomial meningitis in a university hospital between 1993 and 2002

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Original Article

Clinical features, laboratory data, management and the risk factors that affect the mortality in patients with postoperative meningitis

Ilknur Erdem¹, Tayfun Hakan², Nurgul Ceran¹, Fatma Metin¹, Seniha Senbayrak Akcay³, Metin Kucukercan³, M. Zafer Berkman², Pasa Goktas¹

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Background: Nosocomial meningitis is a rare complication following neurosurgical procedures and is associated with high morbidity and mortality. **Aim:** The aim of this study was to describe the clinical characteristics and

Introduction

Nosocomial meningitis is an uncommon hospital-acquired infection and is more frequently seen in

Table IV Distribution of causative micro-organisms

Causative micro-organism	No. of isolates	No. of shunt patients' isolates
Staphylococci	20	11
CNS	7	6
MRSA	7	2
MSSA	6	3
Non-fermentative Gram-negative bacilli	15	9
<i>Escherichia coli</i>	9	7
<i>Klebsiella</i> spp.	9	5
<i>Enterobacter</i> spp. and <i>Proteus</i> spp.	5	2
<i>Pseudomonas</i> spp.	3	2
<i>Candida</i> spp.	3	0
<i>Enterococcus</i> spp.	2	2
α -haemolytic streptococci	1	0
Total	67	38

CNS, coagulase-negative staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S. aureus*.

Table 2: The distribution of isolated 56 microorganisms from CSF cultures

Microorganism	n (%)
<i>S. aureus</i> *	20 (35.7)
<i>Acinetobacter</i> spp.	17 (30.3)
<i>P. aeruginosa</i> **	6 (10.7)
CoNS***	5 (8.9)
<i>Enterobacter</i> spp.	3 (5.4)
<i>E. coli</i> ****	2 (3.6)
<i>Candida</i> spp.	3 (5.4)

Staphylococcus aureus*; *Pseudomonas aeruginosa*; ***Coagulase negative staphylococci; *****Escherichia coli*

Patogenez	Olası Etkenler	Tedavi
Kraniyotomi	Gram negatif basiller (<i>Pseudomonas aeruginosa</i> dahil) <i>S aureus</i> KNS (<i>S epidermidis</i>)	Vankomisin + Meropenem/ Sefepim/ Seftazidim
Ventriküler-lomber kateter	KNS (<i>S epidermidis</i>) <i>S aureus</i> Gram negatif basiller <i>P acnes</i>	
Penetran yaralanma 	<i>S aureus</i> KNS Gram negatif basiller (<i>Pseudomonas aeruginosa</i> dahil)	
Kafa tabanı kırığı	<i>S pneumoniae</i> <i>H influenzae</i> AGBHS	Vankomisin + 3. kuşak sefalosporin (CRO/CTX)

***Propionibacterium acnes*: an under-appreciated cause of post-neurosurgical infection**

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Background: *Propionibacterium acnes* is increasingly recognized as a cause of post-neurosurgical infection. This review of patients with *P. acnes* neurosurgical infection was carried out in order to determine clinical characteristics and outcomes in relation to duration of antimicrobial treatment.

Methods: We retrospectively reviewed the charts of consecutive patients with *P. acnes* isolated from neurosurgical specimens from 1 January 1999 to 30 June 2005. We defined *P. acnes* neurosurgical infection as isolation of *P. acnes* alone from a sterile neurosurgical site in a patient who clinically improved following treatment with an appropriate antibiotic.

Kraniyotomilerde, katater ilişkili MSS infeksiyonlarında düşünölmeli
Sefalosporin/karbapenem/vankomisin yetmeyebilir
Tedavisi Penisilin IV

bacilli on Gram stain should not be discounted as a contaminant in neurosurgical specimens. Associated bone flaps should be removed. Intravenous benzyl penicillin $\pm$ oral penicillin VK remains effective treatment.

Cerebrospinal Fluid Penetration of High Doses of Intravenous Ciprofloxacin in Meningitis

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Nosocomial meningitis due to gram-negative organisms is a difficult clinical problem to manage because of both antibiotic resistance and poor penetration of many antimicrobials across the blood-brain barrier. Ciprofloxacin has potential in treating this condition when used in high doses. We investigated the plasma and cerebrospinal fluid (CSF) levels of ciprofloxacin in a patient with *Pseudomonas aeruginosa* meningitis who was treated with 400 mg of intravenous ciprofloxacin every 8 hours. Ciprofloxacin levels in plasma peaked at 10.29 mg/L without resulting in accumulation (8-hour trough levels, <1 mg/L), whereas the CSF level increased to 0.9 mg/L. This CSF level was confirmed to be similar 1 week later. After 1 week of therapy, during which there were no side effects attributable to ciprofloxacin, the organism was eradicated, and there was some clinical improvement. We recommend that 400 mg of intravenous ciprofloxacin every 8 hours be considered for treatment of difficult-to-treat gram-negative bacillary meningitis.

Table 1. Concentrations of ciprofloxacin in plasma and CSF samples from a patient with *Pseudomonas aeruginosa* meningitis.

Date, time	Hours after dose	Plasma concentration, mg/L	CSF concentration, mg/L
7 August 1999			
9:00 AM	5	1.28	0.049
10:00 AM	6	1.05	0.520
11:00 AM	7	0.78	0.913
12:00 PM	8 ^a	0.67	0.922
1:00 PM	1	10.29	0.914
2:00 PM	2	3.23	
14 August 1999			
2:00 PM	2	2.98	0.955
15 August 1999			
12:00 PM	8 ^a	0.47	

^a Trough level is measured at this time.

Nöbet !!!!!
Literatürde çok görülüyor
diyor

Beta laktam alerjisi/
MDR *P aeruginosa* 'da

Siprofloksasin 3x400 mg
Bir seçenek

Table 2. Selected results of hematologic, chemical pathological, and microbiological analyses of CSF samples from a patient with *Pseudomonas aeruginosa* meningitis.

Date	WBC count, ×10 ⁶ /L	Neutrophils, %	Protein level, g/L ^a	Glucose level, mmol/L ^b	Gram stain ^c	Culture ^d
30 May 1999	8040	88	1.398	0.7	—	+
4 August 1999	960	92	>3	1.1	+	+
5 August 1999	47	63	2.8	0.9	+	+
6 August 1999	150	60	4.2	1.3	+	+
7 August 1999	220	ND	5.48	1.2	+	+
14 August 1999	70	10	1.8	2.9	—	—

NOTE. ND, not determined; —, negative; +, positive.

^a Normal range, 0.15–0.5 g/L.

^b Normal range, 2.5–4.0 mmol/L.

^c For the presence of gram-negative bacilli.

^d For *P. aeruginosa*.



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Central nervous system infections due to vancomycin-resistant enterococci: case series and review of the literature



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SUMMARY

Objectives: To evaluate reported cases of central nervous system (CNS) infections due to vancomycin-resistant enterococci (VRE) and describe the data necessary to better understand clinical characteristics of this rare disease process.

Methods: We report two cases of VRE CNS infection and review 36 cases reported in the literature.

Results: Eighty-two percent (31/38) of cases were due to *Enterococcus faecium*. The median length of stay prior to diagnosis was 14 days (interquartile range 9–33). Fifty-eight percent (22/38) of cases had significant underlying non-malignant CNS disease processes and 63% (24/38) had CNS devices in situ.

Table 1

Characteristics of patients with central nervous system (CNS) infections due to vancomycin-resistant enterococci (VRE)

[Ref.] year	Age, sex	Underlying condition(s)	Clinical features	Treatment	CNS device and management	Outcome
[14] 1994	6 years, M	Seizure disorder s/p brain grid placement	Fever, AMS, headache, meningeal signs, seizures	Am IV $\times$ 7 days; Cm and Rf $\times$ 14 days; Tc IT $\times$ 14 days	Brain grid removed, lumbar drain placed then removed at a later date	Clinical and microbiological cure
[15] 1995	8 months, F	Intraventricular bleed, shunt infections	Fever, AMS	Ch IV and Gn IV and VT; Q/D IV and Q/D VT $\times$ 28 days	Shunt removed, Ommaya placed, intraventricular lavage	Clinical and microbiological cure
[16] 1996	71 years, F	Ethmoid sinus invasive	NR	Q/D IV $\times$ 22 days	NA	Death, microbiological cure

VRE'de bir çok kombinasyon var
1994-2005 arası Kloramfenikol IV+IT/IVT

2005 sonrası Linezolid/Daptomisin/Quinopristin-Dalfopristin
 $\pm$ Genta IT/IVT /Rifampisin NG/PO

~28 gün

		metastasis, EVD to VPS, MI, pneumonia		weeks; Gn IV $\times$ 7 days; Gn VT		cancer, microbiological cure
[24] 2002	7 months, M	Pulmonary HTN, hydrocephalus s/p VPS	Fever, seizures	Lz $\times$ 21 days	VPS removed then replaced after 10 days of Lz	Clinical and microbiological cure
[25] 2003	67 years, M	CNS lymphoma s/p reservoir and chemotherapy	Fever	Q/D IV $\times$ 9 weeks; Lz IV $\times$ 6 weeks; Q/D VT $\times$ 3 doses	Ommaya reservoir replaced	Clinical and microbiological cure
[26] 2004	38 years, M	Oligoastrocytoma s/p resection, abscess, hydrocephalus s/p EVD	Fever, seizures	Ch IV $\times$ 4 days	Frontal abscess resected, EVD replaced	Death, microbiological cure
[27] 2005	46 years, M	SAH s/p craniotomy and aneurysm clipping	Fever	Ch IV $\times$ 47 days; Ch VT $\times$ 35 days	EVD placed on day 12 of Ch	Clinical and microbiological cure
[28] 2006	69 years, M	COPD on chronic steroids, Klebsiella pneumonia, UTI	Fever, AMS, meningeal signs	Cf $\times$ 2 days; Cp $\times$ 2 days; Lz IV $\times$ 2 weeks	NA	Clinical and microbiological cure
[29] 2006	7 months, M	Hydrocephalus s/p VPS, non-VRE meningitis, EVD	Fever	Ch, Rf, and Mp $\times$ 9 days	One week after diagnosis EVD replaced with Rf + Cl impregnated EVD	Clinical and microbiological cure
[30] 2006	51 years, F	Cribriform plate defect s/p lumbar drain placement	Fever, headache	Am and Rf $\times$ 3 weeks	Lumbar drain removed on diagnosis, replaced with lumboperitoneal shunt	Clinical and microbiological cure

Tedavi Süresi?

- KNS ve *P acnes*

- Klinik düzelme ve BOS bulguları düzelme varsa
 - ~10 gün
- Düzelme hemen olmazsa (birden fazla üreme)
 - 10-14 gün

- *S aureus* ve Gram negatif üremelerde

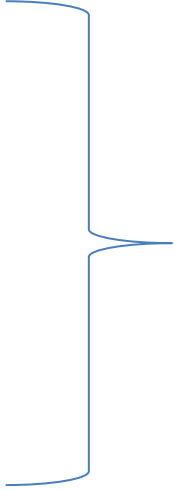
- Klinik ve BOS bulguları düzelmişse
 - 10-14 gün
- Bazı klinisyenler özellikle gram negatifler için 21 gün (rekürrens sık)

Özellikle *Pseudomonas spp* 'de

Tekrarlayan kültürlerde üreme varsa son üremeden sonra 10-14 gün

- Beyin apsesi
- Subdural ampiyem
- Kraniyal-epidural apse
- Süpüratif kraniyal flebit

- Ventrikülit
 - G (+) IV+IVT 1-2 hafta !!!!!
 - G(-) IV± IVT 2-3 hafta !!!!!



6 hafta
Boyut ??
Drenaj???

Apse varlığında kesme kriteri
Radyolojik iyileşme?
(kontrast tutulumu??? Devam ediyor)
Drenaja uygun değilse ve apsenin boyutu büyükse!!!!)

İntraventriküler/İntratekal Tedavi

İyi geçenler	Çok az geçenler	Enflamasyonda geçenler	Hiç geçmeyenler
Kloramfenikol Sikloserin ETB INH Metronidazol TMP-SMZ	Aminoglikozidler Amfoterisin B Sefoksitin 1. Kuşak sefalosporinler Klindamisin	Asiklovir Penisilin G Ampisilin 3 kuşak sefalosporinler 4 kuşak sefalopsorinler Vankomisin Penemler	Basitrasin Ketakonazol Polimiksin B Kolistin

Steroid alıyorsa beklenenden daha az BOS'a geçiş

İntraventriküler/İntratekal Tedavi

- Sistemik antibiyotik BOS'a geçmiyor, yeterli BOS konsantrasyonuna ulaşılamıyorsa
- Tedaviye rağmen üremeler devam ediyorsa uygulanır
- Lateral ventrikül ya da lomber drenajdan antibiyotik uygulanır

Kan beyin bariyeri by-pass edilmiş olur

İntraventriküler/İntratekal Tedavi

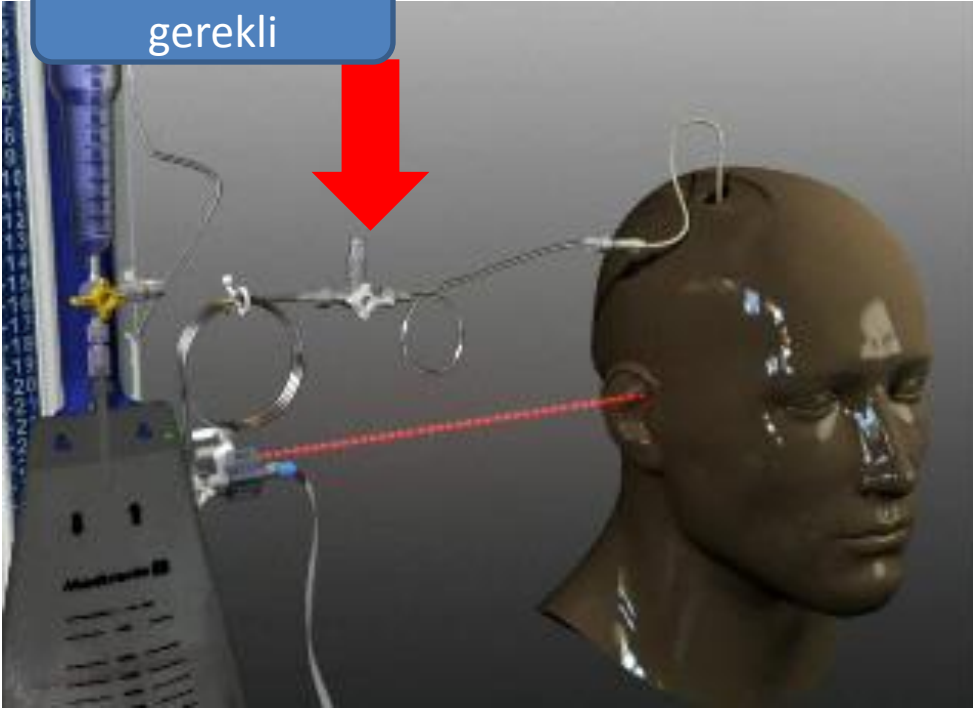
- Antibiyotiğin etkili olabilmesi için BOS'da MIC'in en az 10-20 katı olması gerekli
- Ventrikül hacmi ve günlük ventrikül drenajına göre değişir!!

BOS'a geçen antibiyotik sayısı az

Antibiyotiklere duyarlılık giderek azalıyor

Önemli bir sorun
Yeni bir etken??? Kontaminasyon riski

15-60 dk klemp
gerekli



Sistemik yan etki daha az!!!

Randomize kontrollü çalışma yok
Olgu sunumları yada olgu serileri
Retrospektif çalışmalar

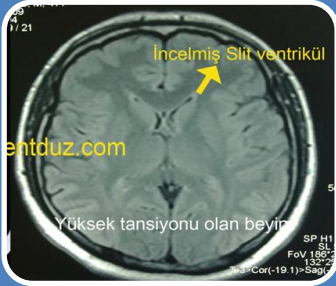


FDA onayı yok

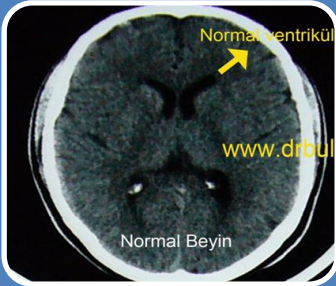
Penisilin ve sefalosporinler
nörotoksik olduğundan
uygulanmaz

Table 3. Recommended Dosages of Antimicrobial Agents Administered by the Intraventricular Route

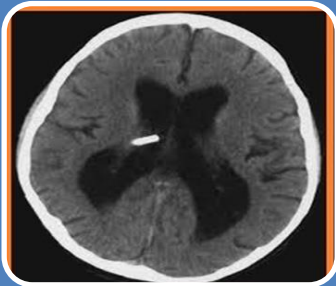
Antimicrobial Agent	Daily Intraventricular Dose
Amikacin	5–50 mg ^a
Amphotericin B deoxycholate ^b	0.01–0.5 mg in 2 mL of 5% dextrose in water
Colistin (formulated as colistimethate sodium)	10 mg
Daptomycin	2–5 mg ^c
Gentamicin	1–8 mg ^{d,e,f}
Polymyxin B	5 mg ^g
Quinupristin/dalfopristin	2–5 mg
Tobramycin	5–20 mg
Vancomycin	5–20 mg ^{e,f,h}



Slit ventrikül:
Vankomisin 5 mg
Gentamisin 2 mg



Normal:
Vankomisin 10 mg
Gentamisin 3 mg



Genişlemiş:
Vankomisin 15-20 mg
Gentamisin 4-5 mg

Vankomisin ve Gentamisinde BOS eksternal ventriküler drenaj miktarına göre uygulama sıklığı

<50 ml/gün ise üç günde bir

50-100 ml/gün ise iki günde bir

100-150 ml/gün ise her gün

150-200 ml/gün ise günlük vankomisin dozu 5 mg, gentamisin dozu 1 mg artırılmalı

200-250 mg/gün ise vankomisin dozu 10 mg, gentamisin dozu 2 mg artırılmalı

Case Report

Successful treatment of vancomycin-resistant *Enterococcus faecium* ventriculitis with combined intravenous and intraventricular chloramphenicol in a newborn

Carolin Hartmann,¹ Corinna Peter,¹ Elvis Hermann,² Benno Ure,³ Ludwig Sedlacek,⁴ Gesine Hansen¹ and Bettina Bohnhorst¹

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Review

Post-neurosurgical multidrug-resistant *Acinetobacter baumannii* meningitis successfully treated with intrathecal colistin. A new case and a systematic review of the literature

Antonio Cascio^{a,*}, Alfredo Conti^b, Luca Sinardi^c, Chiara Iaria^d, Filippo Flavio Angileri^b, Giovanna Stassi^e, Teresa David^c, Antonio Versaci^c, Maurizio Iaria^f, Antonio David^c

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^b Department of Neurosurgery, University of Messina, Messina, Italy

^c Department of Neuroscience, Psychiatric and Anesthesiological Sciences, University of Messina, Messina, Italy

^d AILMI (Associazione Italiana per la Lotta contro le Malattie Infettive; Italian Association for the Control of Infectious Diseases), University of Messina, Messina, Italy

^e Microbiology Unit, University of Messina, Messina, Italy

^f Division of General Surgery, Department of Human Pathology, University of Messina, Messina, Italy

45 literatür taranmış
32 hasta 33 epizod

Table 1
Clinical characteristics, therapy and outcome of patients with *Acinetobacter spp* meningitis treated with intraventricular or intrathecal colistin^a

Authors, year, country (notes) [Ref.]	Age/sex	Primary diagnosis	Foreign bodies	Acinetobacter susceptibility	Initial regimens used	Final regimen	Dosage of intrathecal colistin (colistimethate) ^b	Toxicity	Outcome (comment)
Kaplan and Patrick, 1990, USA [4]	4/NR	Meningitis	EVD	MDR	None	Cefotaxime and aminoglycoside IV, colistin IVR	20 unspecified doses	None	Cure
Fernandez-Viladrich et al., 1999, Spain (2 cases) [5]	16/M	Hemangioblastoma	EVD	Susceptible only to colistin and sulbactam; intermediate to tobramycin and imipenem	Meropenem, tobramycin and, sulbactam IV; tobramycin IVR	Tobramycin IV and colistin IVR	5 mg q12h for 19 days	None	Culture-negative after 2 days Cure
Vasen et al., 2000, Argentina [6]	4								Died of cardiac arrest 40 days later Culture-negative after 6 days
									Cure Follow-up 4 months Culture-negative after 1 day
Benifla et al., 2004, Israel (<i>Staphylococcus aureus</i> was also isolated in one of the cultures) [7]	49/F	Recurrent meningioma, recurrent episodes of meningitis	VP shunt	Susceptible only to colistin and sulbactam	Ceftriaxone IV, co-amoxiclav IV and meropenem IV, ampicillin/sulbactam and vancomycin	Ampicillin/sulbactam and vancomycin IV, Colistin IVR	3.2 mg q24h for 17 days	None	Cure Follow-up 6 weeks Culture-negative after 6 days
Sueke et al., 2005, UK [8]	38/F								Cure Follow-up 4 years Cure
Bukhary et al., 2005, Saudi Arabia [9]	23/F								(Authors do not report total duration of therapy and follow-up) Culture-negative after 7 days
		craniotomy and upper cervical laminectomy			moxifloxacin and colistin IV				Cure

Meropenem IV+Kolistin IV+kolistin IT/IVT
Meropenem IV+ Rifampisin+ Kolistin IT/IVT
Yalnız Kolistin IT/IVT (8 olgu)
Kolistin IV+Kolistin IT/IVT.....

~4,1 günde BOS steril olmuş

5/32 eksitus (hiç biri menenjit nedeniyle değil)
5'inde yan etki (geriye dönüşümlü)

Grubu :	Beyin ve Sinir Cerrahisi	Grup Türü :	Yatarak
Branşı :	2400-Beyin ve Sinir Cerrahisi	Provizyon Tipi :	Normal
Takip Tarihi :	14.09.2017	Protokol No :	12374136
Takip Tipi :	Normal	Taburcu Kodu :	Hastane içinde başka bir bransa sevk
Tedavi Türü :	Yatarak Tedavi	Tedavi Tipi :	Normal Sorgu
İlk Takip No :	2CJIU07	Donör TCK :	0
Hasta Telefon :	2245535160	Hasta Adres :	HAMZABEY MAH. ŞEHİT ZEKİ GÖKGÖZ SK. 15/1 MUSTAFAKEMALPAŞA BURSA
Sevk Edilmiş :	Hayır	Sevk Ediliş Tarihi :	
Yeşil Kart Sevki :	Hayır	Yeşil Kart Sevke Bağlı :	Hayır
Yatış Başlangıç Tarihi :	12.09.2017	Taburcu Tarihi :	25.10.2017
Açıklama :	Öyküsü:Kronik sinüzit nedeniyle dış merkezde operasyon planlanan ve anı başlayan ajitasyon, saldırganlık ve uygunsuz konuşma şikayetleri ile 18.6 servise başvuran tarafımızca Lomber Punksiyon yapılan ve menenjit tedavisi başlanan dış merkeze sevki sonrasında sol göзде görme kaybı gelişen kliniğine yatırılmış. Radyolojik görüntülemeleri ile tarafımızca konsülte edilen hasta yatağında değerlendirildi. Sol frontal sinus ve sol fronto-orbital bölü yaygın ödemli absse görünümülü lezyonlara yönelik operasyon planlanarak Nöroşirürji kliniğine yatırıldı. 2 - Cerrahi Tedavi:18/09/2017 - Uygulanan C 615410 BEYİN APSESİ CERRAHİSİ,KRANIOTOMİ İLE Çıkarılan Materyaller :apse Ulaşılan Bulgular :... Kullanılan Kan Ve Kan Ürün Miktarı :- Kanama Ameliyat Başlangıç ve Bitiş Zamanları :18/09/2017 12:00 18/09/2017 16:00 Yapılan Anestezi:ANESTEZİ BAKIMIAnestezi Notu : ht Anestezi Veren Dr. HULYA,YALDIZ MEHMET,KIZILKALE G		



İlaç	8699814270536-MOPEN 1 GR IV ENJEKTABL TOZ ICEREN 1 FLK	1.0	20,82	20,82	22.09.2017 TAR.KÜLTÜR ANTIYOGRAM SONUCUNDA DİRENÇ BELİRTİLMİŞ.
İlaç	8699814270536-MOPEN 1 GR IV ENJEKTABL TOZ ICEREN 1 FLK	1.0	20,82	20,82	22.09.2017 TAR.KÜLTÜR ANTIYOGRAM SONUCUNDA DİRENÇ BELİRTİLMİŞ.
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Meropenem IV+Kolistin IV+ Kolistin IVT

ÖRNEK GRUBU: STERİL VÜCUT SIVILARI
ÖRNEK: BOS
VÜCUT BÖLGESİ: LOMBER

İŞLEM : BEYİN OMURİLİK SIVISI (BOS) KÜLTÜRÜ

SONUÇ : Pozitif

Üreyen Organizma : 1) ACINETOBACTER BAUMANNII

Yorum : MAKİ VE BROTH YÖNTEMİYLE YOGUMLU UREDİ

Amikacin	>16	R	Ciprofloxacin	>2	R
Colistin	≤1	S	Gentamicin	>4	R
Imipenem	>8	R	Meropenem	>8	R
Netilmicin	>4	R	Trimethoprim-Sulfamethoxazole	>4/76	R

- 39 yaşında kadın hasta, FM (Temmuz 2016)
- İntrakraniyal kitle ile opere oldu
- EVDS+ICP var
- Postop 14. günde ventrikülit gelişti

ÖRNEK GRUBU: STERİL VÜCUT SIVILARI
ÖRNEK: BOS
VÜCUT BÖLGESİ: LOMBER

İŞLEM : BEYİN OMURİLİK SIVISI (BOS) KÜLTÜRÜ

İşlem Tarihi : 06/08/2016

SONUÇ :

ÜREME VAR

Üreyen Organizma : 1) KLEBSIELLA PNEUMONIAE SSP PNEUMONIAE

Amikacin	<=4	S	Amoxicillin-Clavulanate (F)	<=2/2	S
Ampicillin	>8	R	Aztreonam	<=1	S
Cefepime	<=1	S	Ceftazidime	<=0,5	S
Ceftriaxone	<=0,5	S	Cefuroxime	<=2	S
Ciprofloxacin	<=0,125	S	Colistin	<=1	S
Ertapenem	<=0,25	S	Gentamicin	<=1	S
Imipenem	<=0,25	S	Meropenem	<=0,125	S
Netilmicin	1	S	Piperacillin	8	S
Piperacillin-Tazobactam	<=4/4	S	Tigecycline	1	S
Trimethoprim-Sulfamethoxazole	<=1/19	S			

Üreyen Organizma : 3) ENTEROBACTER CLOACAE

Amikacin	<=4	S	Amoxicillin-Clavulanate (F)	>32/2	R
Ampicillin	>8	R	Aztreonam	<=1	S
Cefepime	<=1	S	Ceftazidime	<=0,5	S
Ceftriaxone	<=0,5	S	Ciprofloxacin	<=0,125	S
Colistin	<=1	S	Ertapenem	<=0,25	S
Gentamicin	<=1	S	Imipenem	<=0,25	S
Meropenem	<=0,125	S	Netilmicin	1	S
Piperacillin	<=4	S	Piperacillin-Tazobactam	<=4/4	S
Tigecycline	2	I	Trimethoprim-Sulfamethoxazole	<=1/19	S

- Meropenem (3x2 g IV)+Vankomisin (3x1 g IV)
– Yanıt yok
- Kolistin IV+IVT eklendi



ÖRNEK GRUBU: KATATER
ÖRNEK: SANTRAL SİNİR SİSTEMİ

İŞLEM : YARA KÜLTÜRÜ

İşlem Tarihi : 12/08/2016

SONUÇ : Pozitif

Üreyen Organizma : 1) ACINETOBACTER BAUMANNII

Yorum : MAKİ VE BROTH YÖNTEMİYLE YOGUN
UREDİ

Amikacin	>16	R	Ciprofloxacin	>2	R
Colistin	<=1	S	Gentamicin	>4	R
Imipenem	>8	R	Meropenem	>8	R
Netilmicin	>4	R	Trimethoprim-Sulfamethoxazole	>4/76	R

ÖRNEK GRUBU: KATATER
ÖRNEK: EVDS UCU

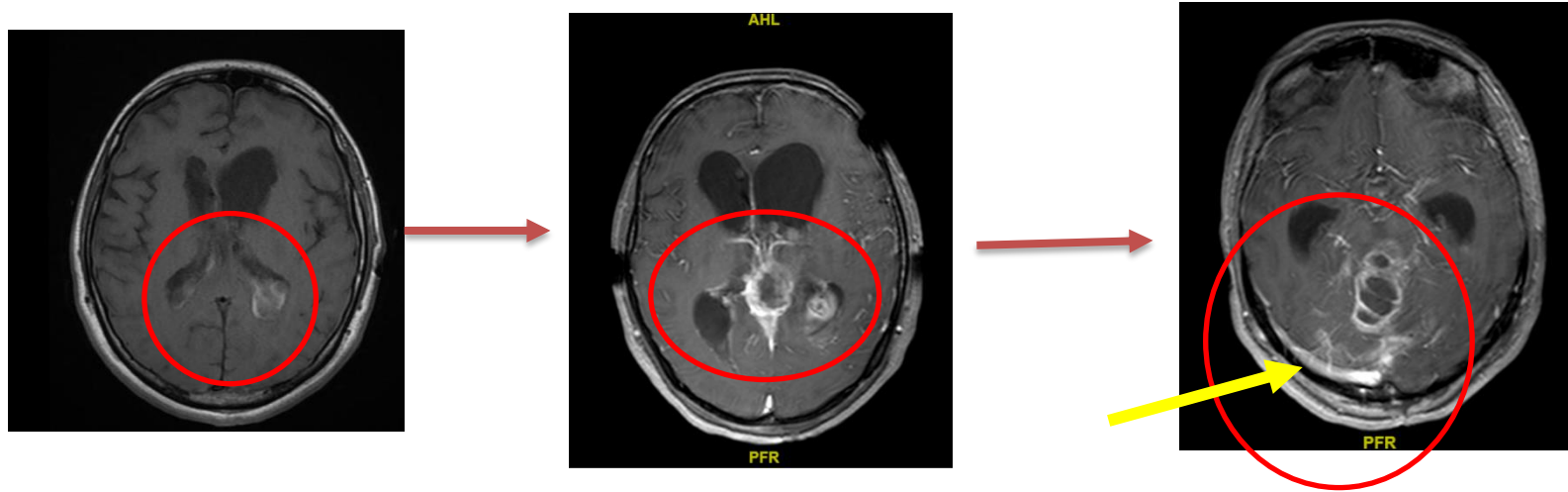
İŞLEM : YARA KÜLTÜRÜ

İşlem Tarihi : 15/08/2016

SONUÇ : Pozitif

Üreyen Organizma : 1) ACINETOBACTER BAUMANNII

Amikacin	>16	R	Ciprofloxacin	>2	R
Colistin	<=1	S	Gentamicin	>4	R
Imipenem	>8	R	Meropenem	>8	R
Netilmicin	>4	R	Trimethoprim-Sulfamethoxazole	>4/76	R



Klinik ve BOS
bulguları düzelmedi

2 kez EVDS revizyonu
Birkaç defa operasyon...

Flukonazol

TMP-SMZ

Meropenem+Kolistin IV+IVT eklendi

Vankomisin/linezolid

Yüksek doz kinolon

- Meropenem 37 gün, kolistin 28. gün, Linezolid 17. günde Rifampisin 3x300 mg (NG) ekledi
- Hastanın 5. gününde ateşi düştü, BOS steril oldu



- Meropenem (86 gün)+Kolistin (77 gün)+Rifampisin (28. günde) BOS bulgusu normal, 3 kültür negatif
 - VP şant takıldı
 - Şant sonrası 10. gün tüm tedaviler kesildi
 - Tedavi kesildikten 10 gün sonra taburcu edildi
 - Aralık 2017’de poliklinik kontrollerine en son geldi



Gerçekler

Masallar

IVT/IT Süre??

- BOS kültürü negatifleşinceye kadar
- <7 gün nüks fazla
- Ortalama 10 gün yeterli
- Ancak standart süre yok



Intraventricular antimicrobial therapy in postneurosurgical Gram-negative bacillary meningitis or ventriculitis: A hospital-based retrospective study

Jui-Hsing Wang^a, Po-Chang Lin^a, Chia-Hui Chou^a,
Cheng-Mao Ho^a, Kuo-Hsi Lin^a, Chia-Ta Tsai^a,
Jen-Hsien Wang^{a,b}, Chih-Yu Chi^{a,b,*}, Mao-Wang Ho^{a,b,*}



IT süre: 3-27 gün
Genelde BOS steril olduktan sonra 6,6 gün daha

Table 4 Clinical characteristics and microorganisms isolated from cerebrospinal fluid (CSF) and treatment and outcomes for 15 episodes of postneurosurgical Gram-negative bacillary meningitis and ventriculitis treated with sequential intraventricular therapy (IVT)

Episode	Age (y) /sex	CSF culture	Concurrent IV antibiotics	IVT therapy			Medical condition	APACHE II score	Length of hospital stay (d)	Outcome
				Daily dose	IVT duration (d)	Elapsed period ^b (d)				
1 ^a	79/F	<i>Acinetobacter baumannii</i>	Imipenem	Amikacin 50 mg	9	32	Brain infarction s/p Ommaya	6	213	Cured
2	28/M	CR <i>Acinetobacter baumannii</i>	Meropenem	Amikacin 30 mg	11	10	ICH s/p EVD	10	139	Cured
3	39/M	CR <i>Acinetobacter baumannii</i> ^c	Meropenem/colistin	Amikacin 10 mg	18	21	Hydrocephalus s/p VP shunt AIDS	9	136	Cured
4	31/M	CR <i>Acinetobacter baumannii</i>	Imipenem/colistin	Colistin 6.4 mg	27	28	TBI/ICH s/p EVD	11	116	Cured
5	70/F	CR <i>Acinetobacter baumannii</i>	Imipenem/sulbactam/colistin	Colistin 3.2 mg	20	23	Brain infarction s/p VP shunt	18	98	Death
6	60/M	CR <i>Acinetobacter baumannii</i>	Meropenem/colistin	Colistin 16 mg	7	30	ICH s/p VP shunt	16	83	Cured
7	15/M	CR <i>Acinetobacter baumannii</i>	Meropenem/colistin	Colistin 2 mg	10	14	Hydrocephalus s/p EVD Hypertensive nephrosclerosis	21	98	Cured
8	53/M	<i>Escherichia coli</i> ^d	Cefepime/ceftazidime	Gentamicin 10 mg	3	19	TBI/ICH s/p EVD	14	177	Cured
9 ^a	79/F	<i>Escherichia coli</i> (ESBL)	Imipenem	Amikacin 10 mg	3	48	Brain infarction s/p VP shunt	6	81	Cured
10	57/M	<i>Klebsiella pneumoniae</i>	Ceftriaxone	Amikacin 30 mg	17	5	Hydrocephalus s/p EVD DM	22	128	Cured
11	77/F	<i>Pseudomonas aeruginosa</i>	Ceftazidime	Amikacin 10 mg	15	12	Intracranial tumor s/p VP shunt	19	172	Death
12	48/F	<i>Pseudomonas aeruginosa</i>	Cefepime	Amikacin 50 mg	10	13	Communicated hydrocephalus s/p Ommaya	7	66	Death
13	25/M	CR <i>Pseudomonas aeruginosa</i>	Ceftazidime Meropenem	Gentamicin 4 mg	15	55	TBI/ICH s/p craniotomy	9	147	Death
14	68/M	<i>Serratia marcescens</i>	Ceftazidime/cefepime	Gentamicin 8 mg	14	8	ICH s/p EVD	15	59	Cured
15	35/M	<i>Sphingobacterium multivorum</i>	Imipenem/ trimethoprim/ sulfamethoxazole	Gentamicin 8 mg	21	63	TBI/ICH s/p VP shunt	16	124	Cured

^a Two separate episodes in one patient.

^b Period from when bacteria were first isolated in the CSF specimen to the initiation of IVT therapy.

^c Mixed infection with *Candida tropicalis*.

^d Mixed infection with methicillin-resistant *Staphylococcus aureus*.

Yan etki
Şimik menenjit
Eozinofilik pleositoz??
İşitme kaybı

Systematic Review of Efficacy, Pharmacokinetics, and Administration of Intraventricular Aminoglycosides in Adults

Systematic Review of Efficacy, Pharmacokinetics, and Administration of Intraventricular Vancomycin in Adults

Karen Ng · Vincent H. Mabasa · Ivy Chow ·
Mary H. H. Ensom

Antibiyotik dozu yaşa, kiloya göre değil ventrikül ve BOS hacmine
ilaç PK'i BOS miktarına
ilaç klirensi BOS üretimi, BOS drenajına bağlı
BOS'da ki düzeyine bakılsın mı (başlangıçta EVET)

External Ventriküler Drenaj Seti (EVDS)-menenjit/ventrikülit

- EVDS süresi >11 gün (>5 gün) enfeksiyon riski
- Sık BOS örneği almak
- İntraventriküler hemoraji
- Cerrahi teknikte aksamalar

S epidermidis %70

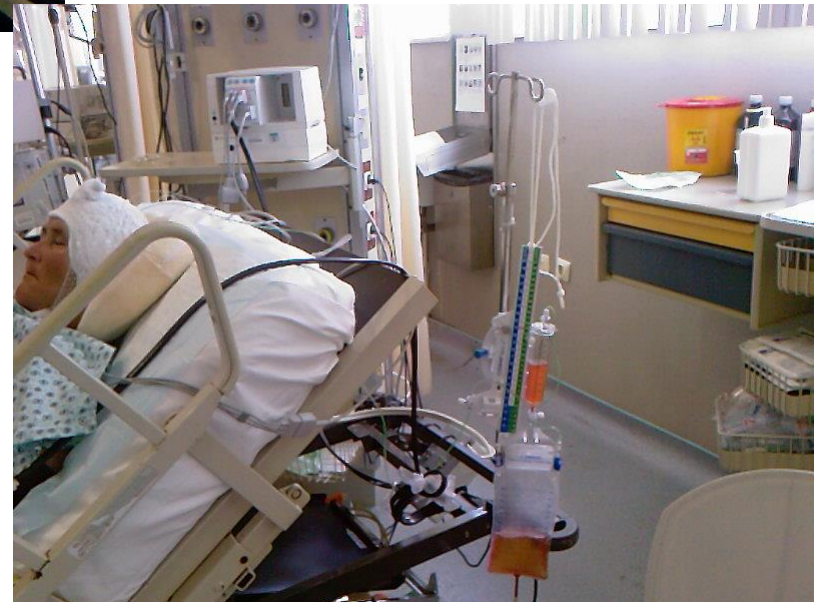
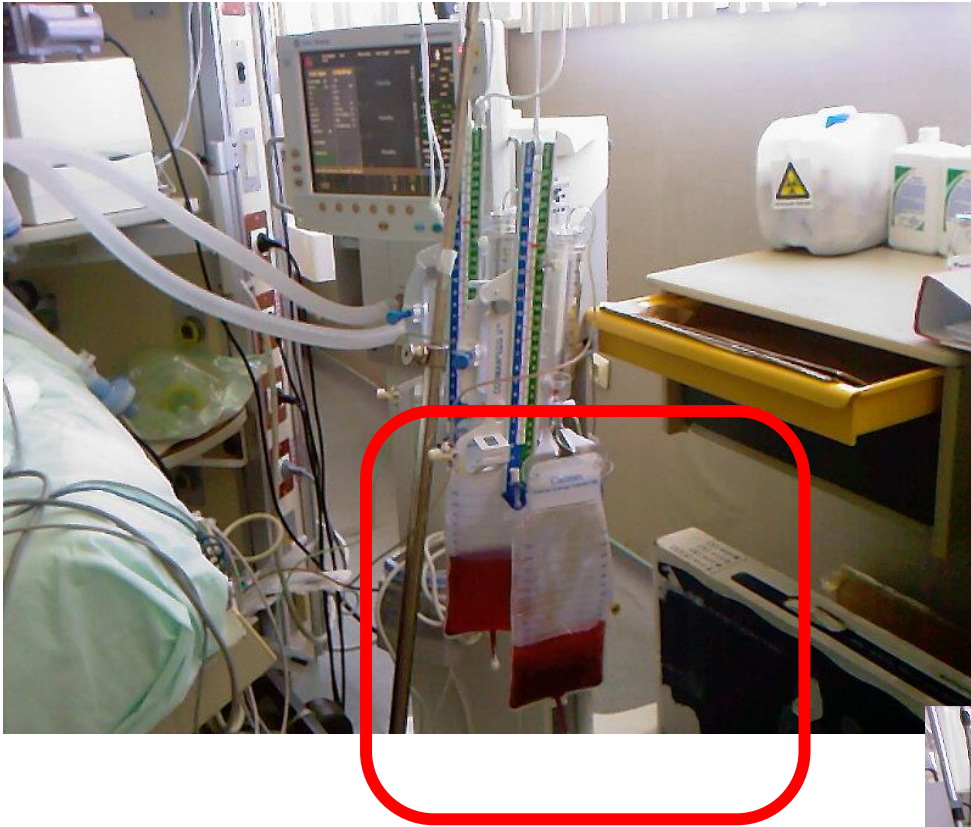
S aureus %10

Diğer <%20

Gram negatif basil %15

Anaerob nadir

Candida spp çok nadir



Katater-Şant İnfeksiyonu??

- Tedavinin başarısı için antibiyotik tedavisi ve infekte şant/dren/infüzyon pompası çekilmeli
- Şant infekte ise çekilmeli , EVDS takılmalı (ağızlaştırma yapılıyor genelde)

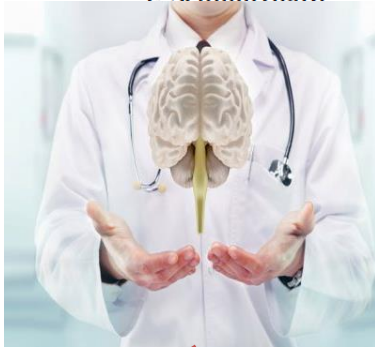
İlk seçenek Vankomisin

Linezolid (başarılı ama ilk seçenek değil)

Daptomisin BOS'a geçişi çok az (%0,8) ama başarılı bulunmuş tek kullanılmaz (rifampisin ile kombine, 10 mg/kg)

Şant menajiti rifampisin (tabii duyarlı ise)

R. Beer
P. Lackner
B. Pfausler
F. Schmutzhard



und External ventricular drainage (EVD) is frequently necessary in neurological and neurosurgical intensive care

EVDS değişimi

Kanama?
Yeni enfeksiyon??
????

Nosocomial ventriculitis and meningitis in neurocritical care patients

in providing an appropriate and timely diagnosis of this disease entity and (3) to propose an algorithm for both rapid diagnosis and



frequently impaired either by the presence of systemic inflammation due to the primary disease or because the hemorrhagic CSF itself

Tedavi başarısı için
EVDS/şant değişimi

Management of Nosocomial External Ventricular Drain-Related Ventriculomeningitis

Ronny Beer · Bettina Pfausler · Erich Schmutzhard

Published online: 4 November 2008
© Humana Press Inc. 2008

Abstract

Introduction Neurocritical care patients requiring external ventricular drainage are at risk for the development of a device-related infection. Infection rate of external ventriculostomy catheters is high with reported incidences ranging from 5% up to more than 20%. Nosocomial ventriculitis or ventriculomeningitis are potential life-threatening conditions which may contribute to a permanent adverse outcome of the patient. Reducing morbidity and mortality is strongly dependent on prompt diagnosis and on the ini-

Keywords Nosocomial infections · External ventricular drainage · Ventriculomeningitis · Antibiotics

Case Report

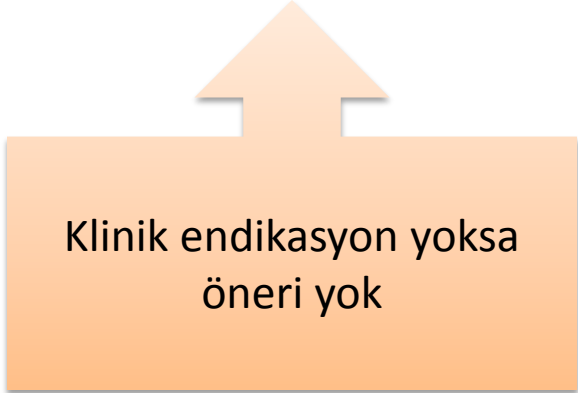
A 47-year-old Caucasian female with unremarkable medical history was admitted to the neurological intensive care unit because of spontaneous subarachnoid hemorrhage grade 2 according to WFNS. Digital subtraction angio-



- SBi vetrikülit ? İle
 - BOS'da önce KNS üremiş
 - Vankomisin IV/IVT (7 gün)
 - Klinik yanıt yok ve BOS bulguları düzelmemiş 2. BOS'da sadece G (-) basil üremiş
 - Vankomisin kesilmiş, Meropenem başlanmış
 - Klinik kötüleşmiş, BOS bulguları tam düzelmemiş, katater çekilmiş (katater kx: KNS)
 - Vankomisin verilmiş yanıt var !!!

Tedavi Süresi?

- Klinik parametreler izlenmeli
- BOS kültürü negatifleşmeli
- BOS bulgusu düzelmeli
- Günlük EVDS ya da kataterden BOS analizi !!!



Klinik endikasyon yoksa
öneri yok

Yeni şant ne zaman takılacak

Etken	Kültür	BOS bulguları	
<i>S epidermidis</i>	Tek kültür pozitif	Normal	3 gün tedavi sonrası kültür negatif ise yeni şant
	Tek kültür pozitif	Anormal	7 gün tedavi sonrası kültür negatif ise yeni şant
	Birden fazla kültür pozitif	Normal veya anormal	10 -14 gün veya BOS kültürü negatifleşene kadar tedavi sonrasında 3 gün daha kültür
Diğer etkenler (<i>S aureus</i> , Gram negatif basiller)	Tek ya da birden fazla kültür pozitif	Normal veya anormal	10-14 gün tedavi ve en az 10 günlük kültür negatifliği varsa yeni şant



- Bazı yazarlar şant takılmadan önce peş peşe 3 kültür negatif olmalı der
 - Kültür üremedi olarak beklenmeli mi?
 - Ortalama 7 gün (+2/3?)
- Antibiyotik aldığı için geç ve güç üreyebilir
- Bu sürede tekrar infekte etme riski olabilir mi?

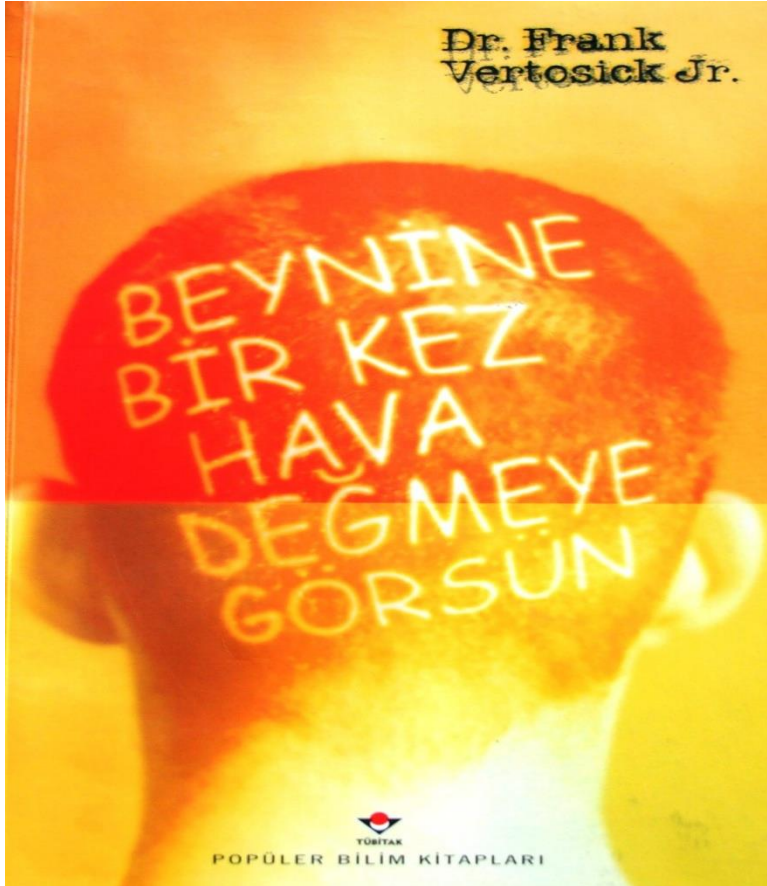
BOS kaçağı varlığında antibiyotik tedavisi/profilaksi

- İnfeksiyon tablosu yoksa
- Kafa tabanı kırığı ve/veya BOS kaçağında profilaksi önerisi yok
- BOS kaçağı >7 gün onarım yapılmalı
- BOS kaçağı, kafa tabanı kırığında mutlaka pnömokok aşısı önerilmeli



- Aslında standart bir protokol yok
- Giderek artan antibiyotik direnci
- BOS'a geçen antibiyotiklerin sayısı zaten azdı, şimdi !!!
- Erken tanı ve tedavi
- En iyisi ENFEKSİYON KONTROLÜ

Bir kez HAVA deęmeye, SU kaçmaya
görsün



Teşekkürler

- 1 mg kolistin baz = 30.000 IU

- 1 mg kolistin baz = 10.500 IU

- 1.000 mg kolistin baz = 10.500.000 IU

1 mg kolistin baz = 2,4 mg kolistimetat sodyum

- 500 mg kolistin baz

- 150 mg kolistin baz = 4.500.000 IU

- ~ 400 mg kolistimetat sodyum

Kolistin İntratekal (IT)/İntraventriküler (IVT) Uygulama

Yapılan çalışmalarda kolistimetat sodyum????;

1-2X5-10 mg/ gün ya da

1-2 X 40.000-125.000 IU

Uygulanacak ilaç miktarı kadar BOS alıp, hazırlanan antibiyotik IT/IVT uygulanır

1-2 saat (hastanın BOS drenaj ihtiyacına göre) klemplenmeli

IDSA: BOS kültürü negatifleşince 10-14 gün verilmeli

Kültür sonuçlanınca 48 saat içinde uygulanmaz ise mortalite artar

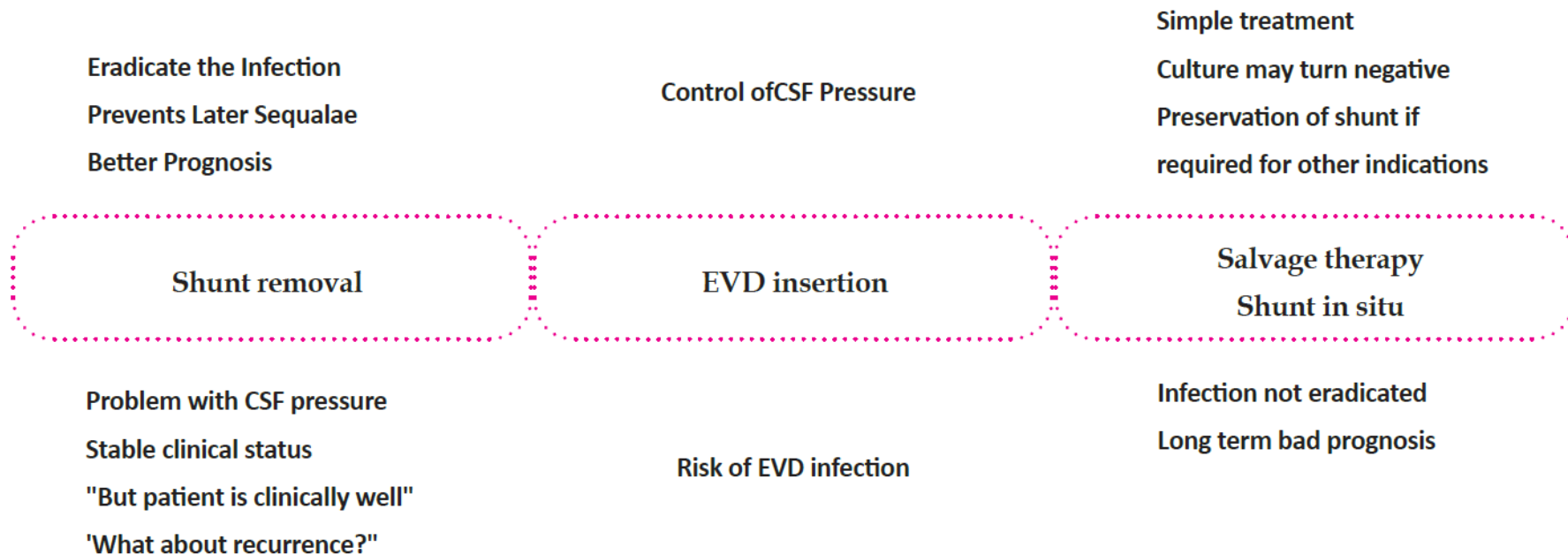


Figure 2. The clinical dilemma of an infected shunt

