Treatment of hospital-acquired meningitis including difficult to treat organisms such as MRSA, VRE, multidrug resistant Gram negatives

Dr. Oğuz Reşat Sipahi
Ege Üniversitesi Tıp Fakültesi
İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD
Bornova-İzmir
http://www.sipahi.tk
Plan

- Definition
- Epidemiology
- Pathogens
- Empirical therapy

- Culture based therapy
  - Gram positives
    - Staphylococci-MRSA-MRCNS
    - Enterococci-VRE
  - Gram negatives
    - Enterobacteriaceae
    - Non-fermentatives
  - Intrathecal therapy

- Prevention
"Primum non nocere"

"The first requirement of a hospital is that it should do the sick no harm"

Sir James Simpson

Florence Nightingale

www.saglik.gov.tr
MEN-Meningitis or ventriculitis

Meningitis or ventriculitis must meet at least 1 of the following criteria:

1. Patient has organisms cultured from cerebrospinal fluid (CSF).
2. Patient has at least 1 of the following signs or symptoms with no other recognized cause: fever (>38°C), headache, stiff neck, meningeal signs, cranial nerve signs, or irritability, and
   at least 1 of the following:
   a. increased white cells, elevated protein, and/or decreased glucose in CSF
   b. organisms seen on Gram’s stain of CSF
   c. organisms cultured from blood
   d. positive antigen test of CSF, blood, or urine
   e. diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for pathogen

and

if diagnosis is made antemortem, physician institutes appropriate antimicrobial therapy.
Nosocomial Healthcare associated infections

- Acquired 48-72 h after hospitalization
- In 30 days post discharge
- Hospitalization in the last 90 days
- 5-15%
- Most are MDR
- More expensive to treat
- Higher fatality

- Meningitis
  - high morbidity
  - high mortality
  - high morbidity associated mortality

- 0.34 in 51133 hospitalized cases in neurosurgery clinic


www.cdc.gov

Bardak-Ozcem S, Sipahi OR MJIMA 2013;1:14

Palabiyikoglu et al Hosp Infect. 2006;62(1),94-7
Epidemiology

- Craniotomy
  - 0.8-1.5%
  - Dura-CSF leakage
  - Concomitant infection at the surgical site
- Internal ventricular catheters (Shunts)
  - 4-17%

Epidemiology

• External ventricular catheters
  – CSF monitoring
  – Treatment of shunt infections
  – 8% infection risk

• External lumbar catheters
  – Risk 5%
  • Routine changing or sampling
  • Blockage
  • CSF leakage
  • Intraventricular hemorrhage

• Head trauma
  – Moderate to severe 1.4%
  – Open compound cranial fractures 2-11%
  – Basillar fracture upto 25%
  – Median time 11 days

• Lumbar puncture
  – 1/50000

Pooled analysis of 2,408 cases of acute adult purulent meningitis from Turkey.

Arda B, Sipahi OR, Atalay S, Ulusoy S.
Department of Infectious Diseases and Clinical Microbiology, Ege University Faculty of Medicine, Bornova, Izmir, Turkey.

Table 1. Distribution of pathogens isolated in the CSF cultures

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>457</td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td>251</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>29</td>
</tr>
<tr>
<td>Enterobacteriaceae (species not mentioned)</td>
<td>8</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>6</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>6</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
<td>5</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>4</td>
</tr>
<tr>
<td>Gram-negative bacilli (species not mentioned)</td>
<td>4</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>3</td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>3</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>3</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>2</td>
</tr>
<tr>
<td><em>Brachymella catarrhalis</em></td>
<td>1</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>1</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>784</strong></td>
</tr>
</tbody>
</table>
Pathogens

• Neurosurgery or patients hospitalized for a prolonged period after penetrating trauma or basilar skull fracture
  – Staphylococci or facultative or aerobic gram-negatives
  – Pneumococci rare

• Foreign bodies
  – Coagulate-negative staphylococci, *Propionibacterium acnes*

• Basillar skull fracture or early otorhinologic surgery
  – Nasopharinx flora
    • Pneumococci

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Holland</th>
<th>Turkey</th>
<th>Taiwan</th>
<th>USA</th>
<th>Germany</th>
<th>Brazil</th>
<th>Korea</th>
<th>France</th>
<th>Total</th>
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<tbody>
<tr>
<td>CNS</td>
<td>3</td>
<td>7</td>
<td>7</td>
<td>13</td>
<td>4</td>
<td>3</td>
<td>34</td>
<td>34</td>
<td>105</td>
</tr>
<tr>
<td>S. Aureus (MR?)</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>MSSA</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>20</td>
<td></td>
<td></td>
<td>32</td>
</tr>
<tr>
<td>MRSA</td>
<td>6</td>
<td>11</td>
<td>3</td>
<td>8</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td>33</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>3</td>
<td>9</td>
<td>5</td>
<td>17</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>2</td>
<td>9</td>
<td>3</td>
<td>13</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>Pseudomonas spp</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>26</td>
</tr>
<tr>
<td>Acinetobacter spp</td>
<td>15</td>
<td>4</td>
<td>6</td>
<td>1</td>
<td>4</td>
<td>27</td>
<td>2</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Pneumococci</td>
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<td>3</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>24</td>
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<tr>
<td>Enterococci</td>
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<td>2</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>4</td>
<td>1</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>9</td>
<td>11</td>
<td>33</td>
<td>1</td>
<td>4</td>
<td>6</td>
<td>38</td>
<td>112</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>60</td>
<td>53</td>
<td>119</td>
<td>12</td>
<td>18</td>
<td>83</td>
<td>106</td>
<td>508</td>
</tr>
</tbody>
</table>

Treatment

- Challenging
  - Blood/brain barrier
    - Penetration into CSF limited
  - Shunt

- CSF/serum
  - 20-40% ceftazidime,
  - 8-16% ceftriaxone,
  - 10% cefepime
  - 8.5% imipenem
  - 2% meropenem
  - 60-70% linezolid
  - 7-14% vancomycin
  - 5-6% daptomycin

Sanford guide 2011
Empirical therapy

• Ceftazidime or cefepime or meropenem
• Vancomycin
  • CSF/blood: 7-14%
• Evidence???
• No comparative trial

Tunkel et al. IDSA 2002 guidelines. CID 2004; 39:1267–84
Mandell’ Principles and Practice of Infectious diseases 2010
Sanford guide 2012
MRSA meningitis

- Mostly postneurosurgery
- 1993-2002 Ankara University
- 51 meningitis attacks
  - 7 MRSA (14%)
  - All post-neurosurgical
  - 26 shunt infections (52%)

EUMF

- 2006-2010
- 89 hospital-acquired meningitis
  - 14 MRSA (15.7%)
Risk factors

MRSA/MDR bacterial meningitis

- Neurosurgery
- Shunt insertion
- EVD
- Lumbar drainage
- Previous meningitis attack
- Head trauma
- CSF leakage
Celsius Library
Practice guidelines for the management of bacterial meningitis.


Staphylococcus aureus
- MSSA
  - Nafcillin or oxacillin
  - Vancomycin, meropenem (B-III)
- MRSA
  - Vancomycin
  - TMP/SMX, linezolid (B-III)

Staphylococcus epidermidis
- Vancomycin
- Linezolid (B-III)
Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus Aureus Infections in Adults and Children: Executive Summary

Catherine Liu,1 Arnold Bayer,3,5 Sara E. Cosgrove,6 Robert S. Daum,7 Scott K. Fridkin,8 Rachel J. Gorwitz,9 Sheldon L. Kaplan,10 Adolf W. Karchmer,11 Donald P. Levine,12 Barbara E. Murray,14 Michael J. Rybak,12,13 David A. Talan,15 and Henry F. Chambers12

MRSA Treatment Guidelines • CID 2011:52 (1 February) • 285
MRSA Meningitis treatment

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Treatment</th>
<th>Adult dose</th>
<th>Pediatric dose</th>
<th>Class</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td>Vancomycin</td>
<td>15-20 mg/kg/dose IV every 8-12 h</td>
<td>15 mg/kg/dose IV every 6 h</td>
<td>BII</td>
<td>Some experts recommend the addition of rifampin 600 mg QID or 300-450 mg BID to vancomycin for adult patients (BIII). For children ≥12 years of age, linezolid 600 mg BID.</td>
</tr>
<tr>
<td>Linezolid</td>
<td></td>
<td>600 mg PO/IV BID</td>
<td>10 mg/kg/dose PO/IV every 8 h, not to exceed 600 mg/dose</td>
<td>BII</td>
<td></td>
</tr>
<tr>
<td>TMP-SMX</td>
<td></td>
<td>5 mg/kg/dose PO/IV every 8-12 h</td>
<td>ND</td>
<td>CIII/ND</td>
<td></td>
</tr>
</tbody>
</table>

- Shunt removal
- No shunt insertment until negative cultures (A-II)
EFNS guideline on the management of community-acquired bacterial meningitis: report of an EFNS Task Force on acute bacterial meningitis in older children and adults

MSSA
- Flucloxacillin 4x2 g (IV)
- Penicillin allergy vancomycin (IV)
- Rifampin may be added

- MRSA linezolid (IVC)

Vancomycin

- High molecular weight
- No comparative trial-historical golden standard
- CSF penetration
  - 7-14%
  - 2-6 µg/ml CSF concentration

- Treatment failure
  - Intrathecal therapy
  - Teicoplanin
  - Linezolid
  - Daptomycin
Vancomycin MIC creep

<table>
<thead>
<tr>
<th>Vancomycin MIC (µg/ml)</th>
<th>No. of isolates</th>
<th>Median DTE</th>
<th>Median duration of vancomycin therapy (days)</th>
<th>Eradication rate by EOT</th>
<th>Median reduction in log_{10} CFU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>13</td>
<td>6.0</td>
<td>13.0</td>
<td>10/13 (77)</td>
<td>3.06</td>
</tr>
<tr>
<td>1.0</td>
<td>7</td>
<td>9.5</td>
<td>17.0</td>
<td>5/7 (71)</td>
<td>3.09</td>
</tr>
<tr>
<td>2.0</td>
<td>14</td>
<td>13.0</td>
<td>18.5</td>
<td>3/14 (21)</td>
<td>2.75</td>
</tr>
</tbody>
</table>

a. DTE, day to eradication.
b. EOT, end of treatment. The eradication rate data represent the number of patients from the organism was eradicated/total number of patients in the group (percent).

The median time to eradication is greater than 15 days, as only 21% of patients showed clearance of bacteremia.
TEICOPLANIN

Meningitis due to methicillin-resistant Staphylococcus aureus (MRSA): Review of 10 cases

Bilgin Arda a, *, Tansu Yamazhan a, Oguz Resat Sipahi a, Sertac Islekel b, Çağrı Buke a, Sercan Ulusoy a

a Ege University, Medical Faculty, Department of Infectious Diseases and Clinical Microbiology, 35100 Bornova, Izmir, Turkey
b Ege University, Medical Faculty, Department of Neurosurgery, 35100 Bornova, Izmir, Turkey

Received 5 August 2004; accepted 17 December 2004

Abstract

We evaluated retrospectively, 10 MRSA meningitis cases in our hospital that occurred between January 1999 and June 2004. All were post-neurosurgical and were considered to have hospital-acquired meningitis. Fever, leukocytosis, variable conscious levels were the most common findings. Six patients were treated with regimens including teicoplanin, and four with vancomycin. Mean duration of treatment was 23.5 ± 18.8 days (range, 3–60 days). One patient died. In cases of MRSA meningitis, intravenous vancomycin is the mainstay of therapy. However, six of these 10 patients were successfully treated with regimens including teicoplanin, suggesting that this agent may be an alternative to vancomycin in the therapy of these cases.

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Keywords: Meningitis; Methicillin-resistant Staphylococcus aureus; Teicoplanin; Vancomycin
Vancomycin versus teicoplanin in the therapy of experimental methicillin-resistant Staphylococcus aureus (MRSA) meningitis

Oguz Resat Sipahi a,*, Bilgin Arda a, Taskin Yurtseven b, Hilal Sipahi c, Erkin Ozgiray b, Bedia Mutay Suntur d, Serkan Unsoy a

a Ege University, Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, 35100 Bornova, Izmir, Turkey
b Ege University, Faculty of Medicine, Department of Neurosurgery, Izmir, Turkey
c Ege University, Faculty of Medicine, Department of Public Health, Izmir, Turkey
d Kuralya State Hospital, Infectious Diseases and Clinical Microbiology Clinic, Kuralya, Turkey

Received 20 April 2005; accepted 7 August 2005

Abstract

The aim of this study was to compare the antibacterial activity of teicoplanin and vancomycin in the treatment of methicillin-resistant Staphylococcus aureus (MRSA) meningitis using a rabbit meningitis model. The MRSA strain ATCC 43300 was used to infect the rabbits. The vancomycin group received 20 mg/kg vancomycin every 12 h (q12h), the teicoplanin group received 6 mg/kg teicoplanin q12h and the control group did not receive any treatment. Drug levels were measured using a bioassay technique. Bacterial counts in the treatment groups were significantly lower ($P < 0.05$) than those of the control group at 12 h and 24 h after treatment. When the treatment groups were compared, the bacterial counts after 12 h or 24 h of treatment were similar ($P > 0.05$). These data suggest that the antibacterial activity of vancomycin and teicoplanin are similar in experimental MRSA meningitis of rabbits.

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Keywords: Pharmacokinetics; Meningitis; MRSA; Bioassay; Teicoplanin; Glycopeptides; Staphylococcus aureus
Vancomycin+Rifampin

- Effective in rabbits
- Rifampin CSF penetration 22%
- Successful case reports

Linezolid

- Oxazolidinon group
- Relatively high CSF penetration – 66%

- Systematic review
  - A total of 20 meningitis cases treated with linezolid
    - 4 MRCNS and 3 MRSA
    - Treatment duration 14-84 days

On day 5: 2 microbiological failures (1 MRSA and 1 MRCNS)

7/10 MRCNS and 4/8 MRSA: one month survival

5/10 MRCNS and 2/8 MRSA six month survival
Vancomycin versus linezolid in the treatment of methicillin-resistant Staphylococcus aureus meningitis in an experimental rabbit model.

Calik S, Turhan T, Yurtseven T, Sipahi OR, Buke C.

Department of Infectious Diseases and Clinical Microbiology, Urla State Hospital, Izmir, Turkey. sebnemozkoren@yahoo.com

Abstract

BACKGROUND: The aim of this study was to compare the antibacterial efficacy of vancomycin and linezolid in a rabbit model of methicillin-resistant Staphylococcus aureus (MRSA) meningitis.

MATERIAL/METHODS: Meningitis was induced by intracisternal inoculation of ATCC 43300 strain. After 16 h incubation time and development of meningitis, the vancomycin group received vancomycin 20 mg/kg every 12 h. The linezolid-10 and linezolid-20 groups received linezolid in 10 and 20 mg/kg dosages every 12 h, respectively. The control group did not receive any antibiotics. Cerebrospinal fluid bacterial counts were measured at the end of 16-h incubation time and at the end of 24-h treatment.

RESULTS: Bacterial counts were similar in all groups at 16 h. At the end of treatment the decrease in bacterial counts in the vancomycin group was approximately 2 logs higher than the linezolid-20 group (p > 0.05) and approximately 4 logs higher than in the linezolid-10 group (p: 0.037). (Vancomycin group: -2.860 ± 4.495 versus Linezolid-20: -0.724 ± 4.360, versus Linezolid-10: 1.39 ± 3.37). Full or partial bacteriological response was higher in vancomycin versus linezolid-10 (p: 0.01), but not vancomycin versus linezolid-20 or linezolid-10 versus-linezolid-20 groups.

CONCLUSIONS: Our results suggest that linezolid is not statistically inferior to vancomycin in the treatment of MRSA meningitis in an experimental rabbit model in 20 mg/kg q12 h dosage; however, it is inferior in 10 mg/kg q12 h dosage. Additional data should gathered to confirm these findings in advance of clinical trials to assess efficacy in humans.

Table 1. Results of bacterial counts.

<table>
<thead>
<tr>
<th>Group</th>
<th>Bacterial count (log^{10} CFU/ML) (Number of rabbits)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16 h</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>4.33±1.42 (11)</td>
</tr>
<tr>
<td>Linezolid-10</td>
<td>3.56±1.04 (14)</td>
</tr>
<tr>
<td>Linezolid-20</td>
<td>3.43±0.91 (11)</td>
</tr>
<tr>
<td>Control</td>
<td>3.85±0.26 (11)</td>
</tr>
</tbody>
</table>
Vancomycin versus Linezolid in the Treatment of Methicillin-Resistant Staphylococcus aureus Meningitis

Oguz Resat Sipahi, Selin Bardak-Ozcem, Tuncer Turhan, Bilgin Arda, Mete Ruksen, Husnu Pullukou, Sohret Aydemir, Tayfun Dalbasti, Taskin Yurtseven, Hilal Sipahi, Mehmet Ziele, and Sercan Ulusoy

• Day 5 microbiological success
  – Vanco 2/9
  – Linezolid 7/9
  – p<0.044

• One month survival in microbiologically successful cases 2/2 vs 4/7

• Vancomycin MIC 2 mg/l
  – 1/6 success with vancomycin
Daptomycin

- Speedy killer
- CSF penetration 5-6%
- Case report
- EUMF-one case
  - Vancomycin
  - Linezolid
  - Linezolid+daptomycin
  - Exitus

Daptomycin is more efficacious than vancomycin against a methicillin-susceptible Staphylococcus aureus in experimental meningitis.

Gerber P, Stucki A, Acosta F, Cottagnoud M, Cottagnoud P.

Clinic of Pneumology, Inselspital, Bern, Switzerland.

Abstract

OBJECTIVES: To test the efficacy of daptomycin, a cyclic lipopeptide antibiotic, against a methicillin-susceptible Staphylococcus aureus strain in experimental rabbit meningitis and to determine its penetration into non-inflamed and inflamed meninges.

RESULTS: Over a treatment period of 8 h, daptomycin (15 mg/kg) was significantly superior to the comparator regimen vancomycin (-4.54 +/- 1.12 log(10)/mL for daptomycin versus -3.43 +/- 1.17 log(10)/mL for vancomycin). Daptomycin managed to sterilize 6 out of 10 CSFs compared with 4 out of 10 for vancomycin. The penetration of daptomycin into inflamed meninges was approximately 5% and approximately 2% into non-inflamed meninges.

CONCLUSIONS: The superior bactericidal activity of daptomycin was confirmed in vivo and in time-killing assays in vitro.
Attenuation of cerebrospinal fluid inflammation by the nonbacteriolytic antibiotic daptomycin versus that by ceftriaxone in experimental pneumococcal meningitis.

Grandgirard D, Oberson K, Bühlmann A, Gäumann R, Leib SL.

Laboratory for Experimental Neuroinfectiology, Institute for Infectious Diseases, University of Bern, Bern, Switzerland.

Abstract

Antibiotic-induced bacteriolysis exacerbates inflammation and brain damage in bacterial meningitis. Here the quality and temporal kinetics of cerebrospinal fluid (CSF) inflammation were assessed in an infant rat pneumococcal meningitis model for the nonbacteriolytic antibiotic daptomycin versus ceftriaxone. Daptomycin led to lower CSF concentrations of interleukin 1beta (IL-1beta), IL-10, IL-18, monocyte chemotactic protein 1 (MCP-1), and macrophage inflammatory protein 1 alpha (MIP-1alpha) (P < 0.05). In experimental pneumococcal meningitis, daptomycin treatment resulted in more rapid bacterial killing, lower CSF inflammation, and less brain damage than ceftriaxone treatment.
Daptomycin versus vancomycin in treatment of methicillin-resistant Staphylococcus aureus meningitis in an experimental rabbit model.

Bardak-Ozcem S, Turhan T, Sipahi OR, Arda B, Pulukcu H, Yamazhan T, Isikgoz-Tasbakan M, Sipahi H, Ulusoy B.

Ege University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Izmir, Turkey.

- ATCC 43300 MRSA
- 16 h incubation
- Vancomycin 20 mg/kg 0. and 4. h
- Daptomycin 15 mg/kg X 1

<table>
<thead>
<tr>
<th>TABLE 1 Cerebrospinal bacterial culture results</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of bacteria (log₁₀ CFU/ml)² after:</td>
</tr>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Daptomycin</td>
</tr>
<tr>
<td>Vancomycin</td>
</tr>
</tbody>
</table>

* Data are means ± standard deviations.
**Enterococcus spp**-guidelines

- Ampicillin sensitive
  - Ampicillin+genta ...
- Ampicillin-resistant
  - Vanco+genta ...
- Ampicillin and genta and or resistant
  - Linezolid (B-III)

Enterococcus spp

- Amp+genta or vanco+genta
  - no comparative study
- Animal study absent (adaptation problem?)
- Linezolid
  - >10 successful case reports
  - Mostly VRE meningitis
  - Failures
- Tigecycline+daptomycin
- Daptomycin

Bardak-Ozcem S MJIMA 2013;2:3
Guidelines- Enterobacteriaceae

• Gram-negative Enterobacteriaceae
  – Ceftriaxone or Cefotaxime or Meropenem

• *Escherichia coli* and other Enterobacteriaceae
  – Third-generation cephalosporin (A-II)
  – Cefepime, meropenem, aztreonam, fluoroquinolone, trimethoprim-sulfamethoxazole


Enterobacteriaceae

- Global problem-Extended-spectrum beta lactamase producers
  - 15-20% carriage in the community-Turkey
  - Prostate biopsy
  - Resistant to third-generation cephalosporins, mostly to the 4th generation too…
  - Meropenem 3x2
  - Carbapenems/carbapenemases
    - No report until now
MDR Gram-negative non-fermentatives

- *Acinetobacter* and *Pseudomonas* spp
  - Mostly resistant to 3. or 4. gen cephalosporins.
  - Carbapenem resistance >60%

- Resistance to empirical therapy
- Treatment problematic

Bardak-Ozçem S, Sipahi OR MJIMA 2012;1:13
Guidelines-Acinetobacter

- For empirical treatment of Acinetobacter meningitis
  - Intravenous meropenem, with or without an aminoglycoside administered by the intraventricular or intrathecal route

References:
MDR/carbapenem resistant non-fermentatives Pseudomonas-Acinetobacter

- Antibiogram based treatment
  - Aminoglycosides
  - Colistin
  - Tigecycline (Acineto)
  - Sulbactam (Acineto)
Acinetobacter meningitis

- Mostly postneurosurgical
- Mortality/morbidity high
- Antibiotic penetration problematic
- Treatment challenging
Ege University Neurosurgery clinic-CSF samples- *Acinetobacter* spp.

Sensitivity pattern (%)

88 strains
- 38% amikacin
- 36% cef/sulb
- 32% carbapenem
- 9% amp/sulb
- 10% cefepime
Colistin-pharmacokinetics

- Penetration of colistin into CSF for MDR A. baumannii meningitis treatment, 5 mg/kg/day of colistin resulted in 25% CSF-serum rate.
  

- Colistin pharmacokinetics prospectively after intravenous administration of colistin
  - in critically ill patients without central nervous system infection (controls, n = 5) 7%
  - in patients with external ventricular drain-associated ventriculitis after intravenous administration (EVDViv, n = 3) 11%
  - combined intravenous/intraventricular administration (EVDVcomb, n = 4). 40-45%

- CSF colistin concentrations above the MIC of 0.5 μg/ml were achieved only in EVDVcomb patients.

Colistin

• IV and/or IT
• In a syst-review of 14 patients with mdr Acinetobacter baumannii meningitis or ventriculitis who were treated with colistin administered either IV or IT
  – CSF sterilization in all cases
  – 13 patients cured.

• In a retrospective review of 51 cases of Acinetobacter meningitis
  – All 8 patients who were treated with IV+IT colistin survived.

Colistin- Ege University

- Neurosurgery clinic
- MDR *A.baumannii* meningitis-two cases
- MDR *P. aeruginosa*-one case
- Only colistin sensitive
- 3x2 million units + 75,000 units IT
- Treatment successful
Tigecycline

• 30S ribosome -protein synthesis
• Broad antibacterial spectrum including
  – MDR gram-negatives Acinetobacter, ESBL-producer *E. coli* or *K. pneumoniae*
  – MDR gram-positives (MRSA or VRE)
• Despite the fact that it is a bacteriostatic agent, it is used successfully as monotherapy or combination therapy for meningitis treatment
Tigecycline pharmacokinetics

• Serial, steady-state, serum, and CSF concentrations of tigecycline when administered in the FDA-approved dose of 50 mg every 12 hours
  – CSF concentrations remained relatively stable, suggesting that tigecycline did not accumulate in the CSF.
  – Tigecycline concentrations in the CSF were between 0.035 and 0.048 mg/L, while corresponding serum concentrations were 0.097-0.566 mg/L.
  – Calculated tigecycline penetration ratio ranged from 0% to 52%

Tigecycline Clinical evidence

- *A. baumannii*-tigecycline monotherapy
- *A. baumannii*-tigecycline+netilmicin
- *A. baumannii*-tigecycline+netilmicin
- *Enterococccus faecium* - tigecycline+daptomycin
- ESBL-producer *Klebsiella pneumoniae*-tigecycline+ciprofloxacin
- *Elizabethkingia meningoseptica* iv piperacillin-tazobactam, iv vancomycin, cotrimoxazole tablet, intrathecal tigecycline

EUMF

• Neurosurgery clinic
  – *A. baumannii* meningitis-7 cases
  – In combination with netilmicin or amikacin
  – 6/7 success
Sulbactam

- Efficacy against *Acinetobacter*
- Upto 12 gr/day
- 12 µg/ml sulbactam after 1-4 h in CSF of patients with bacterial meningitis after 4 gr/day sulbactam


- Two failures with 3-6 gram amp/sulb

Successful reports

• Four cases

• One case

• One case
  – Sipahi et al Ankem Derg 2006 20:236-8
Aminoglycosides

- CSF penetration low/negligible
- Intrathecal
- In combination with other antibiotics
- High dosages 30 up to 150 mg

Bardak-Ozcuem S, Sipahi OR MJIMA 2013;2:1
Guidelines - *Pseudomonas*

- **Pseudomonal meningitis**
  - Meropenem ± Gentamicin

- **Pseudomonas aeruginosa**
  - Cefepime or ceftazidime (A-II)
  - Aztreonam, ciprofloxacin, meropenem
  - Addition of aminoglycoside should be considered


Carbapenem-resistant *Pseudomonas spp.*

- Colistin
- Intrathecal colistin-aminoglycosides
Intrathecal therapy

• Not routinely advised
• No antibiotic
  – FDA approval
  – Randomized controlled trials
• x20 MIC is important
• MBC is usually ≤ x8 MIC
• 50 mg/0.15 L=330 mg/L
  – MIC upto 16-40 mg/l

### Table 3. Recommended Doses of Selected Antimicrobial Agents Administered by the Intraventricular Route.*

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>Daily Intraventricular Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>5–20 mg†</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1–2 mg in infants and children; 4–8 mg in adults</td>
</tr>
<tr>
<td>Amikacin</td>
<td>5–50 mg‡</td>
</tr>
<tr>
<td>Polymyxin B</td>
<td>2 mg in infants and children; 5 mg in adults</td>
</tr>
<tr>
<td>Colistin, usually formulated as colistimethate sodium</td>
<td>10 mg once daily or 5 mg every 12 hr§</td>
</tr>
</tbody>
</table>

* There are no data that define the exact dose of an antimicrobial agent that may be administered by the intraventricular route, but the dose can be estimated through the measurement of the cerebrospinal fluid trough concentration, in the case of agents for which these measurements can be obtained. Medications administered by the intraventricular route should be preservative-free.

† Most studies have used a 10-mg or 20-mg dose.

‡ The usual daily dose is 30 mg.

§ In one study, patients received 10 mg every 12 hours without an increase in side effects.\(^{35}\)

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Treatment duration

• MDR Gr-negatives 21 days
• MDR Gram-positives 14-21 days
• No randomized study
Significant reduction of shunt infection rate in children below 1 year of age after implementation of a perioperative protocol.

Hommelstad J, Madsø A, Eide PK
Department of Neurosurgery, Oslo University Hospital - Rikshospitalet, PB 4950 Nydalen, 0424, Oslo, Norway.

Table 1 Comparison of shunt protocol for patient materials A and B

<table>
<thead>
<tr>
<th>Patient material A</th>
<th>Patient material B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative shower and hair wash with a soap containing 4 % chlorhexidine gluconate (Hibiscrub®) (emergency: not required):</td>
<td></td>
</tr>
<tr>
<td>Patients &gt;1 year of age</td>
<td>+</td>
</tr>
<tr>
<td>Patients &lt;1 year of age</td>
<td>-</td>
</tr>
<tr>
<td>Hair removal:</td>
<td></td>
</tr>
<tr>
<td>Hair removal with clipper</td>
<td></td>
</tr>
<tr>
<td>Hair preserving surgery: hair removal over the incision sites, require preoperative hair wash with Hibiscrub® and wash in 5 % chlorhexidine alcohol</td>
<td></td>
</tr>
<tr>
<td>Operating team wearing surgical attire and face mask</td>
<td></td>
</tr>
<tr>
<td>Operating team covering their head and neck in a surgical hood</td>
<td>+</td>
</tr>
<tr>
<td>Limit the traffic in and out of the operating room</td>
<td></td>
</tr>
<tr>
<td>Limit the number of personnel entering the operating room to necessary personnel</td>
<td></td>
</tr>
<tr>
<td>Keep the patient normotherm</td>
<td></td>
</tr>
<tr>
<td>Prepare the sterile instrument in ultraclean air zone before the patient arrives.</td>
<td></td>
</tr>
<tr>
<td>Cover the instruments until the operation starts</td>
<td></td>
</tr>
<tr>
<td>Prepare the surgical site using a solution of 5 % Chlorhexidine alcohol</td>
<td></td>
</tr>
<tr>
<td>Use Iodine-impregnated incision drape (Ioban®)</td>
<td></td>
</tr>
<tr>
<td>Wear double gloving</td>
<td></td>
</tr>
<tr>
<td>Scrub nurse change the outer gloves after draping</td>
<td></td>
</tr>
<tr>
<td>Surgeon change the outer gloves before touching the shunt</td>
<td></td>
</tr>
<tr>
<td>Use a non-touch method whenever possible</td>
<td></td>
</tr>
<tr>
<td>Use Cefalorin routinely before incision, if not contraindicated</td>
<td></td>
</tr>
<tr>
<td>Test CSF routinely for bacteria, cells, total protein and glucose</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2 The trend plot presents the annual overall infection rate for all patients (solid line) and patients < 1 year (stippled line).
• Neurosurgery ICU (14 beds)
• *S. aureus* search&destroy with mupirocin
• Preintervention – January 2007–2008 June

• Overall *S. aureus* bacteremia
  – decreased significantly (20/3651 cases and 0.41/1000 patient days vs 6/2959 and 0.2/1000 patient days, \( p = 0.02 \)).

• Overall *S. aureus* meningitis rate did not change significantly

Eccmid 2010, poster 1540
• High-risk subgroups
  – prematurity (<35 weeks gestational age),
  – shunts placed immediately post-meningitis,
  – conversion of external ventricular drains (EVD) to shunt
  – replacement of nosocomial shunt infection in patients requiring prolonged hospital stay (>1 month).

• 64 (11.2%) vs 16 (3.2%) patients (p<0.001)
Shunt removal & treatment

• Removal - EVD + antibiotic + reshunt (80-85%)
• Removal + immediate replacement and IV antimicrobial
  – approximately 65% success
• Conservative management (internal catheter in place + antibiotics)
  – approximately 35% success
  – coagulase-negative staphylococci.
• Recurrence
  – Upto 26%

The optimal timing for reimplantation of the shunt is not clear

General guidelines
- coagulase-negative staphylococcus or *P. acnes*
- 7 days is commonly recommended before placement of a new shunt
- If repeat cultures are positive, antimicrobial therapy should generally be continued until cerebrospinal fluid cultures have been negative for 10 consecutive days before a new shunt is placed.

*Staphylococcus aureus* or gram-negative bacilli
- 10 days of antimicrobial therapy after repeated negative cultures

Some experts recommend a 3-day observation period after the completion of antimicrobial therapy before a new shunt is placed to confirm that the CSF is sterile

<table>
<thead>
<tr>
<th>Search</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Search <strong>pneumonia and treatment and antibiotic</strong> Limits: Humans, Randomized Controlled Trial</td>
<td>1057</td>
</tr>
<tr>
<td>Search <strong>meningitis and treatment and antibiotic</strong> Limits: Humans, Randomized Controlled Trial</td>
<td>206</td>
</tr>
<tr>
<td>Search <strong>pneumonia and treatment</strong> Limits: Humans, Randomized Controlled Trial</td>
<td>2450</td>
</tr>
<tr>
<td>Search <strong>meningitis and treatment</strong> Limits: Humans, Randomized Controlled Trial</td>
<td>379</td>
</tr>
</tbody>
</table>

Guidelines IVA-IVC
Disadvantages in meningitis research

• Absence of self-proven golden standard antibiotics
• Inadequate controlled prospective trials
• Systematic reviews of case reports/series
• Animal studies
• End points
• Microbiological success
• Clinical success
  – Mortality
  – Morbidity
    • Apoptosis
    • Hearing loss
    • IQ
Conclusion

- **Ceftriaxone-resistant pneumococci**
  - Relatively rare
  - Vanco, rif, moxi

- **MRSA-MRCNS rare**
  - High morbidity and mortality
  - Mostly HAI
  - Vanco
  - Linezolid
  - Teico
  - Dapto

- **VRE rare**
  - Linezolid or dapto

- **Carbapenem-R Acinetobacter**
  - Colistin (IV+IT)
  - Aminoglycosides (IT)
  - Tigecycline
  - Sulbactam

- **Pseudomonas**
  - Colistin (IV+IT)
  - Aminoglycosides
• Selin Bardak-Özcem
• Sinan Bardak
• Taşkın Yurtseven-Neurosurgery
• Tuncer Turhan-Neurosurgery
• EUMF Neursosurgery Nurses
• Mikrobiology & Clinical Microbiology Dept.
  – Alper Tünger
  – Şöhret Aydemir
Thank you for your attention