Neurosurgical infections: 
New developments and outlook

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Head, Microbiology Laboratory 
Barcelona, Pamplona, Berlin

Overview: What is new?

Post-surgical infections
• Post-craniotomy infection
• Bacterial meningitis
• Brain abscess

Shunt-, drain- and neurostimulator infections
• VP-shunts
• External ventricular drain
• Deep brain stimulation

Spine infections
• Hematogenous
• Hardware infections

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IMPLANTS
Implants improved life quality
### Risk of implant-associated infection

<table>
<thead>
<tr>
<th>Device</th>
<th>No. inserted in the US, per year</th>
<th>Infection rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture fixation devices</td>
<td>2,000,000</td>
<td>5–10</td>
</tr>
<tr>
<td>Dental implants</td>
<td>1,000,000</td>
<td>5–10</td>
</tr>
<tr>
<td>Joint prostheses</td>
<td>600,000</td>
<td>1–3</td>
</tr>
<tr>
<td><strong>Neurosurgical implants</strong></td>
<td>450,000</td>
<td>3–15</td>
</tr>
<tr>
<td>Cardiac pacemakers</td>
<td>300,000</td>
<td>1–7</td>
</tr>
<tr>
<td>Mammary implants</td>
<td>130,000</td>
<td>1–2</td>
</tr>
<tr>
<td>Mechanical heart valves</td>
<td>85,000</td>
<td>1–3</td>
</tr>
<tr>
<td>Penile implants</td>
<td>15,000</td>
<td>1–3</td>
</tr>
<tr>
<td>Heart assist devices</td>
<td>700</td>
<td>25–50</td>
</tr>
</tbody>
</table>

Darouiche RO. *Clin Infect Dis* 2011;33:1567–1572

### Pathogenesis of foreign-body infection

<table>
<thead>
<tr>
<th>References (model)</th>
<th>Foreign body (FB)</th>
<th>Min. infectious dose</th>
<th>Pathogen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elek 1957</strong> (human)</td>
<td>Sutures</td>
<td>$5 \times 10^6$</td>
<td>$3 \times 10^2$</td>
</tr>
<tr>
<td><strong>James 1961</strong> (mice)</td>
<td>Sutures</td>
<td>$10^6$</td>
<td>$&lt;10^3$</td>
</tr>
<tr>
<td><strong>Zimmerli 1982</strong> (guinea pigs)</td>
<td>Cages</td>
<td>$&gt;10^7$</td>
<td>$10^2$</td>
</tr>
<tr>
<td><strong>Widmer 1988</strong> (guinea pigs)</td>
<td>Cages</td>
<td>$&gt;10^7$</td>
<td>$10^3$</td>
</tr>
</tbody>
</table>
Successful treatment concepts based on:

1. Biofilm
2. Diagnosis
3. Surgery
4. Antibiotics

Cure rate >90%
Infection is the best possible complication

Key to success... Interdisciplinary team

Microbiologist  Infectious diseases

Diagnosis  Antibiotics

Surgery

Surgeon
Diagnosis

Normal microbiota of the skin

100,000 bacteria/cm²

- Staphylococci
  - Staphylococcus epidermidis
  - Staphylococcus aureus

- Diphteroids
  - Corynebacterium spp.
  - Propionibacterium acnes
### Classification

<table>
<thead>
<tr>
<th>Time after implantation</th>
<th>&lt;1 month</th>
<th>3–36 months</th>
<th>Any time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of infection</td>
<td>Early postoperative</td>
<td>Delayed (low grade)</td>
<td>Late</td>
</tr>
<tr>
<td>Route</td>
<td>Perioperative</td>
<td>Haematogenous</td>
<td></td>
</tr>
<tr>
<td>Signs</td>
<td>Acute: fever, effusion, warmth, dehiscence</td>
<td>Chronic: Persistent pain, loosening, sinus tract</td>
<td>Acute or subacute</td>
</tr>
<tr>
<td>Pathogen</td>
<td>Staph. aureus, Streptococci, Enterococci</td>
<td>Staph. epidermidis, Propionibacterium acnes</td>
<td>S. aureus, E. coli</td>
</tr>
</tbody>
</table>

### Biofilm

<table>
<thead>
<tr>
<th>Time</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 min</td>
<td>3 h</td>
<td>12 h</td>
<td>1 day</td>
<td>3 days</td>
</tr>
</tbody>
</table>

- Adherent to surface (min-h)
- Embedded in matrix (70%)
- Slowly replicating (stationary-growth)
**Sonication for implants**

Removed implants → Vortex, 30 s → Sonication, 1 min, 40 kHz → Tissue → Sonicate

May 2005–Feb 2007

Standard method (≥3 tissue biopsies)


**Principle of sonication**

Mechanical vibrations >20 kHz

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Sonication fluid

Better sensitivity (80-90%)  
Quantitative (more specific)  
Mixed infections (30%)  
Faster, less expensive  
Fluid for additional investigations

Tissue biopsy

Sonication studies with implants

- Shoulder prosthesis (Piper KE et al. JCM 2009)
- Breast implants (Rieger UM et al. Aesth Plast Surg 2009)
- Electrophysiologic cardiac devices (Rohacek M et al. Circulation 2010)
- Spine implants (Sampedro M et al. Spine 2010)
- Ureteric catheters (Bonkat G et al. W J Urol 2010)
- Pacemaker (Mason PK et al. Pacing Clin Electrophysiol 2011)
- Osteosynthesis material (Portillo ME et al. J Clin Microbiol 2015)
- External ventricular drains (Walti L et al. J Infect 2013)
Antibiotics

Antibiotics are not wonder drugs, but...

... can produce wonders, if ...

1. the microorganism is known
2. given correctly (type, dose)
3. combined with correct surgery
Antibiotics

Bacteriostatic

TETRACYCLINE

GLYCOPEPTIDE

LIPOGLYCOPETIDE

LIPOPEPTIDE

Bactericidal


tigecycline

minocycline

Azithromycin

Doxycycline

Fusidic acid

Oxytetracycline

Streptomycin

Gentamicin

Amikacin

Rifampin

Mupirocin

Methicillin

Nafcillin

Cephaloridine

Ceftaroline

Ampicillin

Oxacillin

Cefazolin

Amoxicillin

Ciprofloxacin

Moxifloxacin

Telavancin

Dalbavancin

Mecilacin

Ceftoridine

Linezolid

Clindamycin

Teicoplanin

Lorian. Antibiotics in Laboratory Medicine. 5th ed.

Error: oral drugs with poor bioavailability

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral bioavailability</th>
<th>Bone penetration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin/clavulanic acid</td>
<td>15%</td>
<td>7%</td>
</tr>
<tr>
<td>Cefuroxim, cefadroxil</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>100%</td>
<td>77%</td>
</tr>
<tr>
<td>Rifampin</td>
<td>80%</td>
<td>51%</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>85%</td>
<td>55%</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>90%</td>
<td>45%</td>
</tr>
<tr>
<td>Linezolid</td>
<td>100%</td>
<td>85%</td>
</tr>
</tbody>
</table>


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Foreign-body infection (FBI) model

- 4 Teflon cages implanted subcutaneously in guinea pigs
- Aspiration of cage fluid (planktonic bacteria)
- Cages removed 5 days after treatment (eradication)


Efficacy in the guinea pig model (MRSA)

Rifampin resistance rate

<table>
<thead>
<tr>
<th></th>
<th>Cure rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl</td>
<td>0%</td>
</tr>
<tr>
<td>RIF (12.5)</td>
<td>33%</td>
</tr>
<tr>
<td>VAN (15)</td>
<td>58%</td>
</tr>
<tr>
<td>VAN (15) + RIF</td>
<td>58%</td>
</tr>
<tr>
<td>LEV (10)</td>
<td>0%</td>
</tr>
<tr>
<td>LEV (10) + RIF</td>
<td>25%</td>
</tr>
<tr>
<td>LIN (50)</td>
<td>0%</td>
</tr>
<tr>
<td>LIN (50) + RIF</td>
<td>0%</td>
</tr>
<tr>
<td>DAP (20)</td>
<td>0%</td>
</tr>
<tr>
<td>DAP (20) + RIF</td>
<td>0%</td>
</tr>
<tr>
<td>DAP (30)</td>
<td>0%</td>
</tr>
<tr>
<td>DAP 30 + RIF</td>
<td>67%</td>
</tr>
<tr>
<td>DAP 40</td>
<td>0%</td>
</tr>
<tr>
<td>DAP 40 + RIF</td>
<td>0%</td>
</tr>
</tbody>
</table>

Antibiotics with antibiofilm activity

1. Staphylococci: Rifampin (in combination)
2. Streptococci: Penicillin (ceftriaxon)
3. Gram-negative bacilli: Ciprofloxacin
4. Enterococci: Fosfomycin + gentamicin (?)
5. Candida: Caspofungin, anidulafungin (?)
**Postsurgical infections / implant**

- **Antibiotic**
  - No surgery
  - Insufficient debridement
  - Extensive debridement (+/- local antibiotics)

- **Bacterial count (log)**

- **Time**

**If implant: Always surgery**

**Surgical and antibiotic treatment concepts**

- **Debridement and retention**
  - Onset of infection: 2–3 weeks i.v.
  - 9–10 weeks p.o.

- **One stage**
  - Explantation and implantation
  - “Biofilm treatment” (with rifampin)

- **Two stage (short interval)**
  - Explantation
  - Implantation
  - “Osteomyelitis treatment” (no rifampin)

- **Two stage (long interval)**
  - Explantation
  - Implantation
  - 6 weeks i.v.
  - (2 weeks)

**References**

Borens O et al. Rev Med Suisse 2009
Implant retention

1. No dysfunction or loosening
2. Known microorganism
3. Good soft tissue

In all cases, debidement is needed (to achieve reduction of bacterial number)!

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Shunt-, drain- and neurostimulator infections
- VP-shunts
- External ventricular drain
- Deep brain stimulation

Spine infections
- Hematogenous
- Hardware-associated infections
Infection following craniotomy

Infection rate: 1-5%
Most common symptoms:
- Change in mental status
- Evidence of wound infection
Cave: Bacterial meningitis!

“Superficial” and deep wound infections

Distinction between superficial and deep wound infection is nonsense:

- Subgaleal and epidural compartments after craniotomy are in contiguity
- Any craniotomy infection should be considered a bone flap osteitis (for the treatment standpoint)
- Requires surgical revision (debridement) to
  - evacuate pus and infected tissue
  - remove infected bone flap

TABLE 1
Presenting symptoms in 50 patients with intracranial infections

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Purulent drainage</td>
<td>17 (34)</td>
</tr>
<tr>
<td>Mental status change</td>
<td>18 (36)</td>
</tr>
<tr>
<td>Headache</td>
<td>26 (52)</td>
</tr>
<tr>
<td>Swelling</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Seizure</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

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Dashti Neurosurg Focus 2008

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Infection following craniotomy

Standard management of bone flap osteitis:
• Delayed cranioplasty (weeks to months)
• With foreign material once the infection is cleared

New concept:
• Immediate cranioplasty in low-grade infection (1-stage)
• Short interval of 2 weeks (2-stage)
• Bone flap reuse (sterilization, disinfection), acryl or other foreign material (impregnated with antibiotics?)

=> Better cosmetic result, protect underlying brain

Postoperative meningitis

Incidence: <1% (recent series) to >8% (without prophylaxis)

Life-threatening complication: mortality >20%

Diagnosis difficult
• The clinical manifestations often mild and non-specific
• CSF characteristics modified by surgical procedure
• Direct bacteriological examination often negative

Risk factors:
• Implantation of foreign body
• CSF leakage
• No antibiotic prophylaxis
• Duration of surgery >4 h
• Interventions involving nasal sinuses
Treatment: postoperative meningitis/abscess

Postoperative meningitis
• Early empirical antibiotic therapy:
  Vancomycin 2 x 1 g + meropenem 3 x 2 g i.v. STAT
• Then targeted treatment, total 2-3 weeks
• If CSF cultures negative after 72 h, treatment stop

Brain abscess
• Surgical revision or stereotactic puncture
• Treatment: same as for meningitis
• Duration: months, after 2 weeks oral (until MRI normal)

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• VP-shunts
• External ventricular drain
• Deep brain stimulation

Spine infections
• Hematogenous
• Hardware-associated infections
VP-shunt & external drain: Symptoms

<table>
<thead>
<tr>
<th>Infection</th>
<th>VP-shunts</th>
<th>External drains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>5-15%</td>
<td>10-15% (increase with time)</td>
</tr>
</tbody>
</table>

VP-shunts: Symptoms

Proximal shunt part: ventriculitis / meningitis
Distal shunt part: peritonitis, abdominal abscess

=> Shunt dysfunction (increased ICP)

Table 4. Microbiological findings for episodes of CSF shunt-associated infection.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Overall (n = 76)</th>
<th>Early (n = 48)</th>
<th>Delayed (n = 22)</th>
<th>Late (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>29 (37)</td>
<td>19</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>14 (18)</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Propionibacterium acnes</td>
<td>7 (9)</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Viridans group streptococci</td>
<td>3 (4)</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>3 (4)</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfermenters</td>
<td>2 (3)</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Enterococcus species</td>
<td>1 (1)</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Polymicrobial</td>
<td>12 (15)</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Culture negative</td>
<td>7 (9)</td>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
VP-shunt infection: CSF leukocyte & culture

Suspicion of shunt-infection: lumbar puncture!

VP-shunts: Therapy

Success: 93%

Retention of VP-shunt possible with antibiotics against biofilms
VP-shunts: When retention?

Shunt retention or immediate reinsertion possible, if:

- No ventriculitis / meningitis
- No dysfunction
- No abscess
- No erosion (intact skin and intestinum)

and

- Microorganisms known
- Susceptible to antibiotics against biofilms

EVD infection / meningitis: Symptoms

<table>
<thead>
<tr>
<th>Parameter</th>
<th>At EVD insertion</th>
<th>At diagnosis of EVD-associated infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever ≥38 °C</td>
<td>7 (15)</td>
<td>38 (79)</td>
</tr>
<tr>
<td>Neurological signs and symptomsã</td>
<td>3 (6)</td>
<td>15 (31)</td>
</tr>
<tr>
<td>GCS, median (range) – points</td>
<td>3 (3–15)</td>
<td>8 (3–15)</td>
</tr>
<tr>
<td>Decrease in GCS scoreã</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No decrease</td>
<td>13 (27)</td>
<td>34 (71)</td>
</tr>
<tr>
<td>1–3 points</td>
<td>4 (8)</td>
<td>8 (17)</td>
</tr>
<tr>
<td>4–6 points</td>
<td>3 (6)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>≥7 points</td>
<td>28 (58)</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

Table 3: Clinical findings at EVD insertion and at diagnosis of EVD-associated infection.

<table>
<thead>
<tr>
<th>Causing microorganisms</th>
<th>n = 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monomicrobial infection</td>
<td></td>
</tr>
<tr>
<td>Coagulase-negative</td>
<td></td>
</tr>
<tr>
<td>Staphylococci</td>
<td></td>
</tr>
<tr>
<td>Peptostreptococcus</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureusã</td>
<td></td>
</tr>
<tr>
<td>Otherã</td>
<td></td>
</tr>
<tr>
<td>Polymicrobial infection</td>
<td></td>
</tr>
<tr>
<td>Culture-negative infection</td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Microbiology of 48 episodes of EVD-associated infections.
EVD infection: CSF leukocyte & culture

![Graph showing CSF leukocytes and culture](https://example.com/graph)

Deep Brain Stimulation: Infection rate 1-15%

When retain the neurostimulator?

- **Pocket infection**: generator change (other site), keep the electrodes
- **Electrode infection**: no brain abscess, skin erosion covered (flap)

If removed: optimal time of reimplantation?

- If organism known and susceptible to anti-biofilm antibiotics:
  - **immediate** (1-stage) or
  - **delayed** (after 2 weeks)
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Osteoarticular infections

S. aureus is the most common pathogen of osteomyelitis
Vertebral osteomyelitis

Hematogenous (urinary, respiratory, intestinal tract, endocarditis, dental):
- *Staphylococcus aureus*, streptococci, enterococci
- *E. coli*, other gram-negative (*Candida albicans*)

„Never“ surgery!

Exogen (skin flora):
- Postoperative (1% after discectomy, 5% after stabilisation, 10% after revision)
- Postinterventional (infiltrations)
  *Staphylococcus epidermidis* (other coagulase-negative staphylococci), *Propionibacterium acnes*

„Always“ surgery!

Hematogenous infection (no implant)

Biopsy (percutaneous CT-guided, open):

1. Large needle (gauge)
2. Bone & discus (fluid/abscess)
3. Histology & microbiology
Antibiotic treatment

Empiric (without meningitis): cover S. aureus & gram-neg.
- Cefepime 3 x 2 g i.v. or
- Piperacillin/tazobactam 3 x 4.5 g i.v.

Empiric (with meningitis): cover everything
- Meropenem 3 x 2 g i.v. (or cefepime 3 x 2 g i.v.) and
- Vancomycin 3 x 1 g i.v. (for MRSA)

Targeted therapy: switch to optimal antibiotic
- 2 weeks i.v., then oral
- Duration: 6 weeks (without implant), 12 weeks (with implant)

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CLINICAL PRACTICE

Vertebral Osteomyelitis

Werner Zimmerli, M.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

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### Table 1. Suggested Antibiotic Regimens for Common Causes of Osteomyelitis in Adults.

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>First Choice</th>
<th>Alternative Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus or coagulase-negative staphylococci (methicillin-sensitive)</td>
<td>β-Lactam at high dose (e.g., nafcillin or oxacillin, 2 g administered intravenously every 6 hr, or cefazolin, 1–2 g administered intravenously every 8 hr)</td>
<td>Fluoroquinolone plus rifampin (e.g., levofloxacin, 750 mg taken orally once daily, plus rifampin, 300 mg taken orally every 12 hr)</td>
</tr>
<tr>
<td>S. aureus or coagulase-negative staphylococci (methicillin-resistant)</td>
<td>Glycopeptide (e.g., vancomycin, 1 g administered intravenously every 12 hr)</td>
<td>Daptomycin, 6–26 mg/kg of body weight once daily, or rifampin, 300 mg taken orally every 12 hr, plus levofloxacin, 750 mg taken orally once daily, or one double-strength tablet containing trimethoprim, 160 mg, plus sulfamethoxazole, 800 mg, taken orally every 8 hr, or fusidic acid, 500 mg taken orally every 8 hr</td>
</tr>
<tr>
<td>Streptococcal species</td>
<td>Penicillin G. 3 million units administered intravenously every 6 hr</td>
<td>Ceftriaxone, 2 g administered intravenously once daily</td>
</tr>
<tr>
<td>Enterobacteriaceae, quinolone-susceptible</td>
<td>Fluoroquinolone (e.g., ciprofloxacin, 750 mg taken orally every 12 hr)</td>
<td>Ceftriaxone, 2 g administered intravenously once daily</td>
</tr>
<tr>
<td>Enterobacteriaceae, quinolone-resistant, including extended-spectrum β-lactamase-producing E. coli</td>
<td>Carbapenem (e.g., imipenem, 500 mg administered intravenously every 6 hr)</td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Cefepime or ceftazidime, 2 g every 8 hr</td>
<td>Piperacillin-tazobactam, 4.5 g every 6 hr (consider a combined regimen with an aminoglycoside), for 2 to 4 wk, followed by ciprofloxacin, 750 mg taken orally every 12 hr</td>
</tr>
</tbody>
</table>

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Debridement and retention

One stage

Two stage (short interval)

Two stage (long interval)

Onset of infection
2–3 weeks i.v.
9–10 weeks p.o.

Debridement

Explantation and implantation

"Biofilm treatment" (with rifampin)

Explantation
Implantation

"Osteomyelitis treatment" (no rifampin)

6 weeks i.v.
(2 weeks)

Borens O et al. Rev Med Suisse 2009

Outlook: diagnosis

All removed implants should be sonicated
Sonication fluid is useful for further analysis
Outlook: New diagnostic methods

Microcalorimetry  Molecular methods (PCR)  MALDI-TOF

Outlook: *Staphylococcus aureus* vaccine

Adults undergoing elective posterior instrumented lumbar spinal fusion procedures

A phase 2b, randomized, double-blind, placebo-controlled study

**Intervention**

Single dose: 10-60 days before surgery
Conclusions

1. Improved diagnostic methods: sonication for implants, new faster and more accurate methods
2. Anti-biofilm antibiotics: retention, 1-stage exchange or short interval until reimplantation
3. Innovative prevention strategies: vaccination

This will likely revolutionize implant surgery: efficient strategy to cure infections without implant removal.

www.pro-implant-foundation.org
Thank you

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Focus on implant, bone and joint-associated infections:
• Surgery: New concepts
• Diagnosis: Fast innovative methods
• Antibiotics: Active against biofilms