

Antibiotics in severe infections

DOT 2023

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Antibiotics in Open Fractures and Fracture-Related Infections (FRI)

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OPEN FRACTURES AND FRI

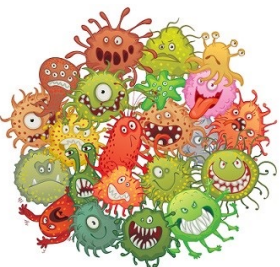
Aetiology



Traffic accident



Open tibial fracture



Bacteria



FRI

Treatment principles



Surgical debridement
+ Fluid irrigation



Fracture stabilization



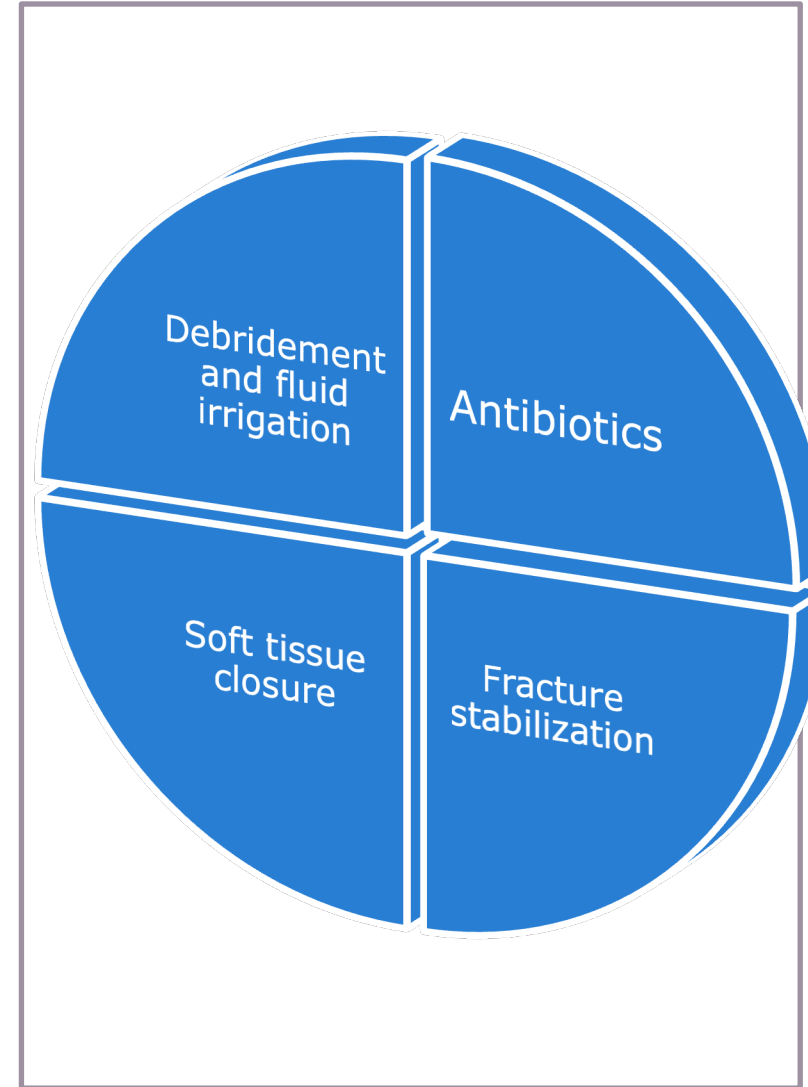
Systemic antibiotics



Sufficient soft
tissue closure

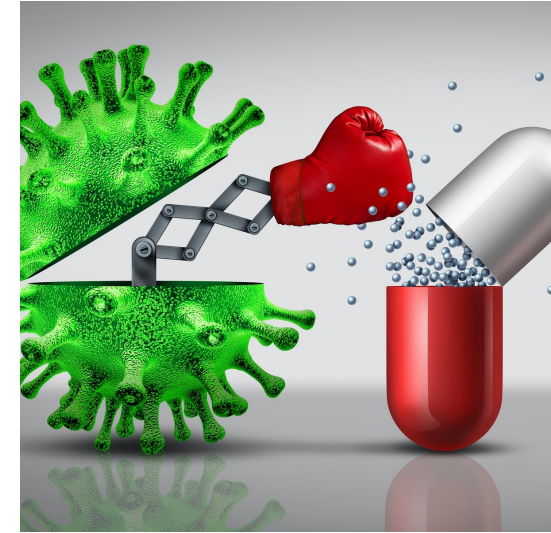


Local antibiotics



- More than 1.3 mio deaths world wide in 2019 due to antibiotic resistant bacteria¹

- Where to adjust?
 - Type of antibiotic
 - Dose and frequency
 - Timing and duration
 - Way of administration and application

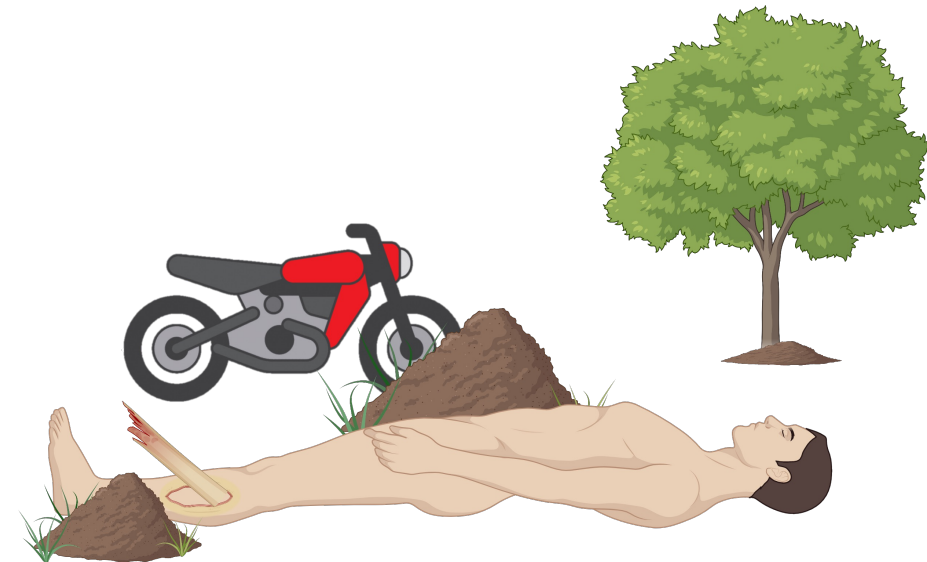


When we choose to administer antibiotics – lets do it in the best possible way !

¹Lancet, 2022: Antimicrobial Resistance Collaborators

- Contamination vs infection ?
- Infection rates following open fractures: up to 50 % *
- Heterogeneity: contamination grade, anatomical location and soft-tissue damage
- Gustilo-Anderson classification → higher grades are associated with both a higher risk of infection and a more diverse contamination *
- RCTs in open fractures is lacking and difficult

*Olesen UK et al., *Int Orthop*, 2015
Sudduth JD et al., *Surg Infect (Larchmt)*, 2020
Patzakis MJ et al., *Clin Orthop Relat Res*, 1989
Papakostidis et al., *Injury*, 2011



- Which drug(s)?
 - Sudduth JD et al: 90/451 (20%) infected (USA)

🏠 Surgical Infections > VOL. 21, NO. 9 | Original Articles

🔒 normal

Open Fractures: Are We Still Treating the Same Types of Infections?

Jack D. Sudduth, James A. Moss, Clay A. Spitler, Vuong-Lam H. Pham, LaRita C. Jones, James Turner Brown, and Patrick F. Bergin ✉

Vancomycin (95.8% sensitivity) demonstrated the highest sensitivity for all gram-positive organisms. Amikacin (98.8% sensitivity), meropenem (96.3% sensitivity), and gentamicin (94.2% sensitivity) demonstrated excellent efficacy for all gram-negative organisms.

A review of forty five open tibial fractures covered with free flaps. Analysis of complications, microbiology and prognostic factors

Ulrik Kähler Olesen · Rasmus Juul · Christian Torsten Bonde · Claus Moser ·
Martin McNally · Lisa Toft Jensen · Jens Jørgen Elberg · Henrik Eckardt

- Which drug(s)?
 - Vancomycin + meropenem?
- Olesen UK et al: 22/45 (49%) infected
 - 93 % coverage vancomycin+meropenem
 - Cefuroxime: 21 %

Bacteria	Number	Vanco	Mero	Cefur
Enterococcus species	11	11	7	0
Coagulase neg. staphylococci (CoNS)	9	9		3
Enterobacteriaceae	6		5	1
Miscellaneous	6	5	6	2
Other pseudomonas	4		2	
Anaerobic bacteria	2		2	
Staphylococcus aureus	2	2		2
Haemolytic streptococci	1	1	1	1
Corynebacterium species	1	1	0	0
Pseudomonas aeruginosa	1		1	
Total	43	29	24	9

- Which drug(s)?
 - Vancomycin + meropenem?

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INFECTION

Tibial bone and soft-tissue concentrations following combination therapy with vancomycin and meropenem – evaluated by microdialysis in a porcine model



SHOULD PATIENTS WITH OPEN FRACTURES HAVE HIGHER DOSES OF ANTIBIOTICS?

**S. Ø. Vittrup,
P. Hanberg,
M. B. Knudsen,
S. K. Tøstesen,
J. O. Kipp,
J. Hansen,
N. P. Jørgensen,
M. Stilling,
M. Bue**



OPEN FRACTURES

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- Which drug(s)?
 - Vancomycin + meropenem?

To encompass any trauma, contamination, or individual tissue differences, a more aggressive dosing approach may be considered to achieve longer T > MIC in all the exposed tissues, and thereby lower the risk of acquiring an infection after open tibial fractures.

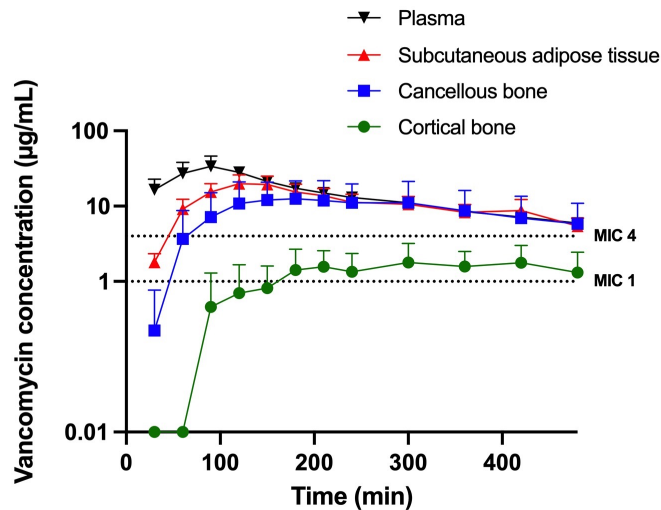
BJR

INFECTION

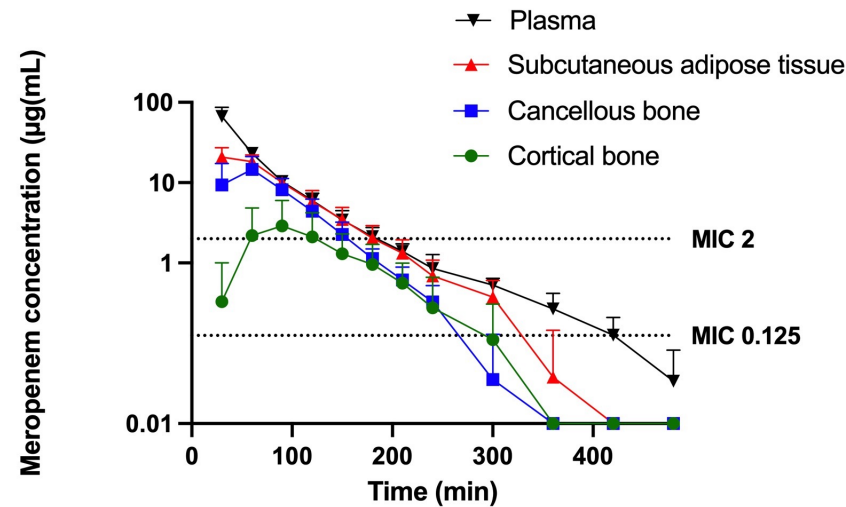
Tibial bone and soft-tissue concentrations following combination therapy with vancomycin and meropenem – evaluated by microdialysis in a porcine model

SHOULD PATIENTS WITH OPEN FRACTURES HAVE HIGHER DOSES OF ANTIBIOTICS?

Vancomycin



Meropenem



OPEN FRACTURES

- Which drug(s)?
 - Vancomycin + meropenem?

Conclusion: We found short T>MIC, particularly for the high MIC targets for vancomycin and meropenem, both inside the cannulated screw and in cancellous bone adjacent to the screw. The presence of a cannulated screw impaired the penetration of especially vancomycin into cancellous bone adjacent to the screw. More aggressive or different vancomycin and meropenem approaches may be considered to encompass contaminating differences and to ensure a theoretically more sufficient antibiotic protection of cannulated screws when used in the management of open lower extremity fractures.



Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury



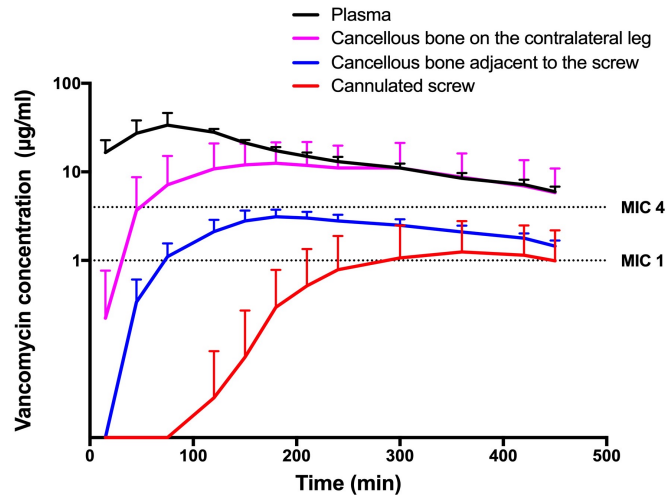
Original article

Concentrations of co-administered vancomycin and meropenem in the internal dead space of a cannulated screw and in cancellous bone adjacent to the screw – Evaluated by microdialysis in a porcine model

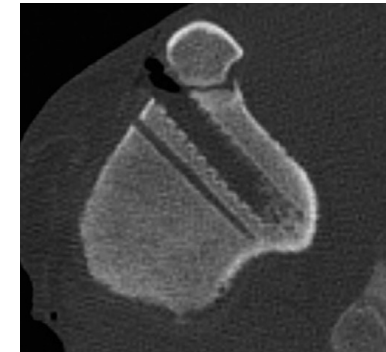
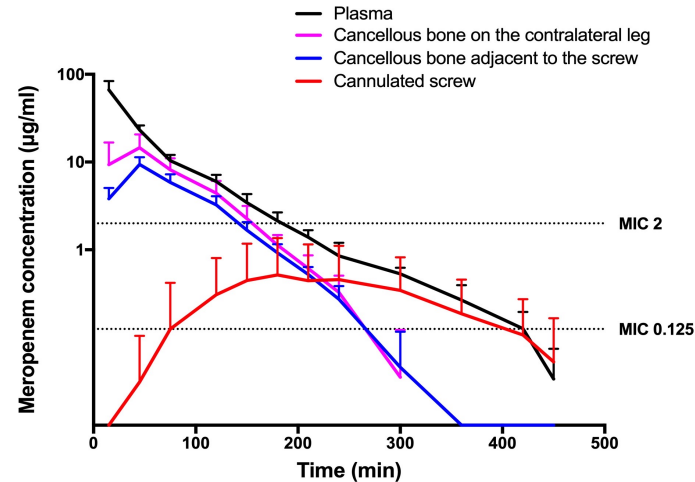


Sofus Vittrup^{a,*}, Maiken Stilling^{a,b,c}, Pelle Hanberg^{a,b}, Sara Kousgaard Tøstesen^a, Martin Bruun Knudsen^a, Josephine Olsen Kipp^{a,b}, Mats Bue^{a,b,c}

Vancomycin



Meropenem



- Which drug(s)?
 - Vancomycin + meropenem?
 - Aggressive dosing? (Weight-based dosing, continuous infusion etc.)

Risk of resistance ??



- Which drug(s)?
 - Vancomycin + meropenem?
 - Aggressive dosing?
- How fast?

Clin Orthop Relat Res (2021) 479:613-619
DOI 10.1097/CORR.0000000000001507

Clinical Orthopaedics
and Related Research®
A Publication of The Association of Bone and Joint Surgeons®

Clinical Research

Early Antibiotic Administration Is Associated with a Reduced Infection Risk When Combined with Primary Wound Closure in Patients with Open Tibia Fractures

David A. Zuelzer MD, Christopher B. Hayes MD, Gavin S. Hautala MD, Adam Akbar MD, Ryan R. Mayer MD, Cale A. Jacobs PhD, Raymond D. Wright MD, Eric S. Moghadamian MD, Paul E. Matuszewski MD

Results Increased time to first administration of antibiotics was associated with an increased infection risk in patients who were treated with primary wound closure; the greatest inflection point on that analysis occurred at 150 minutes, when the increased infection risk was greatest (20% [8 of 41] versus 4% [3 of 86]; odds ratio 5.6 [95% CI 1.4 to 22.2]; $p = 0.01$).

- Which drug(s)?
 - Vancomycin + meropenem?
 - Aggressive dosing?
- How fast?
 - Within maximum 2,5 hours?

ORIGINAL ARTICLE

Type III Open Tibia Fractures Immediate Antibiotic Prophylaxis Minimizes Infection

Lack, William D. MD^{*}; Karunakar, Madhav A. MD[†]; Angerame, Marc R. MD[†]; Seymour, Rachel B. PhD[†]; Sims, Stephen MD[†]; Kellam, James F. MD[†]; Bosse, Michael J. MD[†]

[Author Information](#) ☺

Journal of Orthopaedic Trauma 29(1):p 1-6, January 2015. | DOI: 10.1097/BOT.0000000000000262

infection. greater than 66 minutes to antibiotics ($P < 0.01$) were univariate predictors of

- Which drug(s)?
 - Vancomycin + meropenem?
 - Aggressive dosing?
- How fast?
 - Within maximum 2,5 hours?
- How long?
 - Cochrane review:
One RCT available, 1 vs 5 days



Cochrane Database of Systematic Reviews

[Intervention Review]

Timing of antibiotic administration, wound debridement, and the stages of reconstructive surgery for open long bone fractures of the upper and lower limbs

James K-K Chan^{1,2,3}, Alexander L Aquilina², Sharon R Lewis⁴, Jeremy N Rodrigues^{1,5}, Xavier L Griffin⁴, Jagdeep Nanchahal⁶

Duration of prophylactic antibiotic treatment (1 study, 77 participants available for analysis)

One study compared antibiotic treatment for 24 hours with antibiotic treatment for five days. We are very uncertain about the effects of different durations of antibiotic treatment on superficial infections (risk ratio (RR) 1.19, 95% CI 0.49 to 2.87, favours 5 day treatment; 1 study, 77 participants); this was very low-certainty evidence derived from one small study with unclear and high risks of bias, and with an imprecise effect estimate. This study reported no other review outcomes.

- Which drug(s)?
 - Vancomycin + meropenem?
 - Aggressive dosing?
- How fast?
 - Within maximum 2,5 hours?
- How long?
 - Cochrane review:
 - One RCT available, 1 vs 5 days?
 - Systematic review (6 included studies)
 - 1, 3 or 5 days?





antibiotics



Systematic Review

Duration of Perioperative Antibiotic Prophylaxis in Open Fractures: A Systematic Review and Critical Appraisal

Niels Vanvelk¹, Baixing Chen^{2,3}, Esther M. M. Van Lieshout¹, Charalampos Zalavras⁴, T. Fintan Moriarty⁵ , William T. Obrebsky⁶, Michael H. J. Verhofstad¹ and Willem-Jan Metsemakers^{2,3,*} 

1 day versus 5 days of PAP or included a cut-off at 72 h.

Most studies compared either

Based on the available studies, prolonged PAP does not appear to be beneficial in the prevention of FRI in open fractures.

- Which drug(s)?
 - Vancomycin + meropenem?
 - Aggressive dosing?
- How fast?
 - Within maximum 2,5 hours?
- How long?
 - 1, 3 or 5 days?
- Local antibiotics?

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■ INFECTION

The effect of local antibiotic prophylaxis when treating open limb fractures

A SYSTEMATIC REVIEW AND META-ANALYSIS

**M. Morgenstern,
A. Vallejo,
M. A. McNally,
T. F. Moriarty,
J. Y. Ferguson,
S. Nijs,
WJ. Metsemakers**

Conclusion

This meta-analysis suggests a risk reduction in FRI of 11.9% if additional local antibiotics are given prophylactically for open limb fractures. However, due to limited quality, heterogeneity, and considerable risk of bias, the pooling of data from primary studies has to be interpreted with caution.

- Which drug(s)?
 - Vancomycin + meropenem?
 - Aggressive dosing?
- How fast?
 - Within maximum 2,5 – 3 hours?
- How long?
 - 1, 3 or 5 days?
- Local antibiotics?
 - Maybe? Why not? Which type?

- Empirical systemic treatment?
 - 1/3 polymicrobial

ORIGINAL ARTICLE

OPEN

Recommendations for Systemic Antimicrobial Therapy in Fracture-Related Infection: A Consensus From an International Expert Group

Melissa Depypere, MD, Richard Kuehl, MD,† Willem-Jan Metsemakers, MD, PhD,‡
Eric Senneville, MD, PhD,§ Martin A. McNally, MD, FRCS(Orth),|| William T. Obrebsky, MD, MPH,¶
Werner Zimmerli, MD,** Bridget L. Atkins, MD, MBBS, MSc, FRCP, FRCPath,||
and Andrej Trampuz, MD†† on behalf of the Fracture-Related Infection (FRI) Consensus Group*

Initially, empiric therapy should be broad-spectrum, including a lipopeptide or a glycopeptide and an agent covering Gram-negative

- Empirical systemic treatment?

JOURNAL OF
INFECTION

RESEARCH ARTICLE | VOLUME 79, ISSUE 3, P189-198, SEPTEMBER 2019

The microbiology of chronic osteomyelitis: Changes over ten years

Maria Dudareva ¹ • Andrew James Hotchen ¹  • Jamie Ferguson • ... Matthew Scarborough • Bridget L. Atkins • Martin A. McNally • [Show all authors](#) • [Show footnotes](#)

Published: July 15, 2019 • DOI: <https://doi.org/10.1016/j.jinf.2019.07.006> •  Check for updates

A glycopeptide with an anti-pseudomonal carbapenem remains the post-operative empiric systemic

- Empirical systemic treatment?
 - Vancomycin + meropenem?
 - Aggressive dosing?
- How long?
 - 14 days IV + 4 (or 10) weeks PO?

ORIGINAL ARTICLE

Oral versus Intravenous Antibiotics for Bone and Joint Infection

H.-K. Li, I. Rombach, R. Zambellas, A.S. Walker, M.A. McNally, B.L. Atkins, B.A. Lipsky, H.C. Hughes, D. Bose, M. Kümin, C. Scarborough, P.C. Matthews, A.J. Brent, J. Lomas, R. Gundle, M. Rogers, A. Taylor, B. Angus, I. Byren, A.R. Berendt, S. Warren, F.E. Fitzgerald, D.J.F. Mack, S. Hopkins, J. Folb, H.E. Reynolds, E. Moore, J. Marshall, N. Jenkins, C.E. Moran, A.F. Woodhouse, S. Stafford, R.A. Seaton, C. Vallance, C.J. Hemsley, K. Bisnauthsing, J.A.T. Sandoe, I. Aggarwal, S.C. Ellis, D.J. Bunn, R.K. Sutherland, G. Barlow, C. Cooper, C. Geue, N. McMeekin, A.H. Briggs, P. Sendi, E. Khatamzas, T. Wangrangsimakul, T.H.N. Wong, L.K. Barrett, A. Alvand, C.F. Old, J. Bostock, J. Paul, G. Cooke, G.E. Thwaites, P. Bejon, and M. Scarborough, for the OVIVA Trial Collaborators*

CONCLUSIONS

Oral antibiotic therapy was noninferior to intravenous antibiotic therapy when used during the first 6 weeks for complex orthopedic infection, as assessed by treatment failure at 1 year.

FRACTURE-RELATED INFECTIONS (FRI)

- Empirical systemic treatment?
 - Vancomycin + meropenem?
 - Aggressive dosing?
- How long?
 - Switch to PO according to cultures ASAP (if possible)
 - 6 weeks is golden (pragmatic) standard*
 - DAIR and 1.stage exchange = 12 weeks*

**Depypere M et al., J Orthop Trauma, 2020*

FRACTURE-RELATED INFECTIONS (FRI)

- Empirical systemic treatment?
 - Vancomycin + meropenem?
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 - Switch to PO according to cultures ASAP (if possible)
 - 6 weeks is golden (pragmatic) standard*
 - DAIR and 1.stage exchange = 12 weeks*
- Herlev-regime: +100 pt with OVIVA
 - 7 days IV (penicillin + dicloxacillin) → switch to PO
 - Equal failure rate as OVIVA

**Depypere M et al., J Orthop Trauma, 2020*



- Empirical systemic treatment?
 - Vancomycin + meropenem?
 - Aggressive dosing?
- How long?
 - Switch to PO according to cultures ASAP (if possible)
 - 6 weeks is golden (pragmatic) standard*
 - DAIR and 1.stage exchange = 12 weeks*
- Herlev-regime: +100 pt with OVIVA
 - 7 days IV (pencillin + dicloxacillin) + 5 weeks PO
 - Equal failure rate as OVIVA
- Local antibiotics

*Depypere M et al., J Orthop Trauma, 2020

ORIGINAL ARTICLE

OPEN

Evidence-Based Recommendations for Local Antimicrobial Strategies and Dead Space Management in Fracture-Related Infection

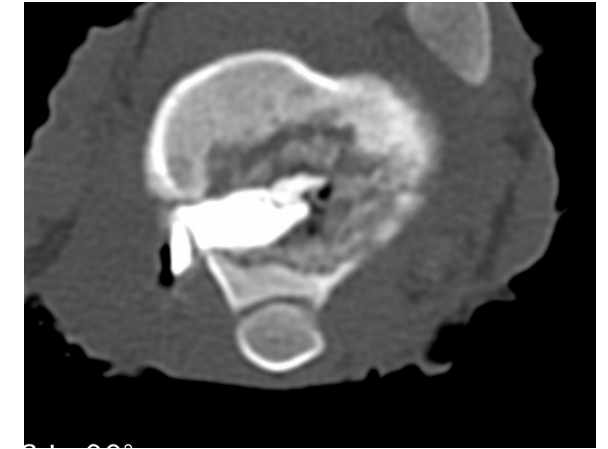
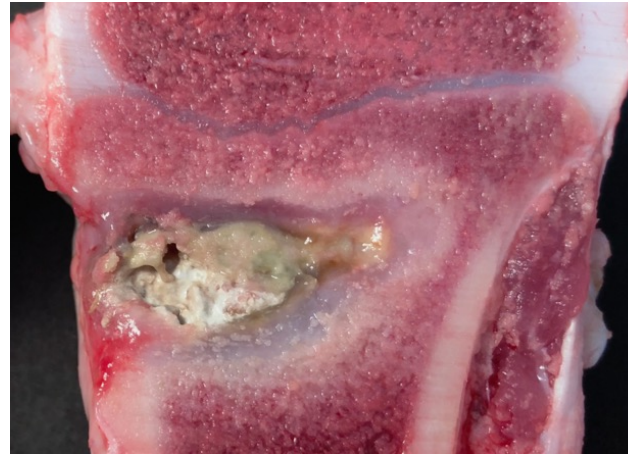
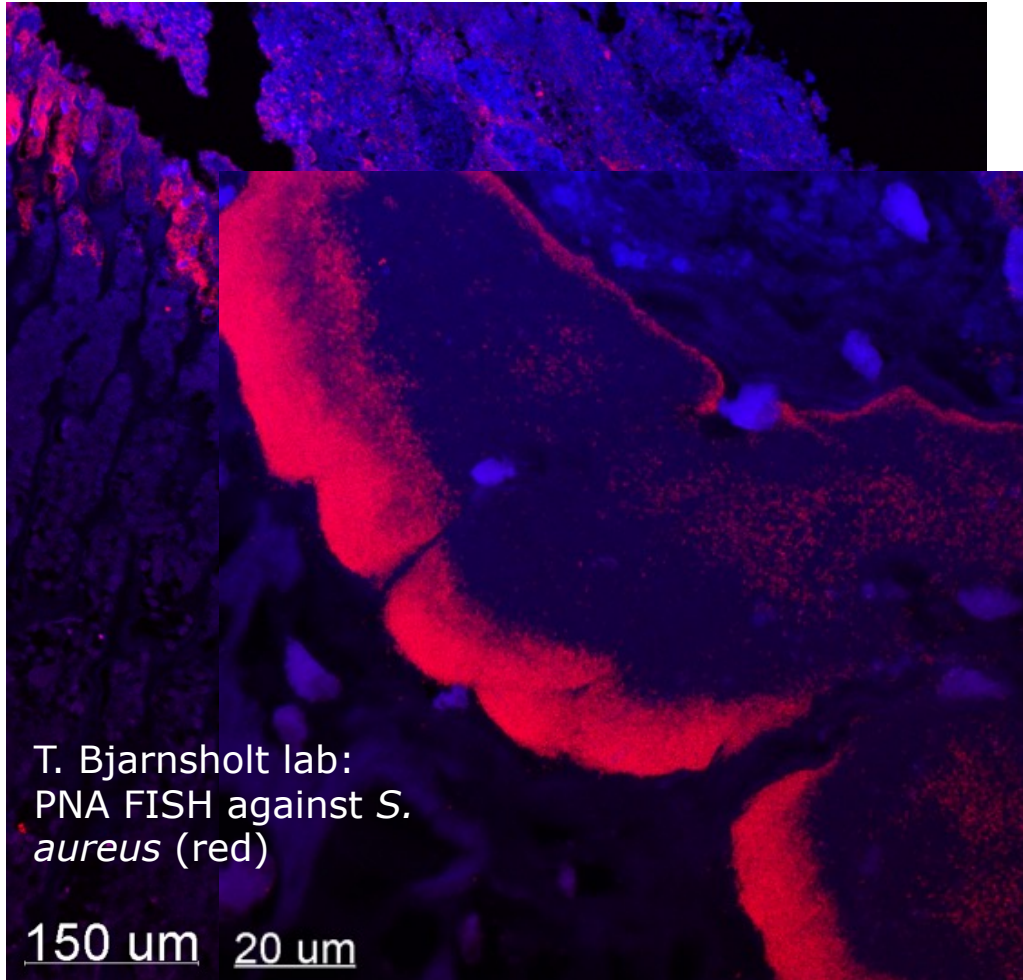
Willem-Jan Metsemakers, MD, PhD,* Austin T. Fragomen, MD,† T. Fintan Moriarty, PhD,‡
Mario Morgenstern, MD,§ Kenneth A. Egol, MD,|| Charalampos Zalavras, MD, PhD,¶
William T. Obrebsky, MD, MPH,** Michael Raschke, MD, PhD,††
and Martin A. McNally, MD, FRCS(Orth)‡‡ on behalf of the Fracture-Related Infection (FRI) consensus group

Weak evidence – but strong recommendations

- Empirical systemic treatment?
 - Vancomycin + meropenem?
 - Aggressive dosing?
- How long?
 - Switch to PO according to cultures ASAP (if possible)
 - 6 weeks is golden (pragmatic) standard*
 - DAIR and 1.stage exchange = 12 weeks*
- Herlev-regime: +100 pt with OVIVA
 - 7 days IV (pencillin + dicloxacillin) + 5 weeks PO
 - Equal failure rate as OVIVA
- Local antibiotics
 - Maybe? Why not? Which type?

LOCAL ANTIBIOTICS: CERAMENTG

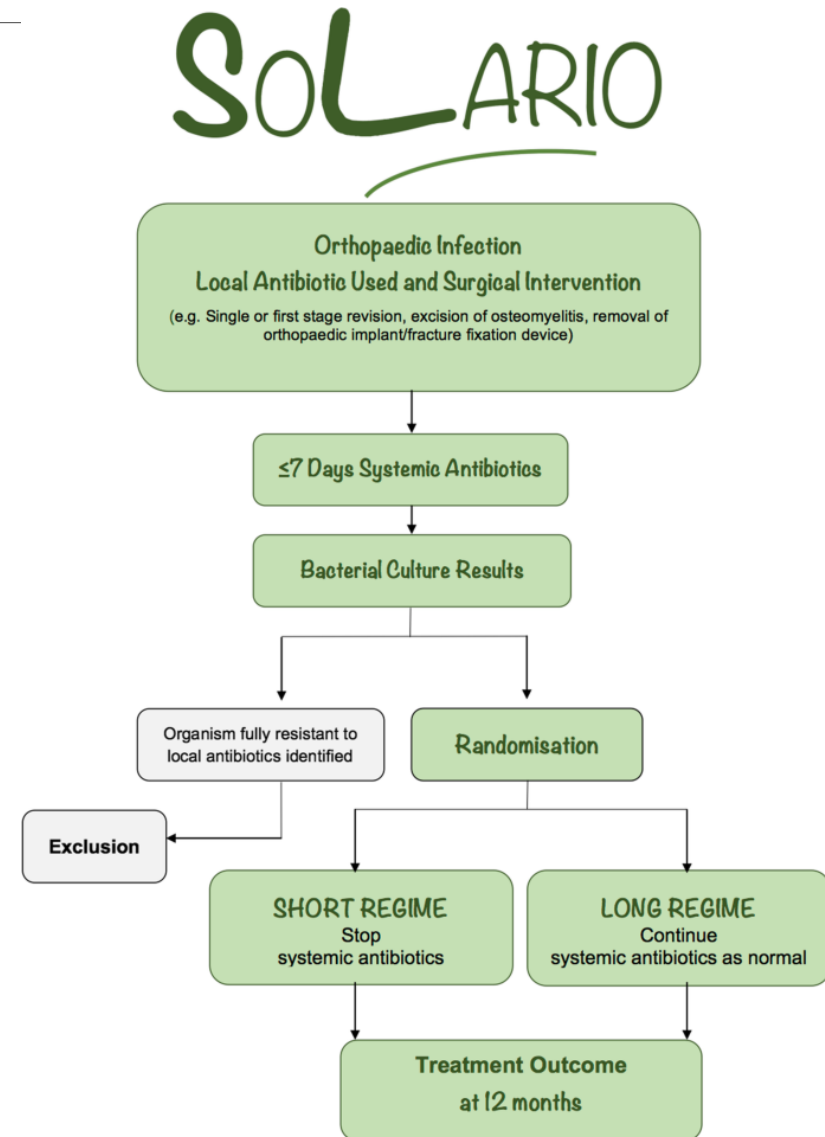
12 days after revision surgery



- Soft tissue infection
- Purulence inside the bone
- Fibrosis
- Irregular contour of bone lesions

SOLARIO

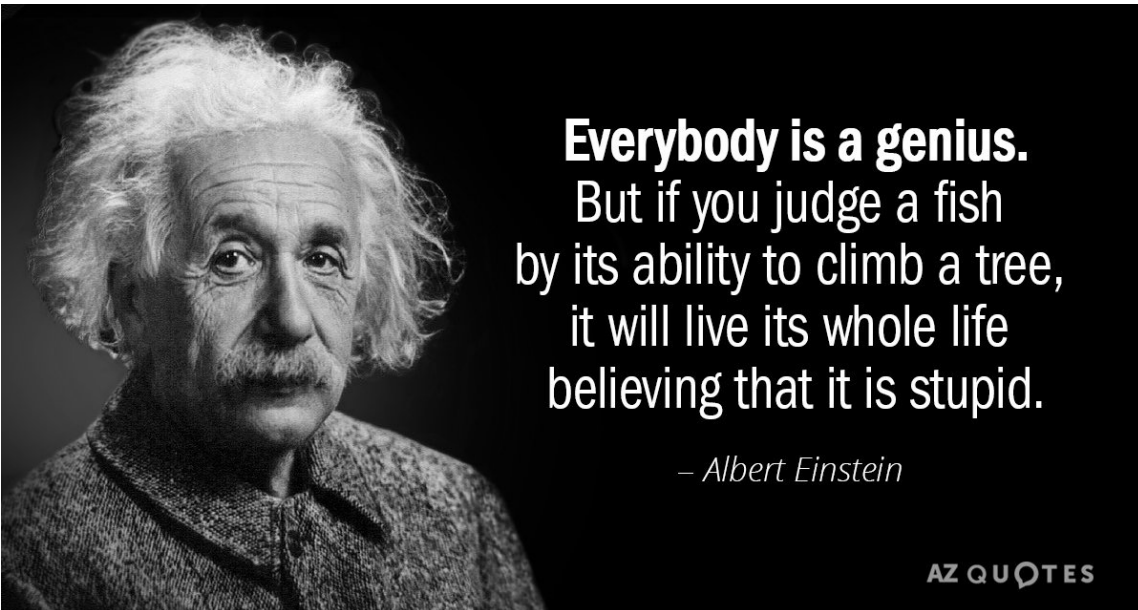
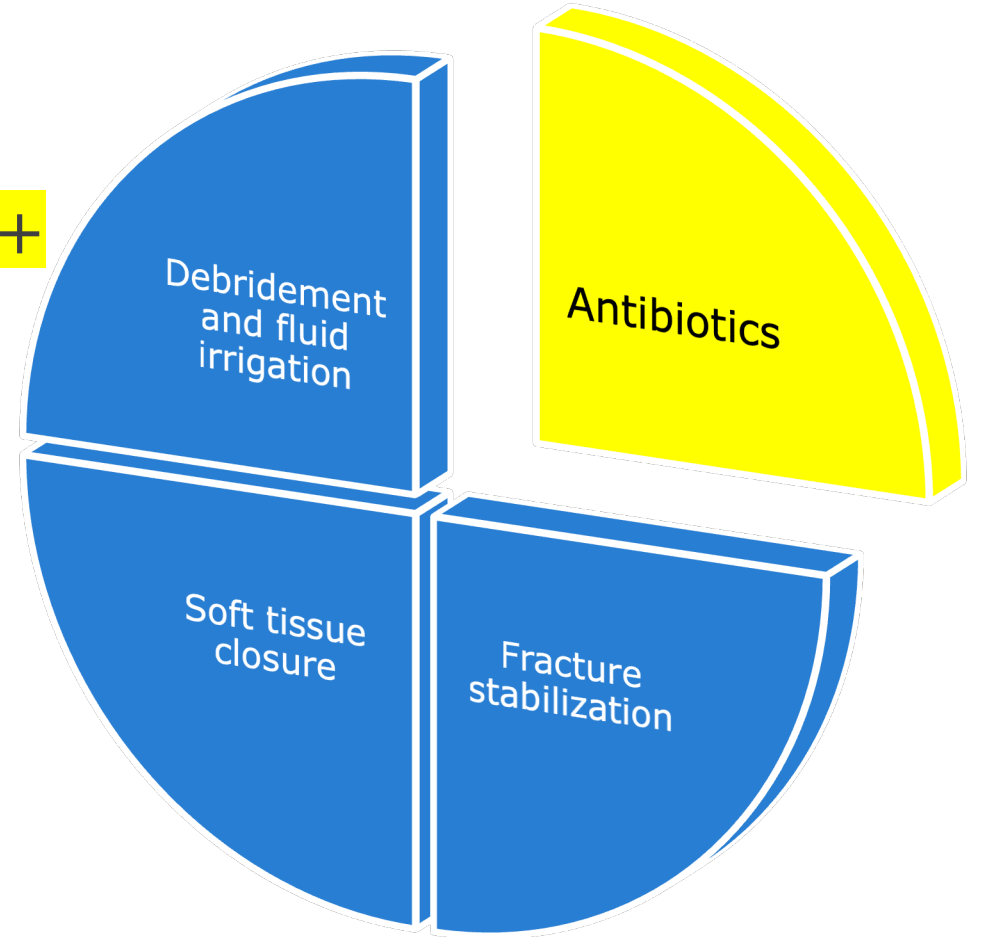
Short Or Long Antibiotic Regimens in Orthopaedics



THE END



MDT-APPROACH +



Antibiotics in Open Fractures and Fracture-Related Infections (FRI)

DOT 2023

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