

Post-traumatic osteomyelitis: drug-resistance and other challenges

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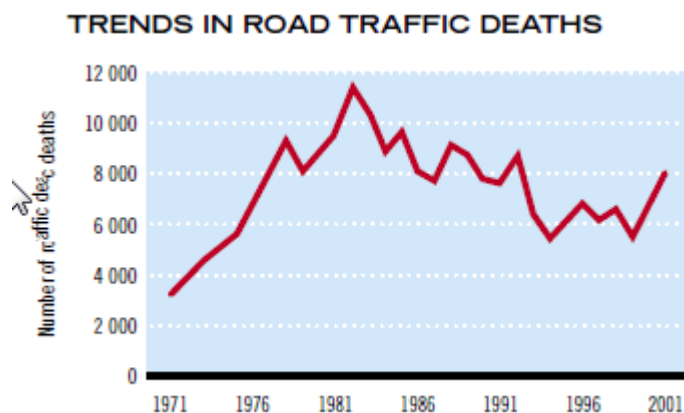
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Post-traumatic chronic osteomyelitis (COM) in poor & conflict-affected regions

- Post-traumatic chronic osteomyelitis (COM) is typically an indolent disease characterized by presence of necrotic bone
- Most commonly it is encountered in contexts with a high trauma burden (eg RTAs, violence) and inadequate surgical services.

Nigeria: Trends in road traffic deaths



Global status report on road safety: time for action. Geneva, WHO, 2009

Post-traumatic COM can be difficult to cure; it disables and stigmatizes far more than it kills.

Common endpoints are:

- Long-term disability
- Amputation



Economic costs are high.



Post-traumatic chronic osteomyelitis: an emerging neglected disease?

“Neglected tropical diseases are a group of chronic, disabling, and disfiguring conditions that occur most commonly in the setting of extreme poverty, especially among the rural poor and some disadvantaged urban populations.”

Hotez PJ, Kamath A (2009) Neglected Tropical Diseases in Sub-Saharan Africa: Review of Their Prevalence, Distribution, and Disease Burden. *PLoS Negl Trop Dis* 3(8): e412.



A word on link between war injury and post-traumatic chronic osteomyelitis...

Contamination and soft-tissue trauma

- (1) War-related extremity injury commonly results in both contamination with environmental debris & severe soft tissue injury

Conflict disrupts health care services

- (2) Conflict is linked to reduced access to health service, lower levels of hygiene in structures, disruptions in HR and access to supplies

Association between war injury and drug-resistant organisms

- (3) Colonization followed by infection with drug-resistant, particularly gram-negative organisms, documented in conflict-affected settings.
 - These resistant organisms are probably acquired in health care structures.



Prevention easier than cure

Reducing frequency of COM after open fracture possible with:

- Early debridement and wash-out after injury
- Prophylactic antibiotics
- External fixation
- Soft tissue coverage (envelope for healing, may deter infection)

Once established, post-traumatic COM can be difficult to cure:

- The standard treatment tools widely available for COM in resource-rich settings are not widely available in poor and conflict-affected settings
- MSF approach:
 - Extensive surgical debridement with removal of all necrotic soft tissue and bone (bone clearance margin of ≥ 5 mm)
 - Pathogen-targeted antibiotic therapy up to 12 weeks after definitive debridement
 - Reconstructive surgery in some contexts (eg Amman)



Christopher M.

- *A patient history* -

Two years earlier, while on a motorcycle, Christopher M. – a 33-year-old oil worker – experienced a traffic accident in which he suffered a severe open (Gustillo grade III) tibial fracture.

At the time of the fracture, he had received early wound debridement, antibiotic prophylaxis and external fracture fixation. During the first hospitalization he underwent placement of a muscle flap and skin graft.

Several months after the trauma, he achieved union of the fracture but developed swelling over his anterior tibia and three sinus tracts.



Challenges in the field

Extent of debridement

Long-term antibiotics initiated in some patients without complete debridement of dead bone (eg debulking).

- Reluctance to create large bone defects or fracture instability
 - Large bone defects require reconstructive surgery (prolonged treatment & significant morbidity).
- Infrequent use of amputation (social, economic, cultural, reasons)
- Belief that there is little risk linked with long-term antibiotics → temptation to “give antibiotics a try.”
 - Exposes patients to toxicities of long-term antibiotics with little chance of cure
 - Renal failure
 - Bone marrow suppression
 - Drug allergy

- The likelihood of cure is low when a complete debridement not performed -



Extent of resection & long-term outcome in COM

Simpson *et.al.* (2001) evaluated 3 surgical strategies for COM (N=50):

- 1) Wide resection, with a bone clearance margin of ≥ 5 mm
- 2) Marginal resection, with a clearance margin of < 5 mm;
- 3) Intralesional biopsy, with only debulking of the infected area.

- All patients antibiotics IV for 6 weeks + PO for a further 6 weeks -

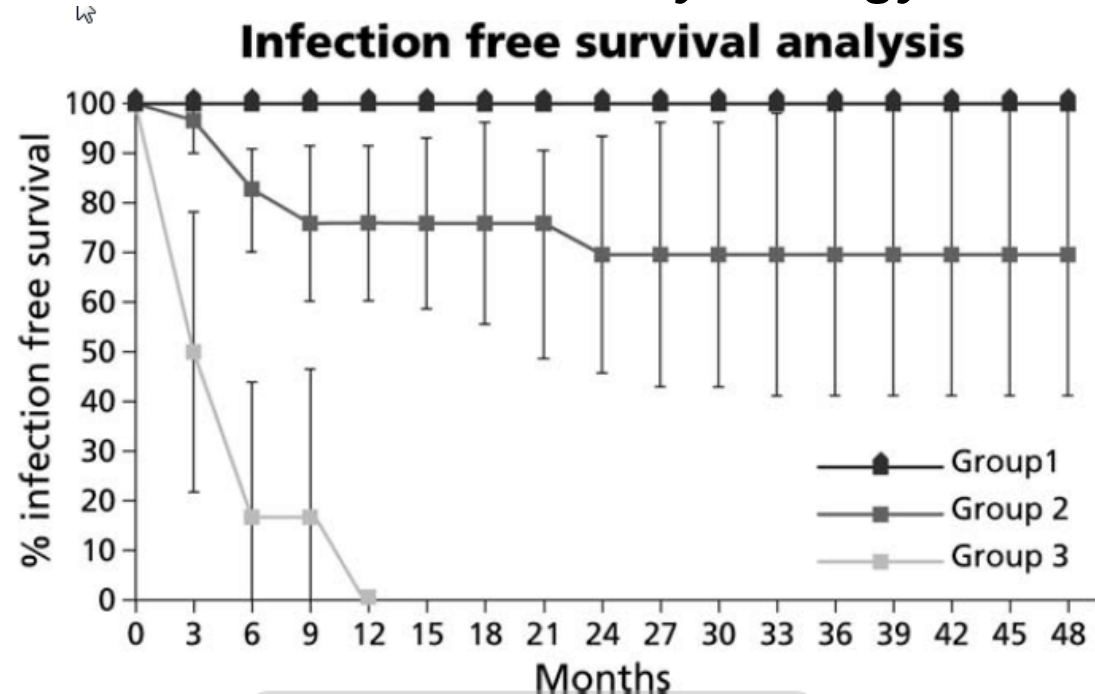
Outcomes:

Group 1 = ≥ 5 mm:
No recurrence (0%)

Group 2 = < 5 mm / marginal
8 of 29 (28%) recurrence.

Group 3 = Debulking
All had a recurrence (100%)
within 1 year of surgery.

Infection free survival by strategy:



Chris M.

A patient history

History of present illness:

He underwent surgical debridement, with excision of dead bone and sinus tracts and intraoperative cultures revealed *Pseudomonas aeruginosa* with resistance to several antibiotic classes.





Illustration: Don Smith

MSF approach to microbiology investigations



Identification of bacterial infection in bone and joint and determining the activity of antibiotics on bacteria = **vital** to the establishment of an **optimal therapeutic strategy**

- ❑ Adapted validation of microbiology laboratory setup in resource-poor context
- ❑ Specimen collection policy
- ❑ Antibiotic resistance surveillance



Validating microbiology laboratory setup

	MSF	Public	Private
Cons	<p>Difficult to implement but not impossible</p> <p>Human resources shortage</p> <p>Long training</p> <p>Cost</p>	<p>Quality of analysis (varies by country)</p> <p>Quality of reagent</p> <p>Quality control are rare</p> <p>Delay of results</p> <p>Difficulty of partnership</p>	<p>Proper assessment (tools, time,...)</p> <p>Memorandum of Understanding</p>
Pros	<p>Standard Operating Procedures (SOP)</p> <p>Quality of reagent</p> <p>Type of reagents (Kit, home made, ...)</p> <p>Quality insurance and control</p> <p>Reliability of analysis</p>	<p>Support on capacity building</p>	<p>Quality of results</p> <p>SOP</p> <p>Partnership and follow-up</p> <p>Cost</p> <p>Quality control and Insurance</p> <p>Guideline for Antibiotic Susceptibility Testing (AST) interpretation</p>



Specimens collection and transport policy

□ Collection:

- Swabbing of the orifice of a fistula had **no diagnosis interest**
- Deep sampling, per operative with different instruments
- **3-5** samples from suspected infected site
- Metaphyseal bone puncture, abscesses or sub-periosteal biopsy performed at the capsule, necrotic tissue, products of curettage
= **Solid samples**
- **No swab samples**
- Sample containers not sterile outside handle by OT assistant



Specimens collection and transport policy

□ Transport = depend on delay to laboratory

- < 12 hours = dry sterile container; *cold chain*



- > 12 H to 48 H = Transport media (Portagerm), *room °C*



- > 48 hours = Broth tubes (Brain-Heart infusion), *room °C*



Antibiotic resistance surveillance

- ❑ Implementation of WHONET analytical database for Antibiotic Susceptibility (AS) pattern follow up and analysis
 - Sulaimania (Irak); 2008
 - Amman, Gaza; 2009
 - Port Harcourt; 2011
 - Haiti; 2012
- ❑ Critical benefits of WHONET in middle east:
 - Allow us to proposed rational empirical antibiotic therapies for patients with burn sepsis in Kurdistan
 - Allow us to identify critical local antibiotic needs/gaps
- ❑ Trends in drug-resistance became clear





Epidemiology of infection and antibiotic resistance in MSF orthopedic projects

Results : Baseline characteristics

	Theme	Drouillard	Amman
Patients with infection (N)	84	44	142
males (%)	71	N/A	88
age median (years)	32	N/A	35
Foreign body at time of surgery (%)			
External fixator	20	N/A	35
internal fixator	6	N/A	13
none	74	N/A	52
Average surgery before	N/A	N/A	6



Results : Antibiotic resistance

	Nb° patient tested		CLI %R		OXA %R		VAN %R		RIF %R		TCY %R	
	Theme	Drouillard	T	D	T	D	T	D	T	D	T	D
<i>Staphylococcus aureus</i>	47	29	12	0	17	0	1	0	8	92	23	75

CLI : Clindamycin , OXA: Oxacilin , VAN: Vancomycin , RIF : Rifampicin , TCY : Tetracyclin

	Nb° patient tested		CAZ %R		CIP %R		GEN %R		SXT %R		IPM %R	
	T	D	T	D	T	D	T	D	T	D	T	D
P. aeruginosa	16	6	6	16	20	15	31	25			0	0
E. cloacae	11	0	87		6		40				0	
A. baumannii	0	5		60		0		33				0
E. coli	10	4	65	0	40	0	20	0	N/A	0	0	0

CAZ : Ceftazidim , CIP : Ciprofloxacin , GEN : Gentamycin , SXT : Cotrimoxazol , IPM : Imipenem



Results : Multi Drug Resistant

	MRSA %	ESBL_E %
Amman	65	86
Theme	17	65
Drouillard	0	0

- Predominance of Multi Drug Resistant bacteria in Irakee patient
- Moderate MDR rate in Theme patients
- No MDR in patient from Haiti



Discussion

- ❑ Etiology of germ similar to developed countries orthopedic centers
- ❑ High MDR rate Amman = poly-operated, ~ 2 years time injury, over use of ATB in all middle East ¹
- ❑ Similar patients in Theme and Drouillard but different resistance pattern ?
 - Nigeria = top country in Africa for ATB misused, counterfeiting, over prescription ².
 - Haiti = difficulty of access to ATB, poverty, etc

1) Murray, CK. Epidemiology of infections associated with combat related injuries in Iraq and Afghanistan. *The Journal of Trauma Injury, Infection and Critical Care*. 2008, Vol. 64, pp. 232-238

2) Okeke IN, Lamikanra A, Edelman R. Socioeconomic and behavioral factors leading to acquired bacterial resistance to antibiotics in developing countries. *Emerg Infect Dis*. 1999, Vol. 5, 1, pp. 18-27.



Challenges in the field

Antibiotic resistant (ABR) bacteria; what are implications?

- Chronic osteomyelitis cannot be treated empirically
 - With the growth of ABR, deep surgical cultures at the time of debridement is essential to plan definitive antibiotic therapy (up to 12 weeks).
 - Use of empirical antibiotics perilous due to varied epidemiology of osteomyelitis globally.
- Few antibiotic choices especially for resistant gram-negatives
 - Patients with COM caused by highly-resistant gut bacteria (E coli, Klebsiella and Enterobacter) or Pseudomonas, generally lack active PO antibiotic options, and required prolonged hospitalization for long-term IV therapy.
 - Fortunately, for MRSA, often some PO options remain if “community” c-MRSA strains are more prevalent than “hospital” MRSA in a given context
- Increased cost of treatment
 - Late-generation antibiotics are typically far more costly than older agents
 - Ex. For COM, the dose of imipenem 4 grams/day
 - 500 mg vial = 6 euros. For 4 grams/day over 6 week course → 2016 euros
 - The cost of prolonged inpatient care is also significant



Post-excision management

Antibiotics

- a. **Route:** When active PO options available, equally effective as IV options

Llarga and colleagues (Spain, 2009)

- After radical debridement, randomized (N=90) with Staph. aureus COM to:

Cloxacillin IV (2 g every 4 h) for 6 wks + Cloxacillin PO (500 mg q6h) for 2 wks

OR

Rifampicin PO + Cotrimoxazole PO for 8 weeks:

(Typically: TMP-SMX 3 SS tabs q12 + Rifampin 600 mg for 8 wks)

Outcome (at 7 years of follow-up):

No difference in cure rate (both ~ 90% cured)

Failures that occurred were associated with internal device retention

- b. **Duration:** Minimum duration of antibiotics not defined.

- In patients with complete debridement and no retained internal devices, 6-8 weeks of pathogen-directed antibiotics may be adequate, with 12 weeks the most conservative option

Antimicrob Agents Chemother. 2009 Jun;53(6):2672-6.



Patient monitoring in COM

Twice monthly:

- Review patient for adherence, side effects and treatment response
- Laboratory (if available)
 - Complete blood count
 - Serum creatinine
 - (C-reactive protein)



C-reactive protein (CRP)

What is the role of CRP in chronic post-traumatic osteomyelitis?

CRP is an acute phase protein, elevated in most patients with COM.

- CRP rises after surgery but -- in absence of infection -- falls by POD 4

CRP has been used to monitor patients with osteomyelitis after interventions and has been shown to be predictive of post-operative course for:

- **Pediatric hematogenous osteomyelitis**
- **Acute device-associated osteomyelitis**



Serial measurement of CRP can be used to monitor therapy and to guide duration of systemic antibiotic therapy.

CRP is preferred by many experts because it is more specific than ESR (less likely to be elevated from other processes).



Post-traumatic chronic osteomyelitis: a neglected area of research?

Research

- Chronic osteomyelitis has not been the subject of sufficient ongoing clinical research.
- Research in osteomyelitis has been hampered by lack of interest among researchers as well as the difficulty in accruing sufficient patients at a single site.
- In the US National Institutes of Health clinical trials database, there is currently only 1 clinical trial addressing osteomyelitis.



Post-traumatic chronic osteomyelitis: a neglected area of research?

Critical questions on the infectious diseases side are unanswered

- What is the ideal duration of antibiotic treatment?
 - **Should extent of debridement guide duration → margins 5 mm vs 0-5mm?**
 - **Standard treatment duration or use CRP (or other marker) to guide?**
- Is there a larger role for local delivery systems (antibiotic cement & beads) in chronic osteomyelitis in MSF contexts?
 - **Local delivery can reduce cost and system antibiotic exposure.**
 - **What patients are optimal for local delivery systems?**
- What are the most appropriate markers of cure? What is the rate of late relapse in our own programs?



Summary

- Post-traumatic COM, a growing problem in contexts with high burden of violence and RTA but with poor access to surgery
- Extent of debridement is critical: antibiotics should never be used as a substitute for adequate surgery
- Drug-resistance may render chronic post-traumatic COM virtually untreatable in some settings because of lack of access to quality microbiology labs & poor access to active, affordable antibiotics.
 - Antibiotic therapy to contribute to cure must be based on results of deep surgical culture specimens
 - PO combinations are effective when active, especially for Staph. aureus
- As a disabling disease with burden falling largely on poor contexts (and ignored area of research), COM may considered a neglected disease.



Merci
Thank you



•Profils de résistance des souches de *Staphylococcus aureus* :

	Moyennes	
	n	%R
Penicillin G	13	92
Cefepime	12	81
Oxacillin	9	64
Gentamicin	6	43
Fusidic acid	3	21
Ciprofloxacin	6	43
Clindamycin	6	39
Rifampin	5	38
Amikacin	4	26
Trimethoprim/ Sulfamethoxazole	5	33
Vancomycin	0	0

•Profils de résistance des souches d'*Escherichia coli*:

Antibiotique testé	Moyennes	
	n	%R
Amikacin	3	20
Ampicillin	12	97
Cefixime	12	93
Cefaclor	12	94
Cefuroxime (CIIG)	12	91
Ceftazidime (CIIG)	11	86
Cefepime (CIVG)	9	91
Ciprofloxacin	5	44
Gentamicin	10	81
Trimethoprim/ Sulfamethoxazole	9	75
Imipenem	0	0

