Causative Pathogens Do Not Differ Between Early, Delayed, or Late Fracture-Related Infections

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INTRODUCTION:

Fracture-related infection (FRI) is classically defined as early (0-2 weeks), delayed (3-10 weeks), or late (>10 weeks) based on hypothesized differences in causative pathogens and biofilm formation and maturation. It has been claimed that more virulent organisms (*Staph. Aureus*, Gram negatives) are responsible for early infections, but delayed or later infections are due to low-grade organisms (coagulase-negative Staphylococci, Cutibacteria spp.) in biofilms. Treatment strategies often reflect this classification, with debridement and implant retention (DAIR) preferentially retained for early FRI.

METHODS:

This study examined pathogens isolated in confirmed FRI to support or refute these hypothesized differences in causative pathogens over time. Cases of FRI, confirmed by the International Consensus definition[1] and managed surgically at three centers, in the United Kingdom and the Netherlands, between 2015- 2019 and followed up for at least one year were included. Patients under 16 years old or with FRI of the skull or spine were excluded. Data were analyzed on patient demographics, time from injury, and pathogens isolated. Resistance profiles of isolates were determined. Patients who underwent DAIR were also analyzed separately.

RESULTS:

A total of 433 FRIs were studied, including 51 early cases (median time from injury 2 weeks), 82 delayed cases (median 5 weeks), and 300 late cases (median 112 weeks, range 11-3432 weeks). Patient demographics are summarized in Table 1.

The type of infection was associated with time since injury. Early or delayed FRI were more likely to be polymicrobial (59% and 56% respectively) compared to late infections (26%; X^2: p=0.0001). Negative cultures were uncommon before 10 weeks but more frequent in late FRIs (4% vs. 24%; %; X^2: p=0.0001). Staphylococcus aureus was the most frequently isolated pathogen at all timepoints, however we found no evidence that the type of pathogens isolated in early, delayed, or late infections were different (p = 0.2). More specifically, we found no evidence for more virulent pathogens (Staphylococcus aureus, Gram negatives) in early infections or less virulent pathogens (non-aureus Staphylococci) in late infections. So called 'difficult-to-treat' organisms (Methicillin-resistant Staph. aureus, Rifampicin-resistant Gram positives, and Ciprofloxacin-resistant Gram negatives) were equally represented in all groups.

DISCUSSION AND CONCLUSION:

In summary, decisions on FRI treatment should not assume microbiological differences related to time from injury. The clinical relevance of classifying FRI by time from injury remains unclear but cannot be supported by models based on potential bacterial isolates.

1 **McNally M, Govaert G, Dudareva M, Morgenstern M, Metsemakers W-J**. Definition and diagnosis of fracture-related infection. *EFORT Open Rev* 2020; 5: 614-619.

Keywords: Fracture related infection; fracture; infection; microbiology; pathogen; early, delayed or late fracture related infection.

Table 1. Patient Demographics and Microbiological Results by Time from Injury

	0-2 weeks	3-10 weeks	>10 weeks	Whole Group	Significance
Patient Demographics					
Number of cases	51	82	300	433	
Age (median, years)	50.0	52.0	50.0	51.0	p = 0.85
Age (range)	17-84	17-77	16-84	17-84	
Sex (% male)	66.7	67.1	76.3	70.0	p = 0.12
BMI[§] (median)	23.6*	25.4	27.8*	27.3	*p = 0.004
BMI[§] (range)	17.2-37.1	14.0-41.8	12.5-46.8	14.0-46.8	
Time since injury (median, weeks)	2	5	112	44	
Time since injury (range)	0-2	3-10	11-3432	0-3432	
Bone Involved					
Tibia/Fibula	24 (47%)	47 (57%)	166 (55%)	237	p < 0.001
Femur	10 (20%)	8 (10%)	76 (25%)	94	P = 0.017 (tibia, femur, upper limb only)
Upper Limb	5 (10%)	8 (10%)	39 (13%)	52	
Pelvis	8 (16%)	11 (13%)	7 (2%)	26	
Foot	4 (8%)	7 (9%)	8 (3%)	19	
Other	0	1 (1%)	4 (13%)	5	
Culture Type					
Culture negative	2 (4%)**	6 (7.3%)	72 (24.0%)**	80 (18.5%)	**p < 0.0001
Monomicrobial	19 (37.3%)	30 (36.6%)	150 (50.0%)	199 (45.9%)	
Polymicrobial	30 (58.8%)*	46 (56.1%)**	78 (26.0%)* **	154 (35.6%)	*p = 0.0004 ** p < 0.0001
Species Isolated					
Staphylococcus aureus	23 (24.4%)	48 (29.8%)	129 (33.8%)	200 (31.4%)	p = 0.20
Staph. epidermidis	11 (11.7%)	15 (9.3%)	34 (8.9%)	60 (9.4%)	
Other Staphylococcus	6 (6.4%)	8 (5.0%)	18 (4.7%)	32 (5.0%)	
Streptococcus	5 (5.3%)	7 (4.3%)	33 (8.6%)	45 (7.1%)	
Enterococcus	9 (9.6%)	13 (8.1%)	27 (7.1%)	49 (7.7%)	
Corynebacterium	6 (6.4%)	7 (4.3%)	13 (3.4%)	26 (4.1%)	
Gram negatives	20 (21.3%)	34 (21.1%)	88 (23.0%)	142 (22.3%)	
Anaerobes	9 (9.6%)	26 (16.1%)	35 (9.2%)	70 (11.0%)	
Other	5 (5.3%)	3 (1.9%)	5 (1.3%)	13 (2.0%)	
Total	94	161	382	637	

[§]BMI: Body mass index