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Monomicrobial *Enterobacter cloacae* Infections in Extensive Hand Injuries - A Case Series

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Abstract

Introduction: Posttraumatic monomicrobial infections with *Enterobacter cloacae* (EC) is rare. Serious complications and subsequent interventions raised the attention to examine such cases in more detail. This is a retrospective analysis of complications, treatment strategy and outcomes of post-traumatic EC monomicrobial infections.

Methods: Patients with EC monomicrobial infections treated from 2008–2017 were considered. Nature of trauma, location, injured structures, time from trauma to surgery, pathogens, number of surgical treatments, antimicrobial therapy, complications, and outcome were assessed.

Results: From 2008-2017, 6 patients with EC monomicrobial infection were identified. They were all male; the median age was 38 years. Two severe cases were initially treated surgically at the day of trauma, 4 milder cases were initially treated conservatively and surgery delayed by at least 1 day. None of the patient had initially positive bacterial swabs but routinely given general antibiotic therapy with amoxicillin/clavulanic acid until EC was confirmed after 3 to 120 days (average 30 days). Infection was successfully controlled with one intervention in 4 cases, 2 interventions in 1 case and 3 interventions in 1 case. Four patients developed complications. Following availability of microbiological tissue samples the antibiotic of choice was tailor made and patients treated with the correct antibiotic cefepime or ciprofloxacin for a median time of 30 days.

Conclusion: Posttraumatic EC monomicrobial infections were rare but may lead to complications with the need of interventions and a loss of hand function. Initial tissue samples of infected tissue extremely important in order to treat the correct contaminant. Early surgical intervention is paramount.

Keywords: *Enterobacter cloacae*; Posttraumatic; Monomicrobial infection; Upper extremity

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Introduction

Soft tissue monomicrobial infections with *Enterobacter cloacae* (EC) as an only pathogen after open trauma in the upper extremity are rare. Our series of cases demonstrate the severe complications possible with this devastating infection. Infections with these bacteria led to complications that require long term antibiotic treatment and several surgical interventions, requiring a prolonged time to healing and residual loss of function. This study contains a retrospective analysis of complications, treatment strategy and outcome of posttraumatic monomicrobial infections with EC infection in upper extremity.

History/Living space

EC was first described in 1890 [1]. The aerobe EC is a Gram-negative bacteria strain [2]. EC is widespread in the environment and nature and can be found in water (e.g. sewage), soil and food [3-7]. From all *Enterobacter* spp. EC is the most frequently isolated species in human tissue [8]. As commensal microflora, EC can also be found in the intestinal tract of humans and animals [2]. Additionally, they can also function as pathogens. Sources of EC infections could be an animal reservoir, a human carriers or an endogenous diffusion of the microorganism [9]. Due to the diversity of habitats, there is a great genetic variability of the nominate species EC [10]. It is known that EC can contaminate medical, intravenous and other hospital equipment [11]. Nosocomial outbreaks due to colonisation of cleaning solutions and surgical equipment are described [3-7].

Human infections

The exact mechanism of pathogenicity is unclear [8]. As a nosocomial pathogen, EC can be responsible for bacteraemia and various infections. Typically, EC causes sepsis, urethritis and lower respiratory tract infections but rarely septic osteoarthritis and other infections [2]. Increasing evidence suggests that EC is also a common source of musculoskeletal and post-operative infections [3,8,12-15]. There is increasing evidence that EC is a source of infection in orthopedic surgery, and therefore also in hand surgery [3,12-15]. The skin and gastrointestinal tract are predominantly affected [2,16]. In recent years it has been shown mainly in intensive care and burn units that EC are the most common nosocomial pathogens, especially in patients with underlying diseases, immunosuppression and prolonged hospitalization [2,4]. Nevertheless, little is known about their virulence-associated properties [11].

Surgical site infections

A prospective randomized controlled trial of surgical site infections by Yang et al. [11] showed growth rates of 17.3% for *S. aureus*, 19.5% for *E. faecalis*, 10.5% for *P. aeruginosa*, 13.4% for *B. fragilis*, 20.4% for *E. coli*, 9.1% for *Enterobacter cloacae*, and 9.8% for *K. pneumoniae*.

Antibiotic therapy

There has been an increasing incidence of enterococci in tissue biopsies since 1990 with an unclear dramatic increase in recent years. Increasing resistance to conventional antibiotic therapies, especially cephalosporin's, is a potential reason [17]. Most EC complexes are sensitive to fluoroquinolones, trimethoprim/sulfa-methoxazole, chloramphenicol, aminoglycosides, tetracyclines, piperacillin-tazobactam and carbapenems. They are naturally resistant to ampicillin, amoxicillin, amoxicillin-clavulanate, first-generation cephalosporins and cefoxitin because they produce a constitutive AmpC-b lactamase [18]. A big problem are ESBL-bacteremias (Extended-Spectrum Beta-Lactamase producing bacteria) which can be caused by EC [19,20]. Production of ESBL by EC is increasingly reported worldwide [21,22]. By depressing a chromosomal gene or acquiring a transferable AmpC gene on plasmids, they gain resistance to antibiotic therapies because they can overproduce AmpC-B lactamases [11]. Independent risk factors for ESBL like admission from a nursing home, presence of a gastrostomy tube and transplantation in the history are well recognised [17]. Unnecessary use of broad spectrum-spectrum cephalosporins and carbapenemens plays a crucial role and leads to the development of resistant strains [8].

Risk factors for infection

Known risk factors are poor hand hygiene, intubation pf patients, prolonged hospital stay, intravenous feeding, use of extended-spectrum antibiotics or use of intravenous catheters [8]. Surgically implanted material can potentially be contaminated with EC which can be a source of infection [23]. The awareness of the limited therapeutic options to treat EC infections demonstrates the importance to slow down and control the worldwide epidemic spread of this bacteria.

Osteomyelitis

EC is known to be the third most common organism (9.5%) causing chronic osteomyelitis [12]. Other data show that about 10.6% of post-traumatic osteomyelitis is caused by EC [13]. EC osteoarticular infections are uncommon and this case suggests that they may infect previously damaged bone without other predisposing factors [24]. The aim of the study is to present the course as well as potential complications of a monomicrobial EC infection based on a retrospective analysis of 6 patients in the upper extremity.

Materials and Methods

This is a retrospective analysis of patient charts for EC monomicrobial infections that were treated from 2008-2017. Follow-up time, patient characteristics (gender, age), date of accident, days from accident until surgery, the mechanism of trauma and involved structures were assessed (Table 1). Localization of injuries are shown in Figures 1-6. All patients were classified with the Hand Injury Severity Score* in a MHISS category. The infected tissue, localization of infections and the time from trauma to infection were collected (Table 2) as well as antibiotic treatments (Table 3). None of the patient had initially positive bacterial swabs but routinely given general antibiotic therapy until EC was confirmed after 3 to 120 days. All patients needed a surgical treatment of EC infection including debridement (1-3), removal of osteosynthetic material (1), and flap coverage (2). Four patients underwent 1 procedure, 1 patient underwent 2 procedures, and 1 patient underwent 3 procedures. Complications from EC infection affected two-thirds of patients (4). Three patients suffered from flexor tendon adhesion. In addition to flexor tendon adhesion, one patient also suffered a flexor tendon rupture. Patient 6 suffered from flexor tendon adhesion and rupture, extensor tendon adhesion and nerve adhesion. One patient developed CRPS. Follow-up interventions due to EC infections were necessary in 4 patients and included arthrolysis (1), tenolysis (2), tendon reconstruction (2), scar correction (1), flap (1), A1 pulley release (1) and neurolysis/synovial flap (2). Patient 6 required all these interventions.

Hand Injury Severity Score: Patients in one of the higher MHISS categories are less likely to return to their previous job [25]. Dominance of the injured hand, status of the main wage earner in the household or behavior in seeking compensation has no influence. Furthermore, the severity of MHISS in patients can predict the time needed to return to work. The higher the MHISS, the longer it takes for the patient to return. The median time to return to work is 30 (mild) to 760 (severe) days for the MHISS categories. Quantified injury severity (MHISS) is an important determinant of returning to work after a hand or forearm injury. According to this significance, the 6 patients in this study were classified according to MHISS.

Results and Discussion

In the 10-year period from 2008 to 2017, a total of 11 patients were identified with microbiological proven EC infection, 6 of them with an isolated EC monomicrobial infections (54.5%). These 6 cases were further analyzed. All the patients were male, the mean age was 35.5 (range 23-45) years with a median age of 38 (IQR 29-42). Follow-up time was between 6 and 38 months.

Localization

Photo documentation was done in all 6 cases (Figures 1-6). Digits and/or the palm were affected in 4 (67%) cases, the forearm in 2 (33%). In addition to soft tissue injuries, which affected all patients (100%), in 5 cases tendons and/or muscles were involved, in 4 (67%) cases neurovascular structures had to be repaired and in 2 (33%) cases with bone involvement and osteosynthesis was required. Additional to the soft tissue injury, in 3 (50%) cases tendons/muscles were involved, in 4 (67%) cases neurovascular structures had to be repaired and in 1 (16%) case with bone involvement osteosynthesis was required.

Table 1: Patient characteristics and details of injury.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Follow-up (month)	13	16	6	10	23	38
Gender	male	male	male	male	male	male
Age	43	27	23	39	45	36
Date of accident	28.05.2008	06.12.2009	06.11.2017	05.06.2017	30.06.2016	18.03.2015
Days until surgery	3	1	1	1	0	0
Mechanism	Fall	Tin	Knife	Knife	Hydraulic roller	Circular saw
Stab/cut	-	yes	yes	yes	-	-
Avulsion	-	-	-	-	-	yes
Crush	-	-	-	-	yes	-
Laceration	yes	-	-	-	-	-
Involved structures						
Soft tissue	yes	yes	yes	yes	yes	yes
Bone	yes	-	-	-	yes	yes
Neurovascular	-	yes	yes	yes	-	yes
Tendon	-	yes	yes	yes	yes	yes

Table 2: Infected tissue, localization, and time from trauma to infection.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Infected tissue						
Soft	1	1	0	1	1	1
Bone	1	0	0	0	0	0
Tendon	0	0	1	1	0	1
Localization						
Forearm	0	1	0	0	1	0
Palma maunus	1	0	1	0	0	1
Digiti	0	0	0	1	0	1
Time of infection						
days	3	14	21	120	8	13
early	yes	yes	yes	-	yes	yes
late	-	-	-	yes	-	-

Table 3: Antibiotic treatment.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Amoxicillin/clavulanic acid						
Preoperative (d)	4	2	2	2	1	1
Postoperative (d)	17	29	5	9	8	19
Other antibiotics						
Tazobactam (d)	3	3				
Cefepime (d)	8			3	8	13
Ciprofloxacin (d)	17	14		12	78	
Sulfamethoxazole-trimethoprim (d)			14			

Hand injury severity score

The traumas were categorized with the Modified Hand Injury Severity Score 1. Two cases were classified as Minor trauma, 2 as Moderate and 2 as Major. The associated trauma was categorized as severe trauma in 2 (33%) cases, and as mild trauma in 4 (67%) cases. The 2 Major traumata were treated surgically at the day of trauma, the other 4 cases (Minor and Moderate) with a delay of at least one day (range 1-3). The 2 severe cases were initially treated surgically at the day of trauma; the 4 milder cases with a delay of at least 1 day (range 1-3).

Antibiotics

All patients underwent a preoperative antimicrobial therapy with amoxicillin/clavulanic acid (range 1 to 4 days). But EC is naturally resistant to amoxicillin-clavulanate. None of the patients had initial

Figure 1: Localization and extent of injury of patient 1.
Description of injury: Milling injury of right Dig I/II and IV with/at: **Dig I:** Lesion of ulnar radial digital nerve branch; **Dig II:** no deeper structures injured, closed osseous avulsion of ulnar collateral ligament MCP; **Dig IV**: small fracture of distal phalanx, nail bed injury, nail fracture/luxation.

Figure 2: Localization and extent of injury of patient 2.
Description of injury: Cut wrists on both sides with: **Left wrist:** two median nerve lesion (70% lesion in the ventral wrist area, 100% lesion 2 cm proximal to it); 100% lesion of palmar branch of median nerve, 100% lesion of radial artery, 50% lesion of FDP II, 100% lesion of FDS II, 50% lesion of FDP III, 100% lesion of FDS III, 10% lesion of FDP IV, 50% lesion of FDS IV, 100% lesion of FDS V, 100% lesion of FPL, 100% double lesion of FCU at muscular junction and 50% tendon lesion, 100% lesion of FCR, 50% lesion of brachioradialis muscle, 100% lesion of palmaris longus tendon. **Wrist right:** Soft tissue injury only.

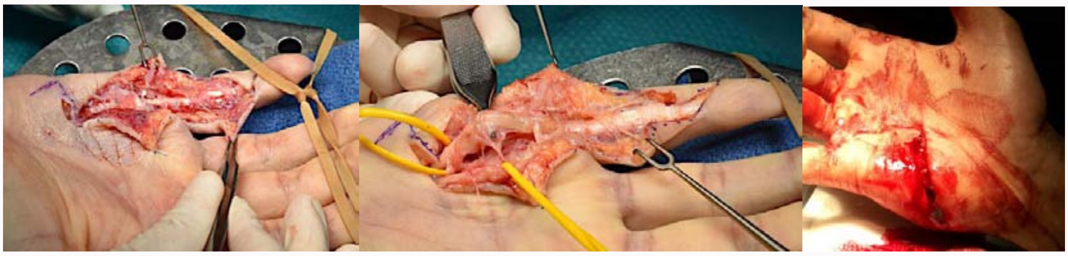

Figure 3: Localization and extent of injury of patient 3.
Description of injury: Cut injury of right **hypothenar** with: 80% transection of hypothenar muscle, 100% lesion of FDP (V) and FDS (V) zone 3, 100% lesion of ulnar digital nerve.

positive bacterial swaps as no swaps were taken in the initial operative intervention. After the initial operative intervention, general antibiotic therapy with amoxicillin/clavulanic acid was routinely administered until EC was confirmed after an average of 30 days (3 to 120 days). The mean postoperative duration of correct antibiotic treatment with cefepime/ciprofloxacin was 48.8 days (range 19-100) with a median duration of correct antibiotic treatment with cefepime/ciprofloxacin of 30 days (IQR 23-78).

EC Infect

The infection occurred on average 30 (range 3-120) days after trauma. It was successfully controlled with one intervention in 4 (67%) cases. In one case, 2 and in one case, 3 operations were required including a flap to resolve the infection in 2 cases.

Complications

Four (67%) patients developed one or more complications (range 1-5) with at least one subsequent required surgery (range 1-8). In total, 3 flexor tendon adhesions occurred, 2 re-ruptures of a flexor tendon repair, 2 nerve compressions due to scarring and one extensor tendon adhesion. In two patients, a CRPS was present in due course.

Conclusion

Posttraumatic EC monomicrobial infections in upper extremity are rare but can result in aggressive disease that requires several interventions and a certain loss of hand function. An initial sample at time of trauma intervention to detect EC and possible early treatment with the correct antibiotic therapy is recommended. It's important to be aware of the limited therapeutic options for treating EC infections. An important factor is to stem the global epidemic spread of these bacteria and especially the emerging carbapenemase-producing strains of the EC complex. The presented case series shows that a monomicrobial infection with EC may have a dramatic course with a multitude of subsequent interventions and complications, as for example in the case of patient 6. This infection occurs not only in severe but also ordinary injuries (patient 4). Due to the frequent occurrence of EC in the environment, it can be concluded that infections are not as rare as originally assumed. The review of the cases presented has shown that 4 (67%) patients developed one or

Figure 4: Localization and extent of injury of patient 4.
Description of injury: Pluridigital cut injury of right hand with **Dig III:** 100% lesion of FDS and FDP zone 1, 100% lesion of ulnar digital nerve, 100% lesion of A4 annular ligament. **Dig IV:** 100% lesion of FDS and FDP zone 2, 100% lesion of ulnar digital nerve. **Dig V:** 100% lesion of FDS and FDP, 100% lesion of ulnar digital nerve, 100% lesion of ulnar digital artery; **Dig II:** soft tissue injury only.

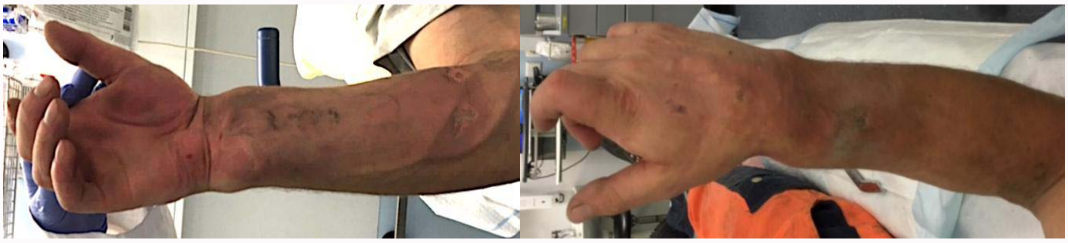

Figure 5: Localization and extent of injury of patient 5.
Description of injury: Severe crush trauma of right hand and forearm in hydraulic roller with: Compartment syndrome of hand and forearm, distal intraarticular radius fracture (AO type B), palmar MCP II joint dislocation, fracture CMC II and damage of median and ulnar nerve in continuities.

Figure 6: Localization and extent of injury of patient 6.
Description of injury: Circular saw injury of left distal palm with: arterial and venous devascularization of Dig II, IV and V; arterial devascularization of Dig III. Destruction of MP joints II-V with defect of the palmar articular surface, base of proximal phalanx Dig III, larger defect of basal phalanx base with majority of joint contour preserved, defect of palmar intra-articular metacarpal V-head. 100% transection of FDS and FDP II-V, defect lesion of extensor tendon zone 4 Dig III, 100% transection of the digital nerves Dig II-V, small skin defects palmar Dig I. Preexisting PIP stump formation in Dig II.

more complications and suffered serious complications from the infection with EC. Finally, special attention is paid to the newly emerging carbapenemase-producing EC complex strains, as they are transmitted by mobile genetic elements. It is important to be aware of the limited therapeutic options for treating EC infections. An important role here is to stem the global epidemic spread of these bacteria, and especially the emerging carbapenemase-producing strains of the EC complex. Effective strategies to control nosocomial infections are immunization with the development of new vaccines and improved hand hygiene. Therefore, further studies are needed to detect risk factors of transmission, the exact mechanism of infection and optimal treatment for patients with EC infections.

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