Clostridium difficile infection in pediatric polytrauma patients - review of literature and case report

Tepeneu N. F. [1),2)]
[1)] ”Victor Babes” University of Medicine and Pharmacy, Timisoara
[2)] Klinikum Klagenfurt am Wörthersee, Austria

Introduction

Clostridium difficile associated disease is a well recognized nosocomial infection evolving as a severe diarrheal illness, associated with significantly higher rates of morbidity and mortality in critically ill patients

The incidence of Clostridium difficile infection is higher and its impact is more severe in trauma patients when compared with general inpatient population

Moreover, managing these patients may prove to be a very challenging task, considering the emergence of novel aggressive Clostridium difficile strains resulting in increased disease severity

Case presentation

Pat. U. L., m, 13 years old

14.02.2017 – ski accident – patient came off the track and drove at high speed against a wooden fence

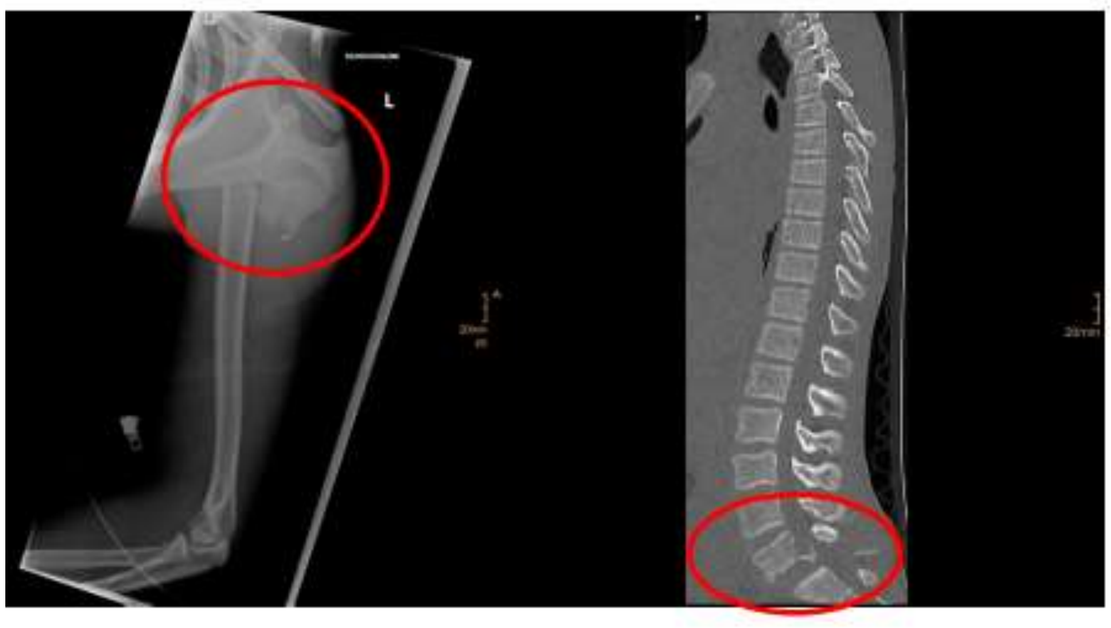
Wore a helmet

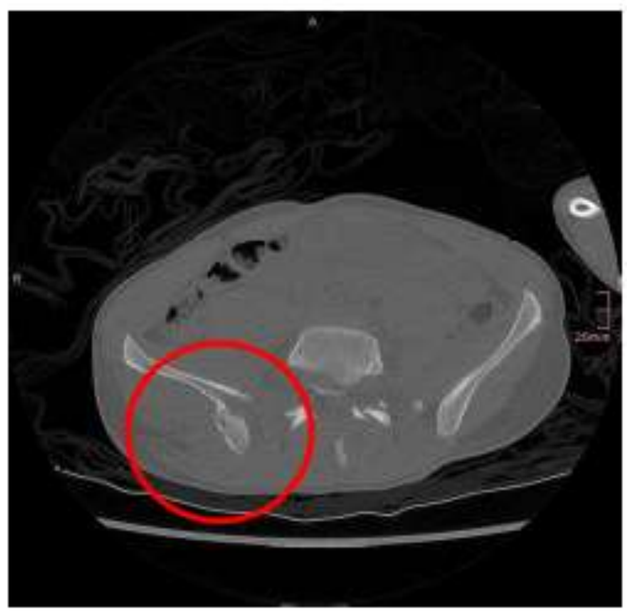
Was responsive after the fall, but complained of severe pain in the left upper arm, lumbar and pelvic area

Patient arrived intubated and ventilated with helicopter transport

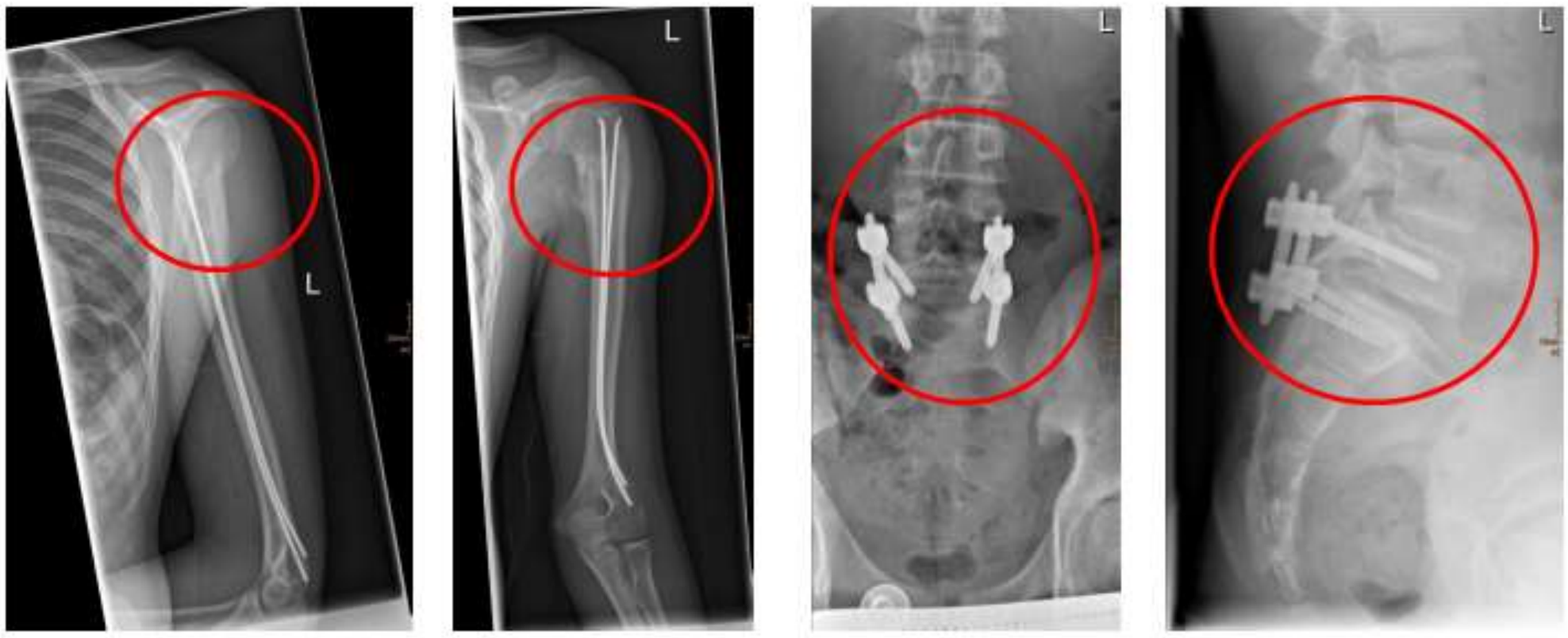
Politrauma after ski accident with

- Mild traumatic brain injury (no abnormality in CT)
- Lumbar vertebral 5 fracture with triangular cortical tear of L5 and dislocation into the spinal canal, subluxation and misalignment of the facet joint L5 / S1 left and right, comminution of a bone lamella of the process transversus L5
- Displaced subcapital humeral fracture (left)
- Fracture of right iliac wing with a step formation of one bone width
- Lung contusion. Minimal pneumothorax right (not requiring intervention)
- Hypothermia





Patient was operated on the same day
- closed reduction of the humerus fracture and elastic intramedullary osteosynthesis using 2 Prevot nails
- Open reduction of LWK 5 fracture and dorsal stabilization of L5 on S1
- Postoperative relocation to the pediatric intensive care unit



Evolution

- Initial CRP : 0,70 mg/dl
- Cardiorespiratory stable, minimal circulatory support with Arterenol up to 0,05 µg/kg/min.
- Extubation on 2nd postoperative day
- Pat. very restless in the sense of a symptomatic transitory psychotic syndrome: motor restlessness, crying, defensive attitude
- Sedation with Catapresan up to 30µg/kg/d
- Antibiotic therapy with **Cefuroxim** 3x1,5 g/day
- CRP of 28 mg/dl on 2nd postoperative day

Day	1	2	3	4	9	10	13	17	21
Parameter									
CRP (mg/dl)	0,7		30,5	31,45	15,22		5,73	3,92	0,47
Leucocytes /µl	13740	13560	13500	14050	13300	16800	31620	10830	10300
Htc %	26,3	24,1	32,2	33,1		37,6	36,8	37	39
Trombocytes /µl	259000			410000	690000	810000	994000	1450000	984000
Lipase U/l	164			57	102				
ALT U/l	148			41	104		162	306	58
Calprotectin mg/kg							3175	1370	1970
D-Dimere mg/l								1,87	1,16
Total protein g/dl					4,53	5,02	6,26	6,85	7,03
Albumin g/dl					1,85	1,97	2,54	2,86	2,68

3rd postoperative day

MRI brain : diffuse axonal injury

US Abdomen:free fluid Douglas‘ pouch, persisplenic and perihepatic. Suspicion of spleen infarction.

CRP rise: 30,5 mg/dl, change of antibiotic therapy to **Meropenem**

- In the further course the patient still shows a clear need for respiratory support with oxygen mask and partially high flow nose- glasses

4 th postoperative day

- CRP rise: 31,45 mg/dl
- Antibiotic therapy supplemented with **Zyvoxid** i.v.
- **Rx thorax**- bilateral pleural effusions. (left >right)
- Patient has fever and diarrhea

6th postoperative day

US abdomen:regressive free fluid, splenic infarction (lover splenic pole), wall-thickened terminal ileum, coecum, and ascending colon.

The suspicion of antibiotic-induced colitis is expressed

7th-12th postoperative day

- Neurologically, there was a pleasing evolution
- The patient continues to develop subfebrile / febrile temperatures and diarrhea.
- Distended abdomen and diffuse pain on palpation

13th postoperative day

CRP – rise 7,19 mg/dl

Leucocytes- massive rise to 31620 /µl

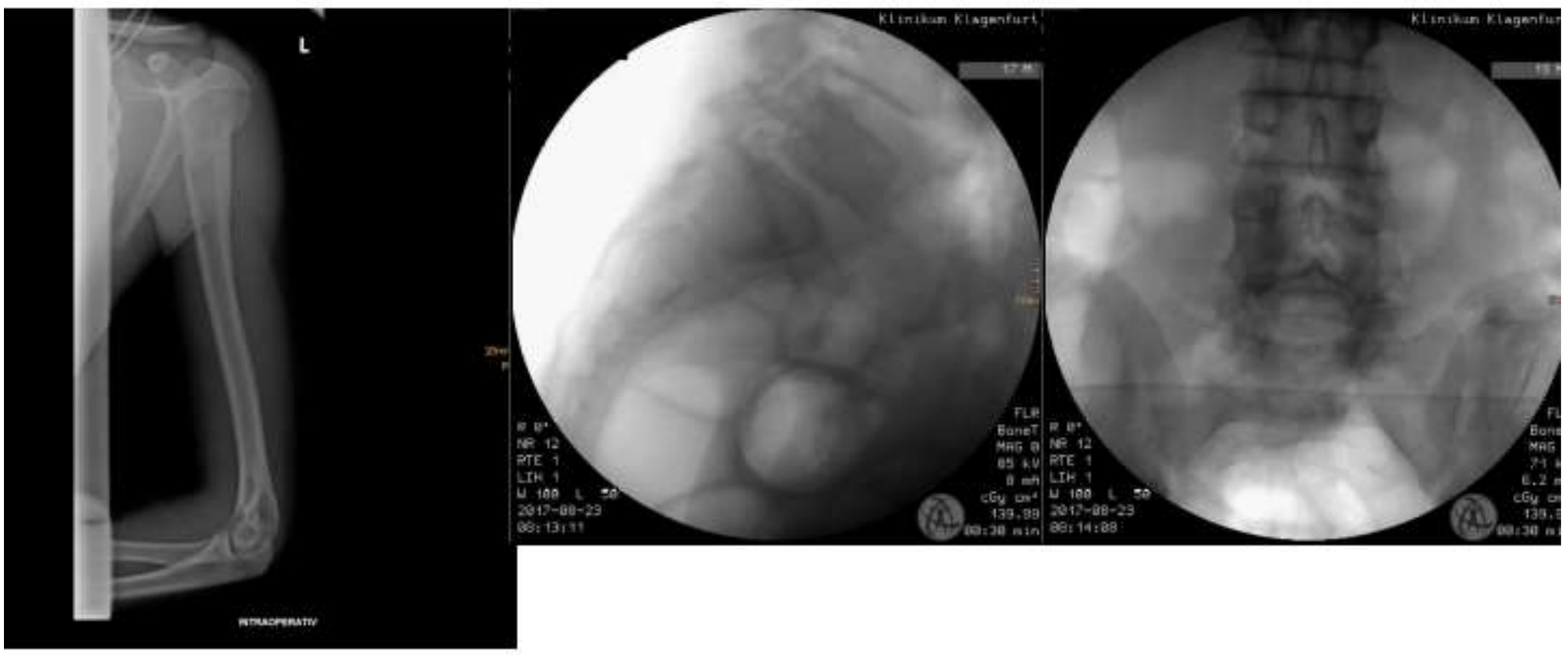
US abdomen :Pronounced colitis

Suspicion of pseudomembranous colitis

Antibiotic therapy with **Metronidazol** 3 x500 mg/day po

14th- 30th postoperative day

- Slow improvement of the general condition, so that on the 29th postoperative day all medication could be discontinued
- From surgical point of view - favourable evolution with excellent wound conditions, under physiotherapy an increasing mobilization becomes possible



4 month postoperative– Removal of the osteosynthesis material from the left humerus

8 month postoperative – Removal of the osteosynthesis material from the spine

Discussion

- CDI : Annual costs, currently estimated at $ 1.1 billion in the US, and at around € 3 billion in Europe
- The Centers for Disease Control and Prevention (CDC) classifies C. difficile as one of the top three health system threats, with 430,000 infections and 29,000 deaths per year
- CDI increased morbidity leads to a prolonged inpatient treatment period and a considerable additional effort in hygiene management

Lessa FC,Mu Y, Bamberg W, Met al (2015) Burden of Clostridium difficile infection in the United States.NEngl JMed372:825–834

Kyne L, Hamel MB, Polavaram R, Kelly CP. Health care costs and mortality associated with nosocomial diarrhea due to Clostridium difficile. Clin Infect Dis 2002; 34: 346 ± 353

Kuijper EJ, van den Berg RJ, Debast S et al. Clostridium difficile ribotype 027, toxinotype III, the Netherlands. Emerg Infect Dis 2006; 12: 827 – 830

CDI – Clostridium difficile Infection

CDAD – Clostridium difficile associated diarrhea

Risc factors for CDAD/CDI

- Intensive therapy / multiple hospital stays
- Age 1-5 years (peak 5 years)
- Severe underlying diseases
- Comorbidities
- Gastrointestinal diseases / Chronic inflammatory bowel disease
- Operations/Abdominal operations
- Multiple Antibiotherapy
- 2nd und 3rd generation–Cephalosporins
- Quinolons?
- Antacids/ PPI (controverse data)

Kim J, Smathers SA, Prasad P, Leckerman KH, Coffin S, Zaoutis T.Epidemiological features of Clostridium difficile-associated disease among inpatients at children's hospitals in the United States, 2001-2006. *Pediatrics* 2008; **122**: 1266-1270 [PMID: 19047244 DOI: 10.1532/peds.2008-0469]

Discussion

- Clostridium difficile-associated diarrhea (CDAD) show various clinical courses:
- ca. 60% asymptomatic
- ca. 40% symptomatic
  - From which in 25% severe evolution
- in ca. 1% life-threatening course with pseudo-membranous colitis and possibly toxic mega-colon
- Lethality of pseudomembranous colitis ca. 6 - 30%

Kwon JH, Olsen MA, Dubberke ER. The morbidity, mortality, and costs associated with Clostridium difficile infection. *Infect Dis Clin North Am* 2015; 29: 123-134 [PMID: 25677706 DOI: 10.1016/ j.idc.2014. 11.003]

Diagnosis

The diagnosis of C difficile disease is based on the presence of diarrhea and of C. difficile toxins in a diarrheal stool specimen

The most common testing method used for C. difficile toxins is enzyme immunoassay (EIA), which detects toxins A and/or B. Mean test sensitivities range from 72% to 82%

Glutamine dehydrogenase test – bed-side test

Molecular assays using nucleic acid amplification tests (NAATs)

Stool culture: time consuming, costly

Therapy

- In acute CDAD under antimicrobial therapy, the current antibiotic should be discontinued first, if this is possible - already in 15-23% of cases this leads to a disappearance of the clinical symptoms
- Oral metronidazole at 4 x 250 mg or 3 x 500 mg / day and oral vancomycin at 4 x 125 mg / day were found to be comparably effective after ten days of therapy

Teasley DG, Gerding DN, Olson MM et al. Prospective randomised trial of metronidazole versus vancomycin for Clostridium-difficile-associated diarrhoea and colitis. Lancet 1983; 2:1043 – 1046

Wenisch C, Parschalk B, Hasenhundl M, Hirschl AM, Graninger W. Comparison of vancomycin, teicoplanin, metronidazole and fusidic acid for the treatment of Clostridium difficile-associated diarrhea. Clin Infect Dis 1996; 22: 813 – 818

Bricker E, Garg R, Nelson R, Loza A, Novak T, Hansen J. Antibiotic treatment for Clostridium difficile-associated diarrhea in adults. Cochrane Database Syst Rev 2005; CD004610 :

Predictors of a severe CDI infection

- Leucocytosis (>15.000/µl)
- Hypoalbuminemia (<30 g/l)
- Creatinin rise >50%
- Lactate ≥5 mmol/l
- Age 1-5 years
- Significant comorbidity (ex. renal failure)
- Immunsuppression (after splenic infarction, polytrauma)

Therapy

Finding	Points
Fever	1
Intestinal obstruction	1
Hypotension	1
Leucocytosis < 15000	0
Leucocytosis > 15000	1
Findings in US or CT : Ascites , Colon thickening, Colon lumen widening	
1 finding	0
2 findings	1
3 findings	2

Score for evaluation of severity of disease and possible failure of metronidazole therapy (>2 points)

Belmares J, Gerding DN, Parada JP et al. Outcome of metronidazole therapy for Clostridium difficile disease and correlation with a scoring system. J Infect 2007; 55: 495–501

Therapy

- Primary therapy of **mild to moderate CDAD / CDI** (no pseudomembranous colitis, moderate leukocytosis, no or only mild fever) - **Metronidazole orally** (4 x 250 mg / day or 3 x 500 mg / day) for five to ten days
  * 20-40 mg/kg /day
- Primary therapy of **severe CDAD/CDI** (pseudomembranous colitis, fever, Leucocytosis > 15000/µl) **Vancomycin orally** (4 x250mg/day up to 4x 500mg/day)* for 10 days
- *40 mg/kg/day

*Vancomycin serum levels!

Fidaxomicin orally *(2x200 mg/day) – significantly fewer relapses than Vancomycin*

Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y, Gorbach S, Sears P, Shue YK - Fidaxomicin versus vancomycin for Clostridium difficile Infection, N Engl J Med 2011; 364: 422 – 431

- In the case of **life-threatening evolution** - vancomycin (4x 500mg / day) orally (or administered via gastric probe or rectal enema) with parenteral metronidazole (3 x 500mg / day)

Therapy

- Recurrence rate in pediatric patients : 10-31%
- After multiple recurrences a fecal microbiome transfer (FMT) can be performed. The healing rate after FMT is about 80%
- Problem: secondary long term effects??

Kronman MP, Nielson HJ, Adler AL, Giefer MJ, Wahbeh G, Singh N, et al. Fecal microbiota transplantation via nasogastric tube for Clostridium difficile infection in pediatric patients. J Pediatr Gastroenterol Nutr. 2015;60:23–6.

Lynch SV. Fecal microbiota transplantation for recurrent Clostridium difficile infection in pediatric patients. J Pediatr Gastroenter 2015;60:1–3.

Therapy

- In patients with a toxic megacolon or an acute abdomen / perforation: total colectomy with terminal ileostomy or loop Ileostomy with intestinal lavage with vancomycin

Lee, Justin, Tashjian, David B., Moriarty, Kevin. (2012). Is partial colectomy the operation of choice in pediatric Clostridium difficile colitis?. Pediatric Surgery International. 28. 603-7.

Mc Laughlin D, Friedmacher F, Puri P. The impact of Clostridium difficile on paediatric surgical practice: a systematic review. Pediatr Surg Int 2014; 30: 853-859 [PMID: 25008231 DOI:10.1007/s00383-014-3543-5]

Trauma und Clostridium difficile?

- Trauma patients with CDI are usually young patients with relative immunosuppression due to injury, often without prolonged periods with antibiotic exposure or long hospital stays
- Incidence of C. difficile infection in trauma patients is equal to that of the hospitalized population
- Cases of C. difficile infection have been described in young trauma patients without antibiotic abuse - different phenotypes for patients after trauma?
- Large numbers are missing for pediatric trauma patients

Efron PA, Liu H, Lottenberg L, et al. An epidemiologic and genomic anaylis of Clostridium difficile infections in blunt trauma patients. J Trauma Acute Care Surg 2013; 74: 334–338

Lumpkins K, Bochicchio GV, Joshi M, et al. Clostridium difficile infection in critically injured trauma patients. Surg Infect 2008;9:497–501

Conclusion

- Our patient had several of the criteria that would qualify him for severe C. difficile infection
- Under treatment with Metronidazole p.o. there was a slow positive trend towards healing
- Because of Clostridium difficile infection a longer hospital stay was necessary with a larger therapy expenditure and increased therapy costs
- No relapse up to now