ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

ESCMID Postgraduate Education Course

Infections in Critically Ill Patients

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Case presentation

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Male 75 years old with diarrhoea and shock

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Clinical course

- The patient is admitted to a regional hospital due to fever with rigors starting 24 hours prior to his transfer to the emergencies
- Episode of loss of consciousness in the ED
- Lethargic, GCS 13, oliguric, tachypneic
- Shock, diarrhoea, one episode of gastroplegic vomiting
- Physical examination: no apparent source of sepsis

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Medical History

- Arterial Hypertension (since the age of 40 years)
  - Irbesartan/hydrochlorothiazide 300/25mg 1x1, Amlodipine 5mg 1x1, Bisoprolol fumarate 10mg 1/2x1, Spironolactone 25mg 1x1,
- Known dilatation of the ascending aorta
- Paroxysmal Atrial Fibrillation
  - Salospir 325 mgx1
- Idiopathic Pericarditis 1.5 years ago, relapsed 6months ago
  - Now receiving Methylprednisolone 4 mg x1 (tappering dosing)
- Unspecified History of Depressive Disorder
  - Sitalopram 20mg 1 x 1

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Laboratory Tests

- Hct 40.1, WBC 21,400 c/mm3 (poly), Plts 203,000 c/mm3
- Glucose 110 mg/dl, Urea 80 mg/dl, Creatinine 3 mg/dl (baseline 0.9),
- AST 1150 iu/l , ALT 192 iu/l, Alcaline Phosphatase 83 iu/l, γGT 95 iu/l, total bilirubin 0.5 mg/dl
- CPK 29310 iu/l, CKMB 432 iu/l, CRP 69 mg/l
- Arterial Blood Gas : lactic acidosis
- Urine microscopy: no significant findings
- Urine antigen pneumococcus-legionella negative

- U/S abdomen without abnormal evidences
- Brain CT ischemic: micro-encephalopathy
- CT thorax: aneurysma with dilatation of the ascending aorta and coarctation (48 mm)-Minimal pleural effusions bilaterally with atelectasis
- Cardiac ECHO- No pericardiac effusion, no valve insufficiency, Ejection fraction 60%

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Treatment

1. Ceftriaxone+ macrolide
2. Fluoroquinolone+metronidazole
3. Piperacillin/Tazobactam
4. Vancomycin
5. Antifungal coverage
6. 1+4
7. 3+4
8. 3+4+5
9. Other

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Regional ICU, Days 1-4

- Fluid resuscitation, vasopressors, inotropes (levosimendan)
- Piperacillin/Tazobactam 2.25g X 3, ciprofloxacin 200mg X2, micafungin 100mg X1
- Vancomycin 500mg X4 per os, Rifaximine 400mgx3
- Administration of γ-globulin for 4 days, total dose 78g
- Renal replacement started day 2
- Clinically improving, not intubated, persisting diarrhoeas
- Blood-urine-feces: cultures no pathogen
- Elisa for Clostridium difficile-toxin negative X3
- CPK peak 142,000 iu/l, thrombocytopenia nadir 61,000 c/mm3
- CT of the abdomen (day 3): not significant

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Transfer to the ICU of ATTIKON Hospital (Day 4)

- CNS
  - Lethargic but oriented, obeys orders, no focal neurology
- Respiratory
  - pH 7.32, pO_2 146, pCO_2 42, HCO_3 22, Lac 1.2 (MV 0.6)
  - Tachypnoea (30/min), cough with minimal secretions
- Heart
  - Paroxysmal Atrial Fibrillation
  - Low dose vasopressors (2-3 γ)
- Abdomen
  - Distended abdomen, diffuse rebound sensitivity, sounds absent
  - Anuric, renal replacement therapy

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Clinical course (Day 4-10)

- Antifungal , per os Vancomycin and Rifaximine: stop
- Addition of Vancomycin 1gX2 iv+ prednisolone (stress dose)

- Patient clinically improving
  - Respiratory and hemodynamic status stable
  - PLT counts are gradually recovering
  - Lethargic, occasionally confused
  - Starts enteral feeding- 1-2 diarrhoea episodes per day
  - Renal function not improved

- Repeated testing for *C.difficile*: negative
- Lumbar puncture: not significant findings

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Intubation (Day 11)

- Hypoxemia, inadequate management of respiratory secretions
- New fever
  - 39°C
  - Leucocytosis
- Re-initiation of low dose vasopressors

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Which are your next diagnostic and therapeutic maneuvers

1. Thorax and abdomen CT scans
2. Change lines (and culture tips)
3. Cardiac echo
4. Change of antimicrobial coverage
5. All the above
6. 1+2+4

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Blood cultures:
Klebsiella spp

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Which is your antibiotic choice?

1. Carbapenem
2. Cefepime
3. Colistin
4. Tigecycline
5. 1+3
6. Other

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Laboratory Evaluation (Day 11)

- Brain CT scan
  - Micro-ischemic lesions
- Thorax CT scan
  - Small pleural effusion of the right hemithorax, small right atelectasis
- Abdomen CT-scan
  - Colonic aperistalsis, mural thickening, located in the sigmoid colon

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Blood cultures : *Klebsiella pneumoniae*

- ESBL(+)
  - Quinolone R
  - Aminoglycoside R
    - genta MIC>8
  - Cephalosporins 1-3rd generation R
  - B-lactam+ inhibitor R
- Susceptible
  - Carbapenems
  - Cefepime (MIC=1mg/L)
  - Tigecycline MIC=1
  - Colistin MIC=1

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Which is your therapeutic choice now?

1. Cefepime + Metronidazole
2. Carbapenem monotherapy
3. Tigecycline 100mg loading followed by 50mgX2
4. Tigecycline double dose
5. Colistin
6. Other

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Which is the appropriate treatment for ESBL-producing Enterobacteriacea?

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Revised (2011) CLSI breakpoints for cephalosporins, in the treatment of strains exhibiting ESBL phenotype

MIC breakpoints (µg/ml):

Agent	Old (M100-S19)			Revised (M100-S20)		
	Susc	Int	Res	Susc	Int	Res
Cefazolin	≤8	16	≥32	≤1	2	≥4
Cefotaxime	≤8	16-32	≥64	≤1	2	≥4
Ceftizoxime	≤8	16-32	≥64	≤1	2	≥4
Ceftriaxone	≤8	16-32	≥64	≤1	2	≥4
Ceftazidime	≤8	16	≥32	≤4	8	≥16
Aztreonam	≤8	16	≥32	≤4	8	≥16

MIC breakpoints (µg/ml)

Agent	M100-S19			M100-S20		
	Susc	Int	Res	Susc	Int	Res
Cefuroxime (parenteral)	≤8	16	≥32	≤8	16	≥32
Cefepime	≤8	16	≥32	≤8	16	≥32
Cefotetan	≤16	32	≥64	≤16	32	≥64
Cefoxitin	≤8	16	≥32	≤8	16	≥32

Reference

Clinical and Laboratory Standards Institute. 2011. Performance standards for antimicrobial susceptibility testing; Twenty-first informational supplement; M100-S21. Clinical and Laboratory Standards Institute, Wayne, PA.

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EUCAST Breakpoints for Enterobacteriaceae (2010)

Cephalosporins[1]	MIC breakpoint (mg/L)	
	S ≤	R >
Cefaclor	-	-
Cefadroxil (uncomplicated UTI only)	16	16
Cefalexin (uncomplicated UTI only)	16	16
Cefazolin	-	-
Cefepime	1	4
Cefixime (uncomplicated UTI only)	1	1
Cefotaxime	1	2
Cefoxitin (screen)[2]	NA	NA
Cefpodoxime (uncomplicated UTI only)	1	1
Ceftazidime	1	4
Ceftibuten (uncomplicated UTI only)	1	1
Ceftriaxone	1	2
Cefuroxime	8[3]	8
Cefuroxime axetil (uncomplicated UTI only)	8	8

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What is the rationale of the revised breakpoints?

- The revised breakpoints eliminate the need to perform ESBL screen and confirmatory tests for making treatment decisions
- Accumulating evidence with PK/PD studies that the MIC of an isolate correlates better with clinical outcome than knowledge of resistance mechanisms

***Wong-Beringer, A. et al, Clin Infect Dis. 34*:135-46**

- MIC values of cephalosporins are reported as they read and no other interpretation is needed

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However

Clinical failures have been reported in the past with cefepime in the treatment of bacteremic patients with ESBL-producing strains, developing full resistance to cefepime on treatment

J Clin Microbiol. 2005 Sep;43(9):4891-4.

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Clinical course (Day 11-18)

- Remains intubated
  - Hemodynamically stable
  - Receives only meropenem

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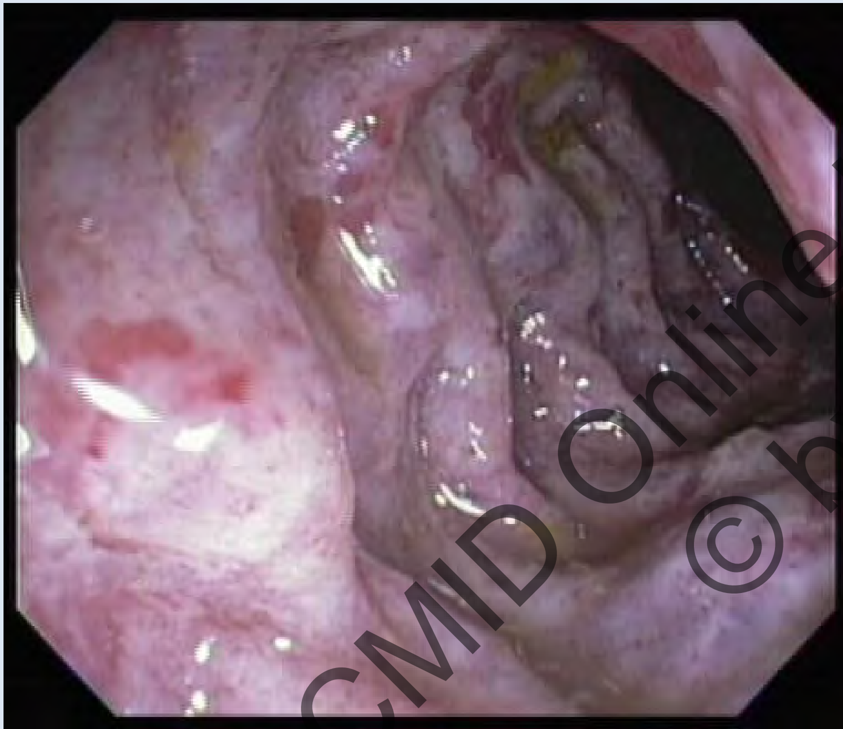
Colonoscopy (Day 18)



- Performed up to the transverse colon
- Oedema, focal areas of pale and edematous mucosa interspersed with areas of petechial hemorrhage or superficial spontaneous ulceration
- Colitis of moderate severity
- Biopsies: ischemic colitis

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Ischemic Colitis

- Ischemic colitis (IC), is the most common form of ischemic injury to the gastrointestinal tract
- The incidence of IC is underestimated because it often has a mild and transient nature often misdiagnosed as inflammatory bowel disease or infectious colitis.
- Frequently occurs in the elderly patient with diffuse disease in small segmental vessels and various co-morbidities. Younger patients may also be affected

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Ischemic colitis

- Conditions that may predispose to the disease: strenuous physical activity, dehydration, illicit drugs, thrombophilic tendency, aortic surgery or cardiac bypass, vasculitis, major cardiovascular episode accompanied by hypotension.
- Isolated right colon ischemia (IRCI) is associated with increased mortality and less specific symptoms (lack of blood in the stools)
- Bacterial translocation and sepsis has been shown to occur with the loss of mucosal integrity

Brandt LJ and Boley SJ Gastroenterology. 2000 May;118(5):954-68

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Ischemic Colitis
Indications for surgery

- In the absence of colonic gangrene or perforation, general measures of supportive care are recommended.
- About 20% of patients with acute IC will require surgery with an associated mortality rate of up to 60%

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New Fever and Shock (Day 19)

- The patient's condition is rapidly deteriorating
  - Fever peaks at 39.4°C
  - Initiation of vasopressors
- Change of lines
- Cultures: blood central-peripheral, catheter tips, bronchial secretions
- Re-evaluation of antimicrobial treatment

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Which combination would you prefer?

1. Meropenem+ Colistin+Vancomycin
2. Colistin +Tigecycline
3. Meropenem+Vancomycin or Daptomycin
4. Carbapenem+ Linezolid+Aminoglycoside
5. Other

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Blood culture

Klebsiella pneumoniae

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Your next thoughts about recurrence

1. Inadequate coverage
2. Possible endocarditis
3. Possible septic thrombophlebitis
4. Continuous ischemia of the bowel-recurrent allothesis
5. All the above
6. 2+3+4

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Diagnostics of recurrent bacteremia

- Thorax CT scan: moderate right pleural effusion, small atelectasis of the right lower lobe, thrombosis of the left subclavian vein
- Abdomen CT scan: Colonic aperistalsis, mural thickening more extended than in the previous scan
- Cardiac Echo-no evidence of endocarditis

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Blood culture

Klebsiella pneumoniae

The same antibiogram as previously

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Which is your therapeutic choice now?

1. Cefepime + Metronidazole
2. Carbapenem monotherapy
3. Tigecycline 100mg loading followed by 50mgX2
4. Tigecycline double dose
5. Colistin
6. 1+5
7. Other

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Colectomy (Day 20)

- Dilatation of the descending colon with imminent rupture. Thin and ischemic enteric wall throughout the transverse and descending colon, with presence of strictures.
- Subtotal colectomy up to the final 5cm of the terminal ileus.
- Biopsy: ischemic colitis

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Patient's course (Day 20-29)

- Antimicrobials
  - Meropenem
  - Colistin
  - Antifungal
- Hemodynamically stable
- Day 29
  - Grossly hemorrhagic stools
  - Lactic acidosis
  - Septic shock
  - Succumbed
  - Bacteremic by the same strain

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Final Diagnosis

- Ischemic colitis
- Recurrent episodes of septic shock due to enteric allothesis
- Uncontrolled ESBL(+) *Klebsiella pneumoniae* infection
  - Enteric bacterial allothesis
  - Septic thrombophlebitis
  - Immunosuppression

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Thank you

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